JOC The Journal of Organic Chemistry

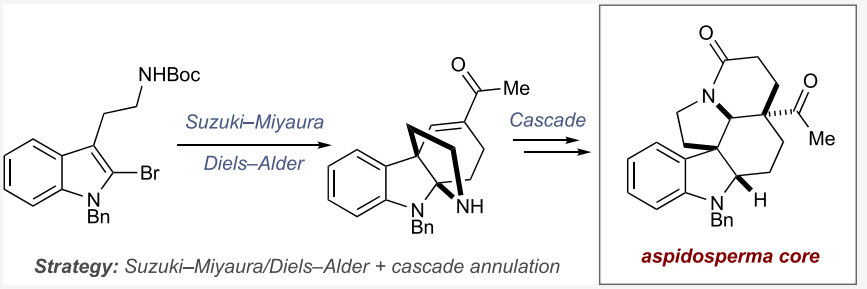
pubs.acs.org/joc Article

Total Synthesis of (±)-Aspidospermidine, (±)-Aspidofractinine, (±)-Limaspermidine, and (±)-Vincadifformine via a Cascade and Common Intermediate Strategy

David L. Cain, Niall A. Anderson, David B. Cordes, Alexandra M. Z. Slawin, and Allan J. B. Watson*

Cite This: https://doi.org/10.1021/acs.joc.2c02099 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information



ABSTRACT: A concise strategy for the total synthesis of several *Aspidosperma* alkaloids is reported. A Suzuki−Miyaura cross-coupling provides access to a 2-vinyl indole that undergoes a Diels−Alder cascade reaction with butyn-2-one to deliver a pyrroloindoline intermediate. This undergoes cascade amidation, reduction, skeletal rearrangement, and intramolecular Michael addition to provide a common intermediate containing the full framework of the *Aspidosperma* alkaloids. The utility of this intermediate is shown in the synthesis of four different natural products.

INTRODUCTION

The *Aspidosperma* alkaloids are a class of monoterpenoid indole alkaloids, which have seen significant interest as synthetic targets (Scheme 1a).[1−4] Their intriguing, densely fused polycyclic structures have inspired numerous strategies and methodologies to enable access to the eponymous aspidospermidine (**1**),[5−8] as well as many other members of this family. Of the strategies employed in total synthesis, divergent approaches based on a common intermediate are arguably the most powerful.[8a,9] These approaches allow the synthesis of multiple natural products by late-stage modification of a single common intermediate.

Here, we report a common intermediate strategy for the synthesis of *Aspidosperma* natural products, where the common intermediate is accessed through cascade reactions, and demonstrate the utility of this cascade strategy in the synthesis of (±)-aspidospermidine,[5−9] (±)-aspidofractinine,[10] (±)-limaspermidine,[11] and (±)-vincadifformine (Scheme 1b).[8d,12]

RESULTS AND DISCUSSION

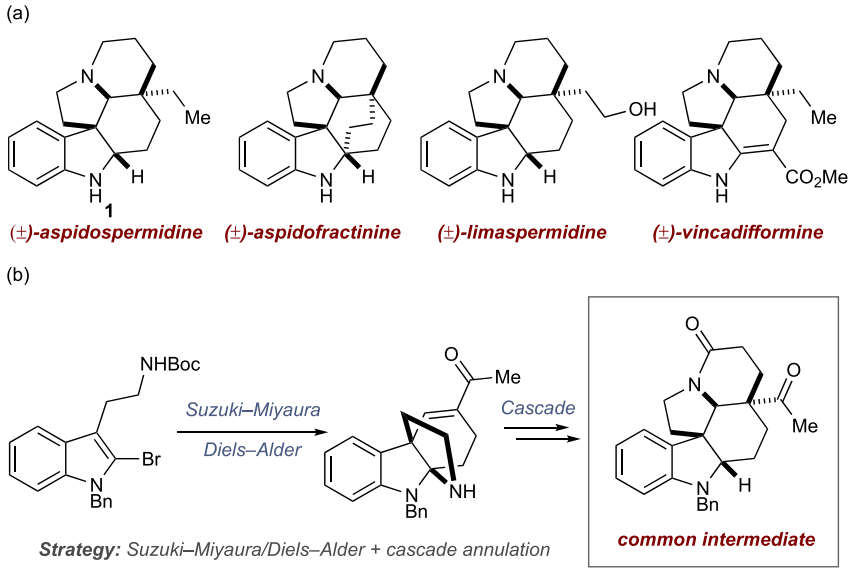
Our retrosynthetic approach is shown in Scheme 2.

We envisioned that (±)-aspidospermidine (**1**) could be accessed by straightforward reduction and deprotection of **2**, which contained the full carbon skeleton of **1**. Indeed, **2** also aligned with our desired divergent synthesis approach as it could be elaborated in several straightforward ways to allow the synthesis of several other members of this class of natural products. As such, **2** was our targeted common intermediate for this overall synthetic campaign. Inspired by previous work,[8a] we believed that **2** could be swiftly accessed in cascade amidation, reduction, skeletal rearrangement, and intramolecular Michael addition by treatment of pyrroloindoline **4** with acryloyl chloride, a suitable hydride reagent, and a base. The key intermediate **4** would be accessed from vinyl indole **5** via a cascade using the Diels−Alder reaction and intramolecular trapping of the generated iminium by the pendant tryptamine. Vinyl indole **5** would be prepared via Suzuki−Miyaura coupling of bromoindole **6**. Based on this proposed sequence, it seemed likely that a cascade synthesis of **4** could be realized beginning from **6**.[13,14]

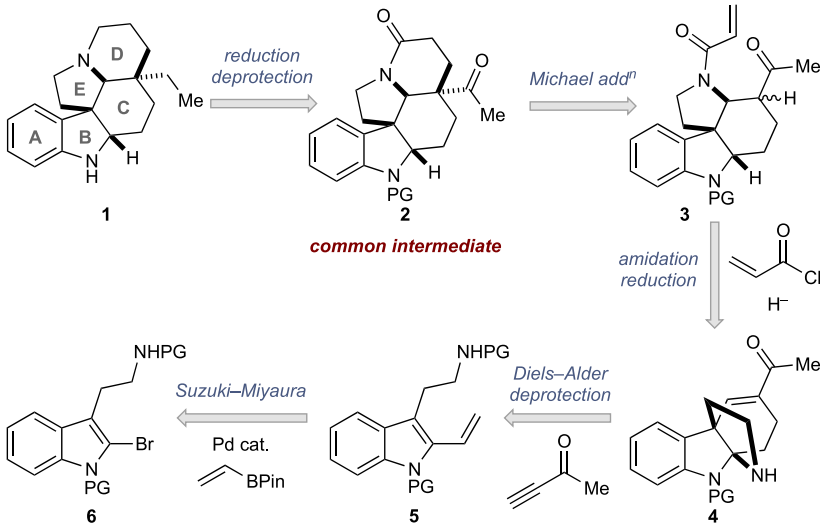
The forward synthesis (Scheme 3) began with the synthesis of the targeted common intermediate (Scheme 3a). Commercial *N*-Boc tryptamine (**7**) was benzyl-protected (**8**) and brominated to provide **9**. Suzuki−Miyaura cross-coupling of **9** with vinyl BPin delivered vinyl indole **10**. At this stage, two alternative sequences delivered access to the key common

Received: August 31, 2022

Scheme 1. (a) *Aspidospermidine* and Several Related Alkaloids and (b) This Work: Divergent Synthesis via a Cascade and Common Intermediate Strategy



Scheme 2. Retrosynthetic Strategy



intermediate **16**. In route A, Diels–Alder reaction of **10** with butyn-2-one using excess $BF_3{\cdot}OEt_2$ provided pyrroloindoline **11**, with concomitant Boc deprotection. This reaction proceeded in good yield, considering the overall number of the overall process involved. Treatment of **11** with acryloyl chloride and reduction of the generated iminium with $NaHB(OAc)_3$ afforded acrylamide **12** in good yield over two steps.

Treatment of **12** with NaH induced an intramolecular aza-Michael reaction to form the E ring and generate enolate **15**, which underwent an intramolecular Michael addition to the acrylamide, forming the D ring, providing common intermediate **16**, and completing the carbon scaffold of (±)-aspidospermidine in almost quantitative yield.

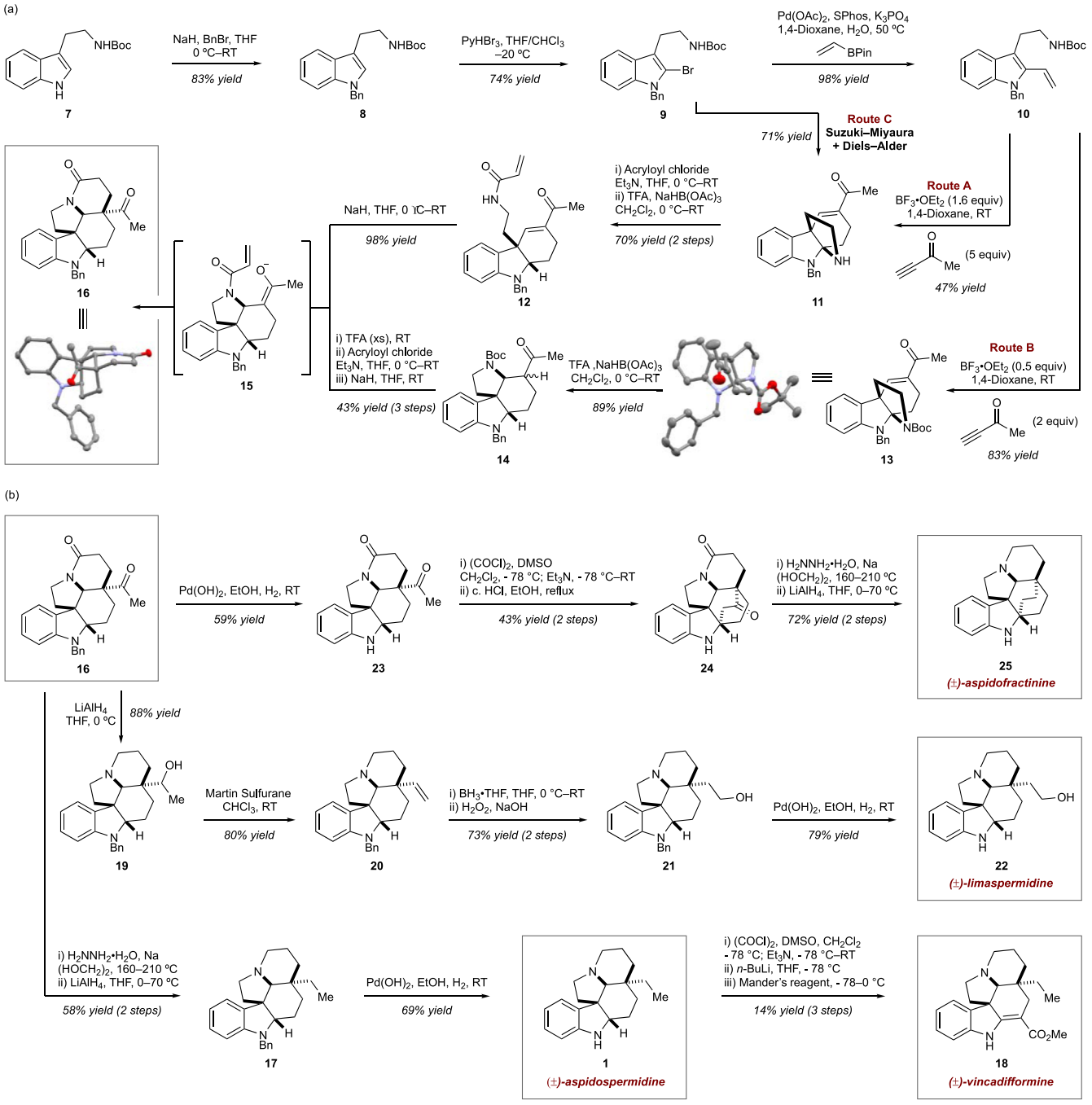
The alternative route B involved a minor adjustment to the sequence of events for route A. Vinyl indole **10** underwent the same Diels–Alder reaction with butyn-2-one; however, lowering the stoichiometry of $BF_3{\cdot}OEt_2$ provided pyrroloindoline **13**, which retained the Boc protecting group, and was a more efficient approach to a similar intermediate. Treatment of **13** with TFA and $NaHB(OAc)_3$ induced skeletal rearrangement to forge the E ring by elimination of the tryptamine nitrogen, reduction of the generated iminium, and aza-Michael addition of the tryptamine to the C ring enone, affording compound **14** in good yield. Use of **14** in a three-step sequence comprising Boc deprotection using TFA, amidation with acryloyl chloride, and intramolecular Michael addition to forge the D ring delivered **16** in moderate yield. Overall, routes A and B were comparable in overall efficiency in accessing **16**.

Finally, it proved possible to access **11** in a telescoped process from **9** by combining the Suzuki–Miyaura and Diels–Alder events (route C). This delivered intermediate **11** in 71% and decreased the number of isolations required for the overall route. Compound **11** was then advanced to **16** using the same sequence of events as route A.

The Lewis acid-mediated Diels–Alder reaction suggested the possibility of an asymmetric process; however, attempts to

https://doi.org/10.1021/acs.joc.2c02099
J. Org. Chem. XXXX, XXX, XXX–XXX

Scheme 3. (a) Synthesis of Common Intermediate 16; (b) *Aspidosperma* Alkaloid Natural Product Syntheses via 16; Thermal Ellipsoids for Compounds 13 and 16 Shown at 50% Probability, with Hydrogens and Solvent Molecules Removed for Clarity



induce enantioselectivity using chiral Lewis acids in this cascade were unsuccessful.

With access to **16**, completion of the synthesis of aspidospermidine was straightforward (Scheme 3b). Reduction of the ketone and lactone was achieved by telescoped Wolff–Kishner and $LiAlH_4$ reductions, affording **17** in good yield. Hydrogenative debenzylation delivered (±)-aspidospermidine **1** (11 chemical transformations and 7 isolations). This also enabled access to (±)-vincadifformine (**18**) via a three-step process including Swern oxidation, deprotonation, and trapping of the generated enaminate with Mander's reagent (14 chemical steps and 8 isolations).

In alignment with the design plan, the utility of the common intermediate **16** was then shown by elaboration to several other members of this class of natural products. Treatment of **16** with $LiAlH_4$ afforded alcohol **19**, which was dehydrated with Martin sulfurane to afford alkene **20**. This allowed Brown hydroboration/oxidation to afford alcohol **21**, which was debenzylated to afford (±)-limaspermidine **22** (13 chemical steps and 9 isolations). Last, debenzylation of **16** afforded amine **23**, which underwent one-pot Swern oxidation and an intramolecular acid-promoted Mannich reaction to afford **24**. Reduction of the ketone and lactam using the Wolff–Kishner/$LiAlH_4$ sequence then provided (±)-aspidofractinine **25** (13 steps and 8 isolations).

https://doi.org/10.1021/acs.joc.2c02099
J. Org. Chem. XXXX, XXX, XXX–XXX

CONCLUSIONS

In summary, a concise, divergent route to the *Aspidosperma* alkaloids has been developed based on a cascade and a common intermediate strategy. The main design element is a cascade cross-coupling/Diels–Alder process, which allows construction of the majority of the necessary ring system. A cascade aza-Michael/Michael reaction then completes the carbon skeleton and provides the key common intermediate, which can be readily elaborated to various members of this natural product family.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.2c02099.

> Characterization data, copies of ^{1}H and ^{13}C NMR spectra, and crystal structure data. The research data supporting this publication can be accessed at https://doi.org/10.17630/b4202d38-1f7c-4344-9816-efdb070d7d37 (PDF)

Accession Codes

CCDC 2191599–2191600 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Author

Allan J. B. Watson − *EaStCHEM, School of Chemistry, University of St Andrews, St Andrews KY16 9ST, U.K.;* orcid.org/0000-0002-1582-4286; Email: aw260@st-andrews.ac.uk

Authors

David L. Cain − *EaStCHEM, School of Chemistry, University of St Andrews, St Andrews KY16 9ST, U.K.;* Present Address: Sygnature Discovery, Biocity, Pennyfoot Street, Nottingham, NG1 1GR, U.K

Niall A. Anderson − *GlaxoSmithKline, Medicines Research Centre, Stevenage SG1 2NY, U.K.;* Present Address: AstraZeneca, Darwin Building, Unit 310, Cambridge Science Park, Milton Road, Cambridge, CB4 0WG, U.K.; orcid.org/0000-0001-8403-9698

David B. Cordes − *EaStCHEM, School of Chemistry, University of St Andrews, St Andrews KY16 9ST, U.K.;* orcid.org/0000-0002-5366-9168

Alexandra M. Z. Slawin − *EaStCHEM, School of Chemistry, University of St Andrews, St Andrews KY16 9ST, U.K.;* orcid.org/0000-0002-9527-6418

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.2c02099

Author Contributions

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

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

D.L.C. thanks EPSRC and GSK for a Ph.D. studentship. We thank Dr. Eva M. Israel for assistance with NMR processing, Dr. Matthew Andrews for assistance with X-ray data processing, and Mr. John M. Halford-McGuff for assistance with manuscript preparation.

REFERENCES

(1) Saxton, J. E. Chapter 9 Synthesis of the Aspidosperma Alkaloids. In *The Alkaloids: Chemistry and Biology*; Cordell, G. A., Ed.; Academic Press: San Diego, CA, 1998; Vol. *50*, pp 343–376.

(2) Lopchuk, J. M. Recent Advances in the Synthesis of Aspidosperma-Type Alkaloids. In *Progress in Heterocyclic Chemistry*; GribbleJoule, G. W. J. A., Ed.; Elsevier: Oxford, U.K., 2011; Vol. *23*, pp 1–25.

(3) Saxton, J. E. *Chemistry of Heterocyclic Compounds*; Wiley-Interscience: New York, 1983; Vol. *25*, pp 331–437.

(4) Saxton, J. E. Alkaloids of the Aspidospermine Group. In *The Alkaloids: Chemistry and Biology*; Cordell, G. A., Ed.; Academic Press: San Diego, 1998; Vol. *51*, pp 1–197.

(5) O'Connor, S. E.; Maresh, J. J. Chemistry and Biology of Monoterpeneindole Alkaloid Biosynthesis. *Nat. Prod. Rep.* **2006**, *23*, 532–547.

(6) Biemann, K.; Friedmann-Spiteller, M.; Spiteller, G. An Investigation by Mass Spectrometry of the Alkaloids of Aspidosperma Quebracho-blanco. *Tetrahedron Lett.* **1961**, *2*, 485–492.

(7) Biemann, K.; Spiteller-Friedmann, M.; Spiteller, G. Application of Mass Spectrometry to Structure Problems. X.1 Alkaloids of the Bark of Aspidosperma quebracho blanco. *J. Am. Chem. Soc.* **1963**, *85*, 631–638.

(8) For selected examples, see: (a) Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C. Collective Synthesis of Natural Products by Means of Organocascade Catalysis. *Nature* **2011**, *475*, 183–188. (b) Pritchett, B. P.; Kikuchi, J.; Numajiri, Y.; Stoltz, B. M. Enantioselective Pd-Catalyzed Allylic Alkylation Reactions of Dihydropyrido[1,2-a]indolone Substrates: Efficient Syntheses of (−)-Goniomitine, (+)-Aspidospermidine, and (−)-Quebrachamine. *Angew. Chem., Int. Ed.* **2016**, *55*, 13529–13532. (c) Zhao, S.; Andrade, R. B. Development and Scope of the Arene-Fused Domino Michael/Mannich Reaction: Application to the Total Syntheses of Aspidosperma Alkaloids (−)-Aspidospermidine, (−)-Tabersonine, and (−)-Vincadifformine. *J. Org. Chem.* **2017**, *82*, 521–531. (d) Wang, N.; Du, S.; Li, D.; Jiang, X. Divergent Asymmetric Total Synthesis of (+)-Vincadifformine, (−)-Quebrachamine, (+)-Aspidospermidine, (−)-Aspidospermine, (−)-Pyrifolidine, and Related Natural Products. *Org. Lett.* **2017**, *19*, 3167–3170. (e) Xu, H.; Huang, H.; Zhao, C.; Song, C.; Chang, J. Total Synthesis of (+)-Aspidospermidine. *Org. Lett.* **2019**, *21*, 6457–6460. (f) Martin, G.; Angyal, P.; Egyed, O.; Varga, S.; Soós, T. Total Syntheses of Dihydroindole Aspidosperma Alkaloids: Reductive Interrupted Fischer Indolization Followed by Redox Diversification. *Org. Lett.* **2020**, *22*, 4675–4679. (g) Katahara, S.; Sugiyama, Y.; Yamane, M.; Komiya, Y.; Sato, T.; Chida, N. Five-Step Total Synthesis of (±)-Aspidospermidine by a Lactam Strategy via an Azomethine Ylide. *Org. Lett.* **2021**, *23*, 3058–3063.

(9) (a) Wilson, R. M.; Danishefsky, S. J. Pattern Recognition in Retrosynthetic Analysis: Snapshots in Total Synthesis. *J. Org. Chem.* **2007**, *72*, 4293–4305. (b) Mizoguchi, H.; Oikawa, H.; Oguri, H. Biogenetically Inspired Synthesis and Skeletal Diversification of Indole Alkaloids. *Nat. Chem.* **2014**, *6*, 57–64. (c) Yang, Y.; Bai, Y.; Sun, S.; Dai, M. Biosynthetically Inspired Divergent Approach to Monoterpene Indole Alkaloids: Total Synthesis of Mersicarpine, Leuconodines B and D, Leuconoxine, Melodinine E, Leuconolam, and Rhazinilam. *Org. Lett.* **2014**, *16*, 6216–6219. (d) Krüger, S.; Gaich, T. Enantioselective, Protecting-Group-Free Total Synthesis of Sarpagine Alkaloids—A Generalized Approach. *Angew. Chem., Int. Ed. Engl.* **2015**, *54*, 315–317. (e) Xu, Z.; Wang, Q.; Zhu, J. Total Syntheses of (−)-Mersicarpine, (−)-Scholarisine G, (+)-Melodinine

E, (−)-Leuconoxine, (−)-Leuconolam, (−)-Leuconodine A, (+)-Leuconodine F, and (−)-Leuconodine C: Self-Induced Diastereomeric Anisochronism (SIDA) Phenomenon for Scholarisine G and Leuconodines A and C. *J. Am. Chem. Soc.* **2015**, *137*, 6712−6724. (f) Krüger, S.; Gaich, T. Total Syntheses of Vellosimine, N-Methylvellosimine, and 10-Methoxyvellosimine and Formal Synthesis of 16-Epinormacusine B through a [5+2] Cycloaddition. *Eur. J. Org. Chem.* **2016**, *2016*, 4893−4899. (g) Gerlinger, C. K. G.; Krüger, S.; Gaich, T. Total Synthesis of Parvineostemonine by Structure Pattern Recognition: A Unified Approach to Stemona and Sarpagine Alkaloids. *Chem.—Eur. J.* **2018**, *24*, 3994−3997. (h) Varga, S.; Angyal, P.; Martin, G.; Egyed, O.; Holczbauer, T.; Soós, T. Total Syntheses of (−)-Minovincine and (−)-Aspidofractinine through a Sequence of Cascade Reactions. *Angew. Chem., Int. Ed.* **2020**, *59*, 13547−13551.

(10) (a) Wenkert, E.; Liu, S. Total Synthesis of (±)-Aspidofractinine and (±)-Aspidospermidine. *J. Org. Chem.* **1994**, *59*, 7677−7682. (b) Cartier, D.; Ouahrani, M.; Lévy, J. Cyclization of Oxindolic methylketones with acid : A rapid synthesis of (±)-aspidofractinine. *Tetrahedron Lett.* **1989**, *30*, 1951−1954. (c) Dufour, M.; Gramain, J.-C.; Husson, H.-P.; Sinibaldi, M.-E.; Troin, Y. Total Synthesis of (±)-Aspidofractinine. *Tetrahedron Lett.* **1989**, *30*, 3429−3432. (d) Ban, Y.; Honma, Y.; Oishi, T. The Total Synthesis of (±)-Aspidofractinine. *Tetrahedron Lett.* **1976**, *17*, 1111−1114. (e) Kinoshita, H.; Ohnuma, T.; Oishi, T.; Ban, Y. Application of the New Acylating Agents [PhS(O)−CH=C(OMe)Cl and $PhSO_2$−CH=C(OMe)Cl] to the Synthesis of Indole Alkaloids. A Total Synthesis of (±)-Aspidofractinine. *Chem. Lett.* **1986**, *15*, 927−930. (f) Zhao, R.; Sun, Z.; Mo, M.; Peng, F.; Shao, Z. Catalytic Asymmetric Assembly of C3-Monosubstituted Chiral Carbazolones and Concise Formal Synthesis of (−)-Aspidofractinine: Application of Enantioselective Pd-Catalyzed Decarboxylative Protonation of Carbazolones. *Org. Lett.* **2014**, *16*, 4178−4181. (g) 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. Iodospirocyclization of Tryptamine-Derived Isocyanides: Formal Total Synthesis of Aspidofractinine. *Angew. Chem., Int. Ed.* **2018**, *57*, 15232−15236. (h) Gagnon, D.; Spino, C. Stereoselective Synthesis of (+)-Aspidofractinine. *J. Org. Chem.* **2009**, *74*, 6035−6041. (i) Kuehne, M. E.; Seaton, P. J. Studies in Biomimetic Alkaloid Aynthetses. 13. Total Syntheses of Racemic Aspidofractine, Pleiocarpine, Pleiocarpinine, Kopsinine, *N*-Methylkopsanone, and Kopsanone. *J. Org. Chem.* **1985**, *50*, 4790−4796.

(11) (a) White, K. L.; Movassaghi, M. Concise Total Syntheses of (+)-Haplocidine and (+)-Haplocine via Late-Stage Oxidation of (+)-Fendleridine Derivatives. *J. Am. Chem. Soc.* **2016**, *138*, 11383−11389. (b) Overman, L. E.; Robertson, G. M.; Robichaud, A. J. Use of Aza-Cope Rearrangement-Mannich Cyclization Reactions to Achieve a General Entry to Melodinus and Aspidosperma alkaloids. Stereocontrolled Total Syntheses of (±)-Deoxoapodine, (±)-Meloscine, and (±)-Epimeloscine and a Formal Synthesis of (±)-1-Acetylaspidoalbidine. *J. Am. Chem. Soc.* **1991**, *113*, 2598−2610. (c) Tan, S. H.; Banwell, M. G.; Willis, A. C.; Reekie, T. A. Application of a Raney-Cobalt-Mediated Tandem Reductive Cyclization Protocol to Total Syntheses of the Aspidosperma Alkaloids (±)-Limaspermidine and (±)-1-Acetylaspidoalbidine. *Org. Lett.* **2012**, *14*, 5621−5623. (d) Du, J.-Y.; Zeng, C.; Han, X.-J.; Qu, H.; Zhao, X.-H.; An, X.-T.; Fan, C.-A. Asymmetric Total Synthesis of Apocynaceae Hydrocarbazole Alkaloids (+)-Deethylibophyllidine and (+)-Limaspermidine. *J. Am. Chem. Soc.* **2015**, *137*, 4267−4273. (e) Honma, Y.; Ban, Y.; Ohnuma, T. A Total Synthesis of (±)-Fendleridine. *Heterocycles* **1976**, *5*, 47−51. (f) Pritchett, B. P.; Donckele, E. J.; Stoltz, B. M. Enantioselective Catalysis Coupled with Stereodivergent Cyclization Strategies Enables Rapid Syntheses of (+)-Limaspermidine and (+)-Kopsihainanine A. *Angew. Chem., Int. Ed.* **2017**, *56*, 12624−12627.

(12) (a) Pandey, G.; C, P. Iminium Ion Cascade Reaction in the Total Synthesis of (+)-Vincadifformine. *Org. Lett.* **2011**, *13*, 4672−4675. (b) Tan, P. W.; Seayad, J.; Dixon, D. J. Expeditious and Divergent Total Syntheses of Aspidosperma Alkaloids Exploiting Iridium(I)-Catalyzed Generation of Reactive Enamine Intermediates. *Angew. Chem., Int. Ed.* **2016**, *55*, 13436−13440. (c) Kuehne, M. E.; Matsko, T. H.; Bohnert, J. C.; Kirkemo, C. L. Studies in Biomimetic Alkaloid Syntheses. 3. Syntheses of Ervinceine and Vincadifformine Analogs from Tetrahydro-gamma-carbolines through Secodine Intermediates. *J. Org. Chem.* **1979**, *44*, 1063−1068. (d) Kutney, J. P.; Chan, K. K.; Failli, A.; Fromson, J. M.; Gletsos, C.; Nelson, V. R. Total Synthesis of Some Monomeric Vinca Alkaloids: *dl*-Vincadine, *dl*-Vincaminoreine, *dl*-Vincaminorine, *dl*-Vincadifformine, *dl*-Minovine, and *dl*-Vincaminoridine. *J. Am. Chem. Soc.* **1968**, *90*, 3891−3893. (e) Pandey, G.; Khamrai, J.; Mishra, A.; Maity, P.; Chikkade, P. K. Iminium Ion-Enamine Cascade Reaction Enables the Asymmetric Total Syntheses of Aspidosperma Alkaloids Vincadifformine and Ervinceine. *Tetrahedron* **2018**, *74*, 6317−6327. (f) Mijangos, M. V.; Miranda, L. D. A Unified Synthesis of Topologically Diverse Aspidosperma Alkaloids through Divergent Iminium-Trapping. *Org. Biomol. Chem.* **2018**, *16*, 9409−9419.

(13) Cain, D. L.; McLaughlin, C.; Molloy, J. J.; Carpenter-Warren, C.; Anderson, N. A.; Watson, A. J. B. A Cascade Suzuki-Miyaura/Diels-Alder Protocol: Exploring the Bifunctional Utility of Vinyl Bpin. *Synlett* **2019**, *30*, 787−791.

(14) Molloy, J. J.; Seath, C. P.; West, M. J.; McLaughlin, C.; Fazakerley, N. J.; Kennedy, A. R.; Nelson, D. J.; Watson, A. J. B. Interrogating Pd(II) Anion Metathesis Using a Bifunctional Chemical Probe: A Transmetalation Switch. *J. Am. Chem. Soc.* **2018**, *140*, 126−130.

https://doi.org/10.1021/acs.joc.2c02099
J. Org. Chem. XXXX, XXX, XXX−XXX