

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*

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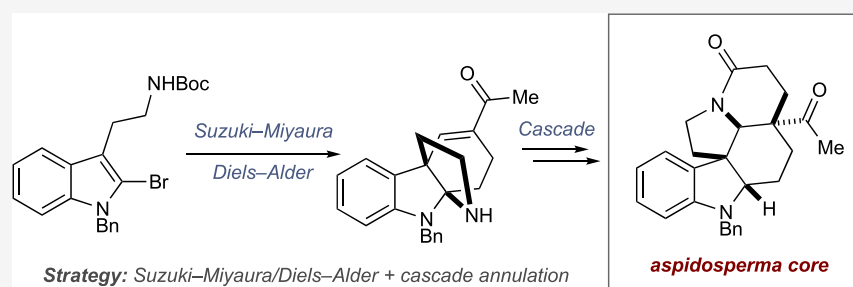
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ABSTRACT: A concise strategy for the total synthesis of several *Aspidosperma* alkaloids is reported. A Suzuki–Miyaura cross-coupling provides access to a 2-vinyl indole that undergoes a Diels–Alder cascade reaction with butyn-2-one to deliver a pyrroloindoline 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 monoterpene 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

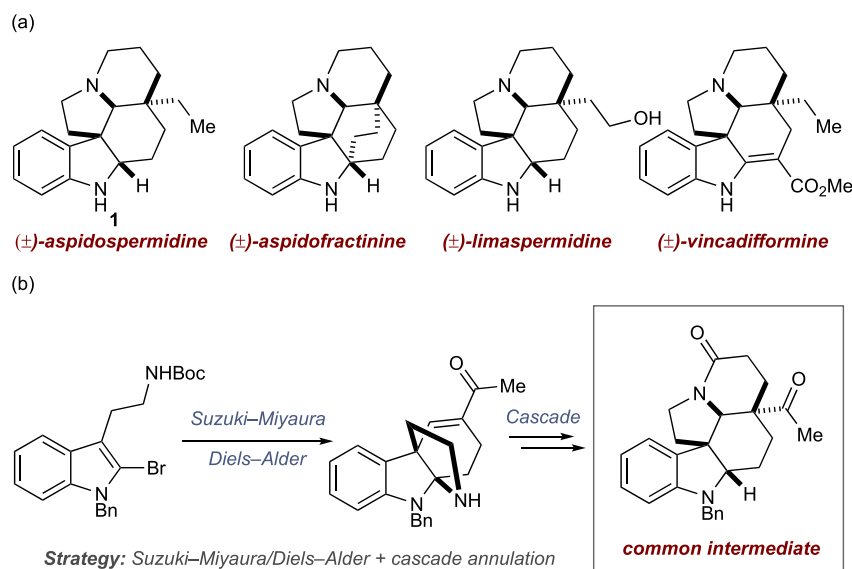
products. As such, 2 was our targeted common intermediate for this overall synthetic campaign. Inspired by previous work,^{8a} we believed that 2 could be swiftly accessed in cascade amidation, reduction, skeletal rearrangement, and intramolecular Michael addition by treatment of pyrroloindoline 4 with 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

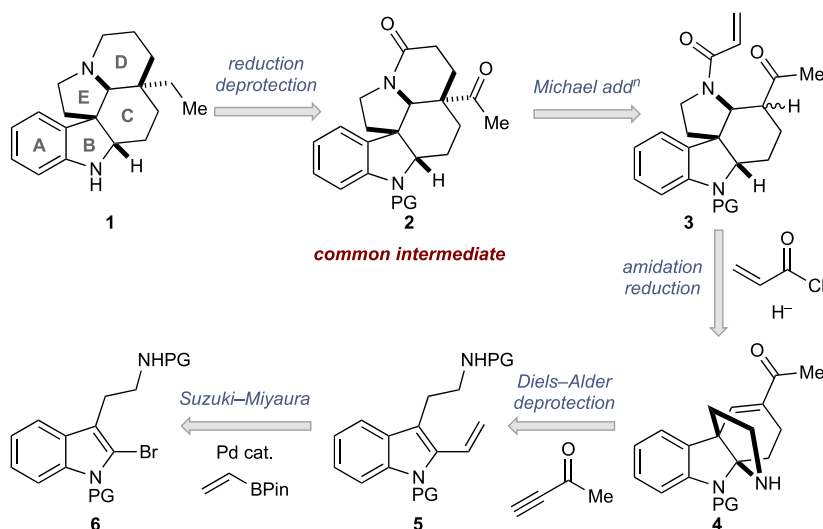
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Scheme 1. (a) *Aspidospermidine* and Several Related Alkaloids and (b) This Work: Divergent Synthesis via a Cascade and Common Intermediate Strategy

Scheme 2. Retrosynthetic Strategy



intermediate **16**. In route A, Diels–Alder reaction of **10** with butyn-2-one using excess $\text{BF}_3 \cdot \text{OEt}_2$ 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 $\text{NaHB}(\text{OAc})_3$ 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 $\text{BF}_3 \cdot \text{OEt}_2$ provided pyrroloindoline **13**, which retained the Boc protecting group, and was a

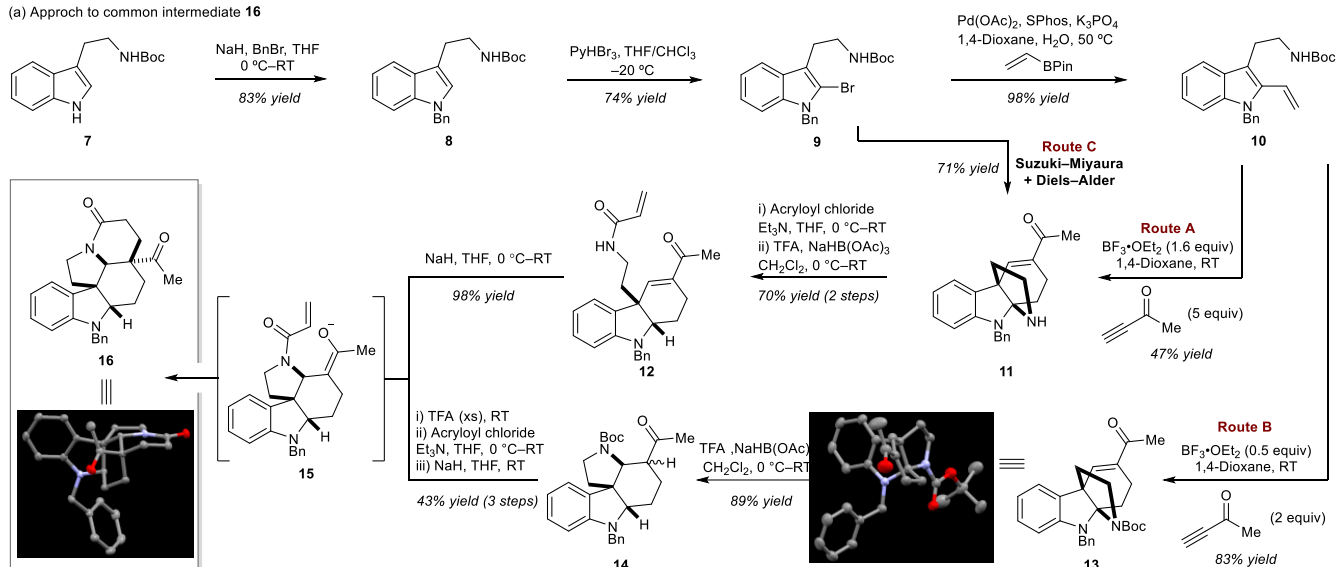
more efficient approach to a similar intermediate. Treatment of **13** with TFA and $\text{NaHB}(\text{OAc})_3$ induced skeletal rearrangement to forge the E ring by elimination of the tryptamine nitrogen, reduction of the generated iminium, and aza-Michael addition of the tryptamine to the C ring enone, 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.

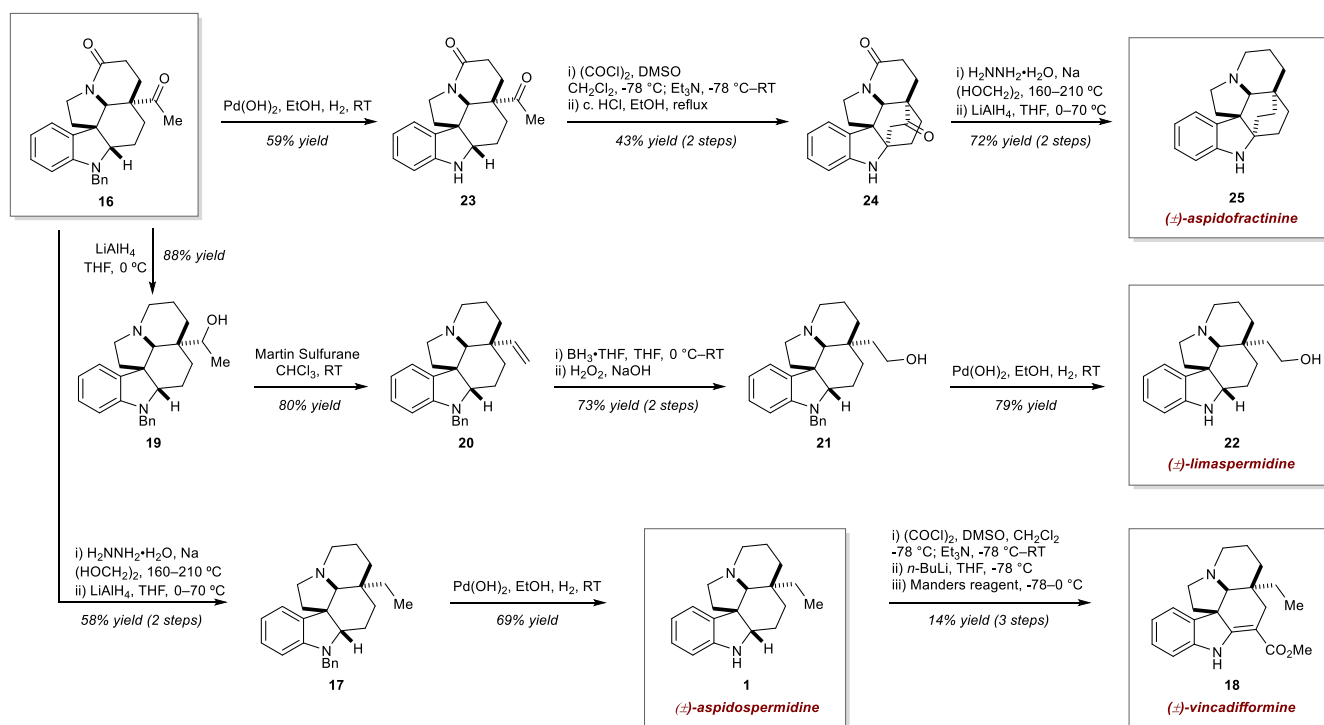
The Lewis acid-mediated Diels–Alder reaction suggested the possibility of an asymmetric process; however, attempts to

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

(a) Approach to common intermediate 16



(b) *Aspidosperma* natural product synthesis via common intermediate 16



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 debenzoylation delivered ($\pm$)-aspidospermidine **1** (11 chemical transformations and 7 isolations). This also enabled access to ($\pm$)-vincadifformine (**18**) via a three-step process including Swern oxidation, deprotonation, and trapping of the generated enamine 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 debenzoylated to afford ($\pm$)-limaspermidine **22** (13 chemical steps and 9 isolations). Last, debenzoylation 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 ($\pm$)-aspidofractinine **25** (13 steps and 8 isolations).

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 ^1H 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.

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