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Total Synthesis of (−)-Kopsifoline A and (+)-Kopsifoline E

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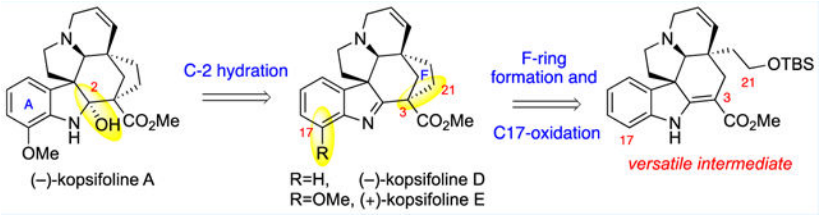
Abstract

We report the first total synthesis of (−)-kopsifoline A and (+)-kopsifoline E. Our synthetic strategy features a biogenetically inspired regioselective C17-functionalization of a versatile intermediate containing the pentacyclic core of aspidosperma alkaloids. The vinylogous urethane substructure of this intermediate affords (−)-kopsifoline D via C3–C21 bond formation under the Mitsunobu reaction conditions, while it enables selective C17-functionalization en route to (−)-kopsifoline A and (+)-kopsifoline E.

Graphical Abstract



The molecular complexity and the biological activity of the aspidosperma family of alkaloids continue to draw attention from the scientific community.[1,2] A subset of these diverse alkaloids includes the hexacyclic kopsia alkaloids that contain the characteristic pentacyclic aspidosperma core (Figure 1, rings A–E).[3] Kopsifolines were first isolated from

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Author Contributions
The authors declare no competing financial interest.

ASSOCIATED CONTENT
Supporting Information
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Experimental procedures, spectroscopic data, copies of ^{1}H and ^{13}C NMR spectra (PDF)

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Malayan Kopsia species, *K. fruticose* (Ker) A. DC. and reported by Kam and Choo.[4] While there are no reported syntheses of the C17-oxygenated (−)-kopsifoline A (**1**) and (+)-kopsifoline E (**3**), (−)-kopsifoline D (**2**) has been synthesized by the Boger and the Peng research groups in 2014 and 2019, respectively.[5] As an outgrowth of our studies of complex aspidosperma alkaloids,[6] we describe the first total synthesis of (−)-kopsifoline A (**1**) and (+)-kopsifoline E (**3**) via the late-stage C-17 functionalization of an advance intermediate that also affords rapid access to (−)-kopsifoline D (**2**). Specifically, we disclose the use of a vinylogous urethane substructure for regioselective C17-functionalization of a common versatile intermediate and a dehydrative synthesis of the C3–C21 bond to afford the F-ring of the desired targets.

Our biogenetically inspired retrosynthetic analysis of (−)-kopsifoline A (**1**) and (+)-kopsifoline E (**3**) is illustrated in Scheme 1. We envisioned access to kopsifoline A (**1**) via hydration of the C2-imine of (+)-kopsifoline E (**3**). We anticipated the formation of the key C3–C21 bond, providing the F-ring of kopsifolines, via a net dehydrative cyclization of a C21-oxygenated aspidosperma derivative **8** with the C2-vinylogous urethane serving as the nucleophile. Recognizing that regioselective oxygenation of intermediate **8** would lead to kopsifoline A (**1**) and (+)-kopsifoline E (**3**), whereas F-ring formation from this versatile intermediate would give direct access to (−)-kopsifoline D (**2**) as well, we posited the potential utility of the C2-vinylogous urethane **8** to enable selective late-stage C17-functionalization. Informed by our earlier synthetic studies of complex aspidosperma alkaloids, we envisioned concise access to the versatile intermediate **8** from enantiomerically enriched and previously reported N1-*para*-methoxybenzyl (PMB) lactam **9**.[6c,7]

The use of the pentacyclic intermediate **8** as a common precursor to access kopsifoline alkaloids **1–3** required the development of reaction conditions for selective C17-functionalizaiton. On the basis of our prior success in late-stage C17-functionalization of complex substrates,[6a,c] we considered both C17-oxygentation[8] and indirect C17-boronation.[9] The absence of an N1-amide to direct C17-acetoxylation,[6a] and inspired by mild conditions for effective C–H boronation of arenes,[10] prompted us to consider selective C17-boronation to secure the C17-ether of alkaloids **1** and **3**. Encouraged by our prior application of iridium-catalyzed boronation of complex indole substrates[11] and the protocol we later developed for selective C7-boronation of substituted indoles,[12,13] we began our studies with preparation of the desired key intermediate **8** from lactam **9**, prepared in six steps from a readily available indole derivative (Scheme 2).[6a,7b]

Our synthesis of the versatile intermediate **8** commenced by silylation of the enantiomerically enriched C21-alcohol (+)-**9**[6a,14] to give the silyl ether (+)-**10** in 90% yield. Exposure of N1-PMB indole (+)-**10** to Birch reduction conditions[15] afforded the indole (+)-**11** in 92% yield. Treatment of lactam (+)-**11** with diisobutylaluminum hydride led to stereoselective transannular cyclization by formation of the C12–C19 bond,[6c] and the resulting C2-imine was deprotonated and intercepted by methyl cyanoformate[16] to afford vinylogous urethane (−)-**8** in 80% yield.[17]

We next focused on development of a strategy for direct and selective C17-boronation of the vinylogous urethane (−)-**8**. After significant experimentation, we found that exposure of

pentacycle (−)-**8** to (1,5-cyclooctadiene)(methoxy)iridium(I) dimer $[Ir(cod)OMe]_2$ (10 mol %)[10c] in the presence of 3,4,7,8-tetramethyl-1,10-phenanthroline (tmphen, 20 mol %) along with stoichiometric pinacolborane (HBpin, 5 equiv) and bis(pinacolato)diboron (B_2pin_2, 5 equiv) in THF at 23 °C for 20 h afforded the desired intermediate (−)-**12** (Scheme 3A). The use of B_2pin_2 alone under the same conditions did not lead to boronation of pentacycle (−)-**8**. Similarly, while the use of HBpin alone under otherwise identical $[Ir(cod)OMe]_2$ (10 mol %), and tmphen (20 mol %) in THF at 23 °C for 20 h, conditions led to only 12% yield of the product **12** along with recovery of the starting material (−)-**8** (68%), warming the reaction mixture (60 °C) led to significant decomposition. Notably, the use of conditions we had previously applied to boronation of a complex indole[6c] employing 4,4′-di*tert*-butyl-2,2′-dipyridyl (dtbpy, 20 mol %)[10c,l] with HBpin (5 equiv) only returned the starting vinylogous urethane (−)-**8**. It is important to note that the C2-vinylogous urethane substructure of intermediate (−)-**8** was particularly effective in allowing for selective C17-boronation.

For comparison, in an earlier approach to kopsifolines, we examined the boronation of indole **11** (Scheme 3B), an indole similar to the substrate used successfully in our synthesis of (−)-vallesine (**4**) via late-stage C17-boronation.[6c] However, we observed faster C7-alkene boronation using substrate **11** as compared to the desired C17-boronation. It is expected that a combination of functional group directing, steric, and electronic factors contribute[10k] to the observed regioselectivity in the boronation reaction of substrates **8** and **11** (Scheme 3). Indeed, the variations of the electron density at N1, C7, and C17 are readily apparent by comparison of these substrates.[14,18] We note that the conversion of lactam (+)-**11** to pentacyclic vinylogous urethane (−)-**8** not only provides greater structural rigidity but also leads to an increase in the electron density at both N1 and C17 relative to the alkene.[13d] Importantly, the optimal conditions described above (Scheme 3A)[14] provided an effective means of accessing the desired C17-boronated urethane (−)-**12** with minimal double boronation (<2%) and no alkene boronation byproducts.

With a successful strategy for selective C17-boronation of vinylogous urethane (−)-**8** in hand, we examined our projected approach for securing the F-ring via C3–C21 bond formation.[5] Treatment of the pentacycle (−)-**8** with tetra-*n*-butyl-ammonium fluoride provided the C21-alcohol (−)-**15** in 96% yield (Scheme 4A). Consistent with a biogenetically inspired late-stage dehydrative F-ring formation, exposure of C21-alcohol (−)-**15** to diisopropyl azodicarboxylate and triphenylphosphine afforded (−)-kopsifoline D (**2**) in 70% yield.[19] All spectroscopic data for our synthetic (−)-kopsifoline D (**2**) were consistent with literature reports.[4b,5] The optical rotation for alkaloid **2** (observed $[\alpha]_D^{25}$ = −87.9 (*c* 0.10, $CHCl_3$); lit. $[\alpha]_D$ = −69 (*c* 0.08, $CHCl_3$),[5a] $[\alpha]_D^{23}$ = −82 (*c* 0.30, $CHCl_3$)[5b]) was in agreement with literature values.

Our concise synthesis of (−)-kopsifoline A (**1**) and (+)-kopsifoline E (**3**) is illustrated in Scheme 4B. With rapid access to C17-boronopentacycle (−)-**12** via late-stage boronation of the versatile intermediate (−)-**8** (Scheme 3A), we examined two options for introduction of the required C17-ether. Treatment of aryl boronic ester (−)-**12** with diethyl-hydroxylamine afforded the phenol (−)-**16** in 64% yield. The selective *O*-methylation of phenol (−)-**16**

using methyl iodide and cesium carbonate quantitatively afforded the desired C17-methyl ether (−)-**7**. Alternatively, exposure of a solution of intermediate (−)-**12** in dichloromethane–methanol to copper-(II) acetate and 4-dimethylaminopyridine directly gave the C17-methyl ether (−)-**7** in modest yield.[13l,m,20] Unveiling the C21-alcohol afforded the pentacyclic alcohol (−)-**17** in 80% yield. Sequential application of a bioinspired condensative F-ring cyclization conditions, as described in our synthesis of (−)-kopsifoline D (**2**, Scheme 4A), provided (+)-kopsifoline E (**3**) in 78% yield, which upon formic acid catalyzed C2-hydration yielded (−)-kopsifoline A (**1**) in 73% yield. All spectroscopic data for our synthetic (+)-kopsifoline E (**3**) and (−)-kopsifoline A (1) were consistent with the corresponding literature reports.[4b,14] The optical rotations for synthetic (+)-kopsifoline E (3) (observed $[\alpha]_D^{25}$ = +44.3 (c 0.07, $CHCl_3$) and $[\alpha]_D^{25}$ = +65.1 (c 0.07, CH_2Cl_2); lit. $[\alpha]_D$ = +84 (c 0.15, $CHCl_3$)[4b])[14] and (−)-kopsifoline A (1) ($[\alpha]_D^{25}$ = −11.7 (c 0.10, $CHCl_3$); lit. $[\alpha]_D$ = −11 (c 0.43, $CHCl_3$)[4b]) were agreeable with reported values.

In summary, we describe the first total synthesis of (−)-kopsifoline A (**1**) and (+)-kopsifoline E (**3**). Our synthetic approach to these alkaloids is based on a biogenetically inspired regioselective C17-functionalization of an advance vinylogous urethane (−)-**8**. While F-ring synthesis from this intermediate gives (−)-kopsifoline D (**2**), regioselective C17-boronation allows for introduction of the A-ring methyl ether en route to (+)-kopsifoline E (**3**) and (−)-kopsifoline A (**1**). Notably, the C-ring vinylogous urethane of intermediate (−)-**8** not only offers regioselective C17-functionalization but also it serves as a carbon-nucleophile in a condensative F-ring synthesis under Mitsunobu reaction conditions.[21]

Supplementary Material

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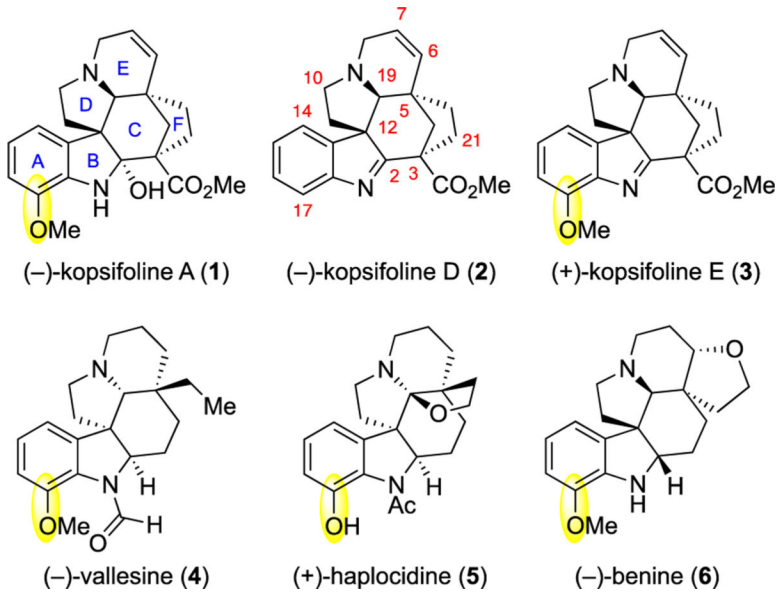
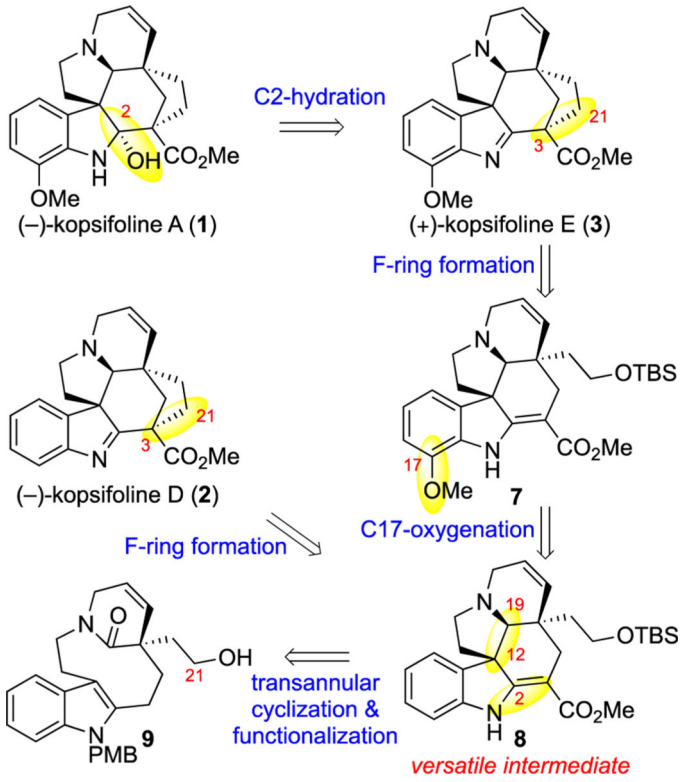
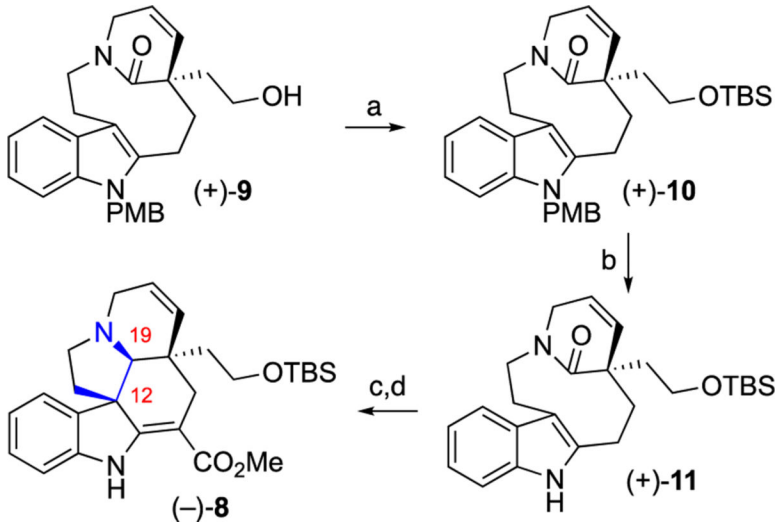


Figure 1.
Representative kopsifolines and related C17-oxygenated aspidosperma alkaloids.

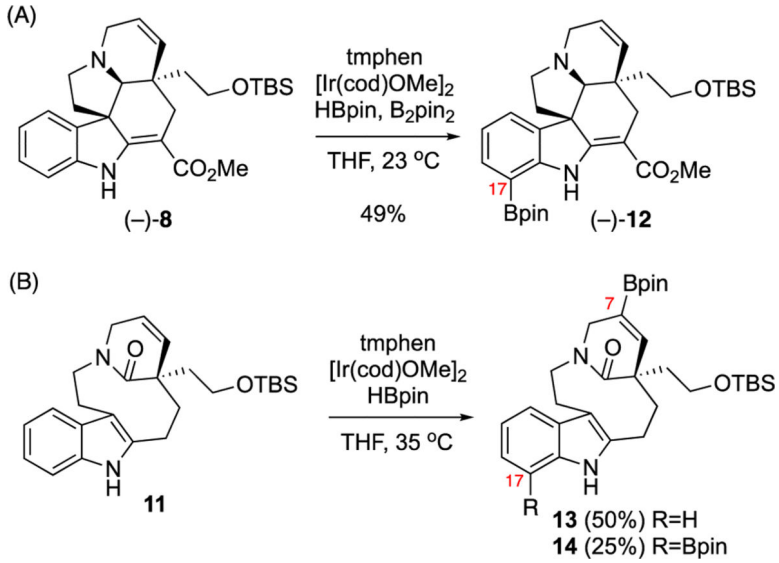


Scheme 1. Retrosynthetic Analysis

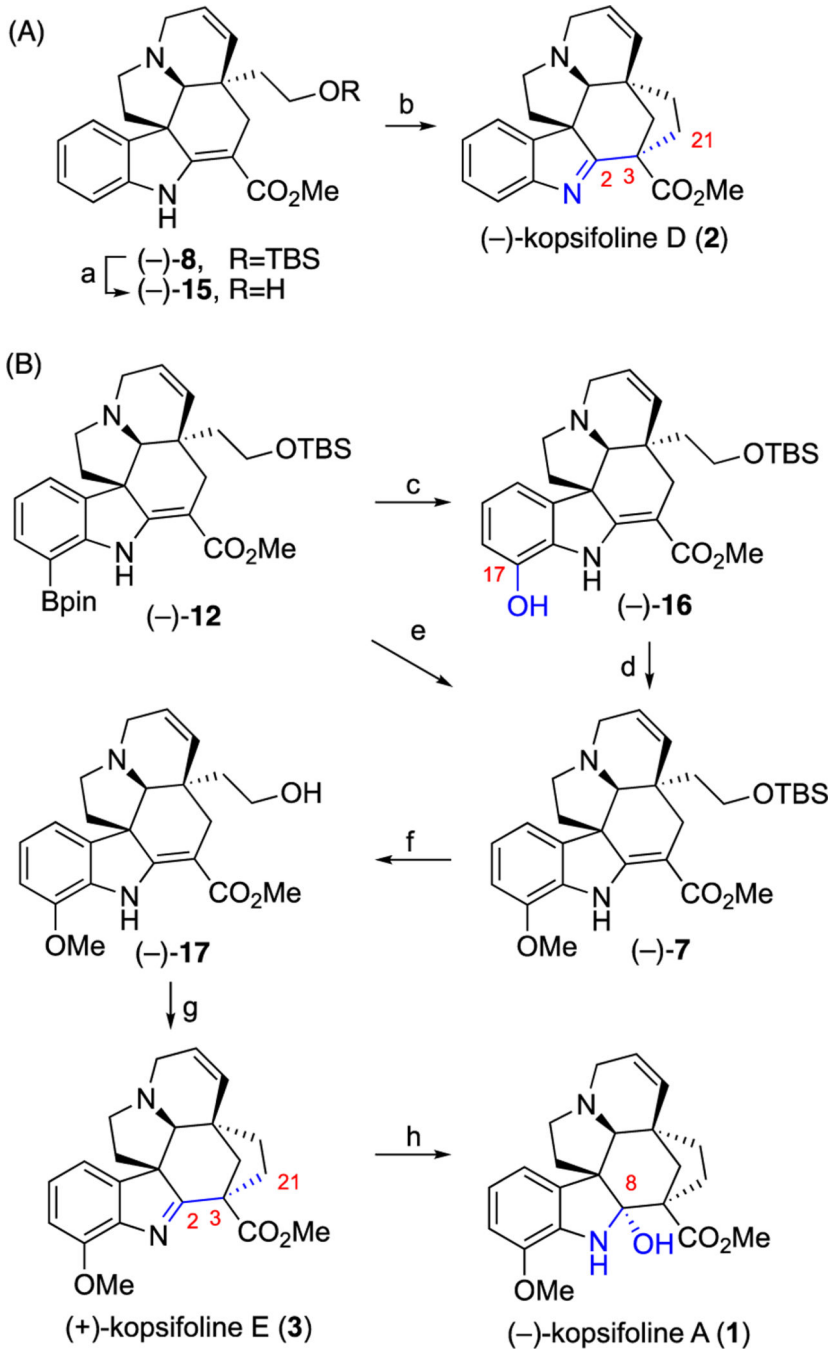


Scheme 2. Synthesis of Advance Intermediate 8[a]

[a]Reagents and conditions: (a) TBSCl, imidazole, DMAP, DMF, 23 °C, 2 h, 90%; (b) Na, NH3 (liq.), THF − 78 °C, 1.5 h, 92%; (c) DIBAL-H, THF, 0 °C, 1.5 h; (d) *n*-BuLi, methyl cyanoformate, THF, −78 °C, 1 h, 80% (2 steps).



Scheme 3. C17-Boronation of Vinylogous Urethane (−)-8, and Indole 11



Scheme 4. Synthesis of (−)-Kopsifoline A (1), (−)-Kopsifoline D (2), and (+)-Kopsifoline E (3)[a]

[a]Reagents and conditions: (a) TBAF, THF, 0 to 23 °C, 5 h, 96%; (b) diisopropyl azodicarboxylate, PPh_3, THF, 23 °C, 8 h, 70%; (c) Et_2NOH, MeOH, 23 °C, 48 h, 64%; (d) Cs_2CO_3, MeI, Acetone, 23 °C, 1 h, 100%; (e) $Cu(OAc)_2$, DMAP, MeOH, CH_2Cl_2, 23 °C, 48 h, 42%; (f) TBAF, THF, 0 to 23 °C, 2.5 h, 80%; (g) diisopropyl azodicarboxylate, PPh_3, THF, 23 °C, 14 h, 78%; (h) H_2O, Formic acid, THF, 23 °C, 2 h, 73%.