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COMMUNICATION

The Enantioselective Synthesis of Eburnamonine, Eucophylline, and 16'-*epi*-Leucophyllidine

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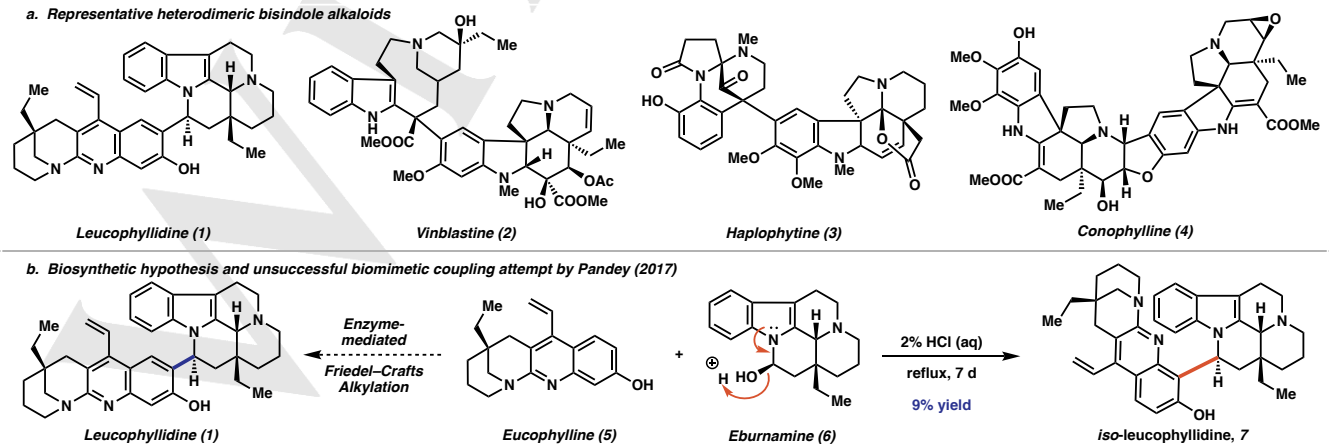
Abstract: A synthetic approach to the heterodimeric bisindole alkaloid leucophyllidine is disclosed herein. An enantioenriched lactam building block, synthesized through Pd-catalyzed asymmetric allylic alkylation, serves as the precursor to both hemispheres. The eburnamonine-derived fragment is synthesized through a Bischler–Napieralski/hydrogenation approach while the eucophylline-derived fragment is synthesized by a Friedländer quinoline synthesis and two sequential C-H functionalization steps. A convergent Stille coupling and phenol-directed hydrogenation unite the two monomeric fragments affording 16'-epi leucophyllidine in 21 steps from commercial material.

Heterodimeric bisindole alkaloids comprise a diverse class of over 200 natural products, which arise from the union of two monoterpenoid indole alkaloids with at least one C–C bond (Scheme 1a).[1] While monomeric indole alkaloids are frequently pursued synthetic targets, reports toward their dimeric counterparts are far less prevalent due to a number of additional synthetic challenges.[2] Each monomer is often a natural product or close derivative thereof, meaning one must essentially complete two total syntheses *en route* to one higher-order structure. Furthermore, the successful execution of convergent disconnection strategies demand reactions that forge sterically congested C–C bonds between densely functionalized frameworks with complete regio- and stereocontrol.[3] A majority of examples to date rely on biomimetic reactions to accomplish these convergent couplings, but as these reactions are *substrate*-controlled, the inherent reactivity can be difficult to overturn[4] and prohibitive to analog synthesis.[5]

Leucophyllidine **(1)** is a heterodimeric bisindole alkaloid that was first isolated from the bark of the Malaysian woody climber *Leuconotis griffithi* in 2009.[6] It is composed of two polycyclic fragments: a southern tetracyclic vinylquinoline fragment derived from eucophylline **(5)** and a northern pentacyclic indole-containing fragment derived from eburnamine **(6)**. Biosynthetically, an enzyme-mediated electrophilic aromatic substitution of an eburnamine-derived iminium ion is proposed to unite the two hemispheres (Scheme 1b, left). Structurally, the molecule contains nine rings, four stereogenic carbons (including two all-carbon quaternary centers) and a sterically hindered $C(sp)^3$–$C(sp)^2$ bond that joins the two natural products.

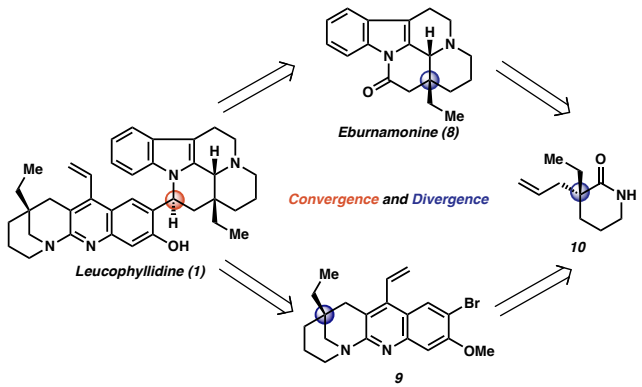
Biologically, leucophyllidine **(1)** is cytotoxic toward drug-sensitive and drug-resistant human KB cells and a dose-dependent inhibitor of nitrous oxide (NO) synthase.[7] Dimeric alkaloids generally exhibit stronger biological activities than their component monomers,[8] and though the mechanisms of action are poorly understood, they are hypothesized to promote higher target affinity or greater stabilization of protein-protein interactions.[9] Despite successful synthesis of both eucophylline **(5)** [10,11] and eburnamine **(6)** [12,13] no successful synthesis of



Scheme 1. Heterodimeric bisindole alkaloids and efforts toward leucophyllidine

10.1002/anie.202106184

leucophyllidine **(1)** has been completed to date. A report from Pandey and coworkers details an assumed "biomimetic" Friedel–Crafts alkylation that generated isoleucophyllidine **7** as the exclusive product (Scheme 1b, right).

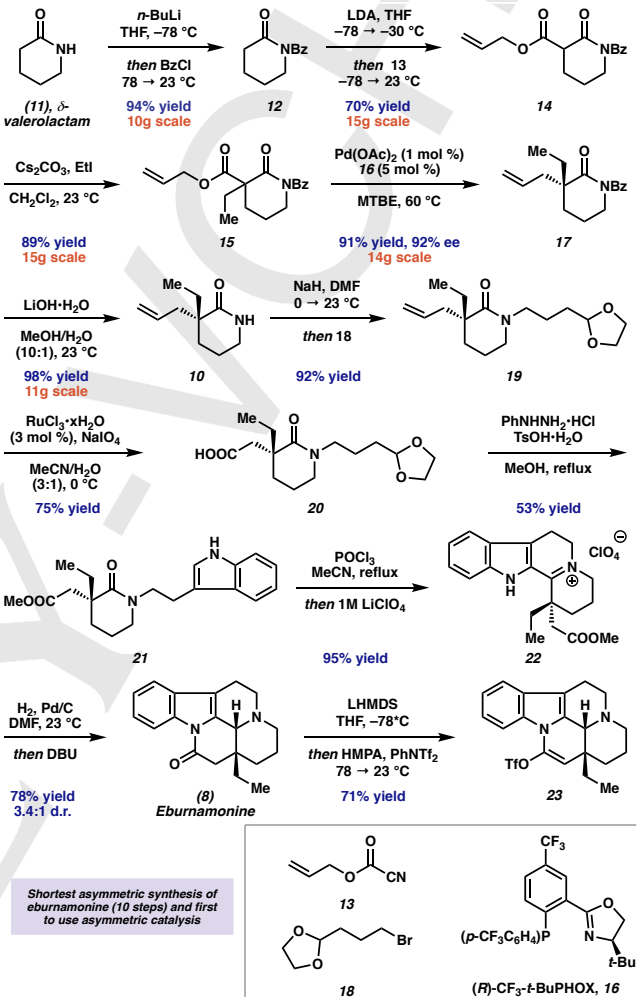


Scheme 2. Retrosynthetic analysis of leucophyllidine. Red circle = α-amino stereogenic center. Blue circle = all-carbon quaternary stereogenic center.

Given the structural challenges and promising bioactivity of leucophyllidine **(1)**, we began synthetic studies toward this important target.[14] Our retrosynthetic analysis was guided by a "convergent-divergent" strategy, where a *convergent* late-stage cross-coupling and hydrogenation would forge the α-amine stereocenter—a motif found in multiple natural products within this class—from oxidized congener eburnamonine **(8)** and eucophylline derivative **9** (Scheme 2). Both fragments would then be accessed in *divergent* fashion[15] from enantioenriched lactam **10**, bearing an all-carbon quaternary stereocenter accessible through our laboratory's Pd-catalyzed asymmetric allylic alkylation technology.[16] We believe that a route to leucophyllidine **(1)** leveraging *catalyst*-control to synthesize these strategic C–C bonds would ultimately provide a foundation for a general strategy toward natural and unnatural dimeric alkaloids.

Our synthesis of eburnamonine commences with a revised approach to our previously-disclosed lactam **10** (Scheme 3).[16] Benzoyl protection of δ-valerolactam (**11** → **12**) is followed by *C*-acylation to yield β-amidoester **14** and alkylation to generate racemic quaternary lactam **15**. An enantioselective decarboxylative allylic alkylation using low loadings[17] of a Pd-(II) precatalyst and (*R*)-CF_3-*t*-BuPHOX ligand **16** forges the all-carbon quaternary center of lactam **17** in 91% yield and 92% ee. Finally, Bz-cleavage affords divergent intermediate **10**, completing the five-step sequence on decagram scale and providing enough material to synthesize both monomers.

While direct *N*-alkylation of lactam **10** with β-indolyl electrophiles proved challenging due to their instability under basic conditions, we successfully employ alkyl bromide[18] **18** to synthesize acetal **19**. Oxidative cleavage of the allyl group furnishes carboxylic acid **20**, which undergoes Fischer indole synthesis with concomitant esterification to afford indole **21**. Though Bischler–Napieralski cyclization to iminium perchlorate **22** proceeds smoothly, we were disappointed to observe the diastereoselective hydrogenation conditions described by Schlessinger[10f] fail to deliver any reduced products.[19] After further optimization, we discovered that heterogeneous hydrogenation in DMF [20] with subsequent addition of DBU promotes diastereoselective hydrogenation and lactamization in one pot, completing the synthesis of eburnamonine **(8)** in five steps from lactam **10** and ten steps from commercially available material. To our knowledge, this is the shortest asymmetric synthesis of eburnamonine to date and the first to employ asymmetric catalysis.[21] Eburnamonine **(8)** is finally advanced to enamine triflate **23**, thus completing the first coupling partner.



Scheme 3. Enantioselective total synthesis of eburnamonine.

Our approach to eucophylline **(5)** begins with amide reduction and Boc-protection of the divergent intermediate (Scheme 4, **10** → **24**). Anti-Markovnikov Wacker oxidation[22] then generates aldehyde **25** with no detectable amount of the ketone isomer. Using modified Friedländer conditions,[23] aldehyde **25** and amino alcohol [24] **26** are advanced to quinoline **27,** incorporating a bromide to facilitate the late-stage convergent coupling. Finally, Re-catalyzed oxidation[25] affords *N*-oxide **28** on gram-scale.

Our strategy toward eucophylline **(5)** hinges on a sequence involving two C–H functionalization events to complete the core: intramolecular quinoline amination at C2, followed by alkylation at C4. Optimization of both transformations led to the discovery of unexpected reactivity. N-oxide **28** is first subjected to $Sn(OTf)_2$ to cleave the Boc-protecting group.[26] Following the addition of triethylamine at elevated temperatures, we were surprised to find the desired C–N bond of tetracycle **29** had formed in 79% yield.

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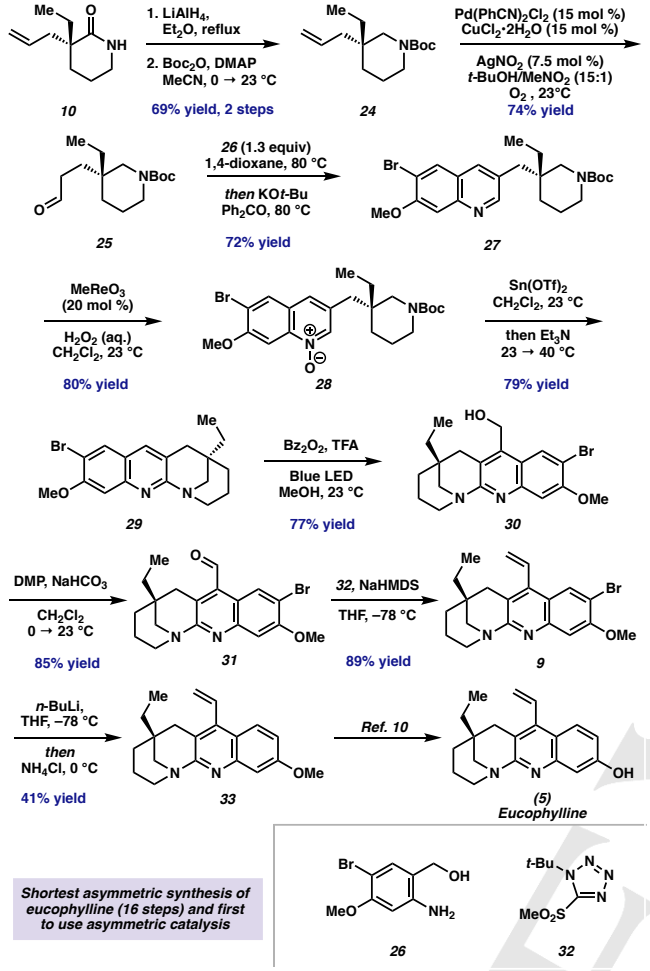
Though *N*-oxide activation typically requires a more strongly electrophilic activating group (e.g. PyBrOP[27]), we believe the Sn(II) cation promotes the intramolecular cyclization.[28]

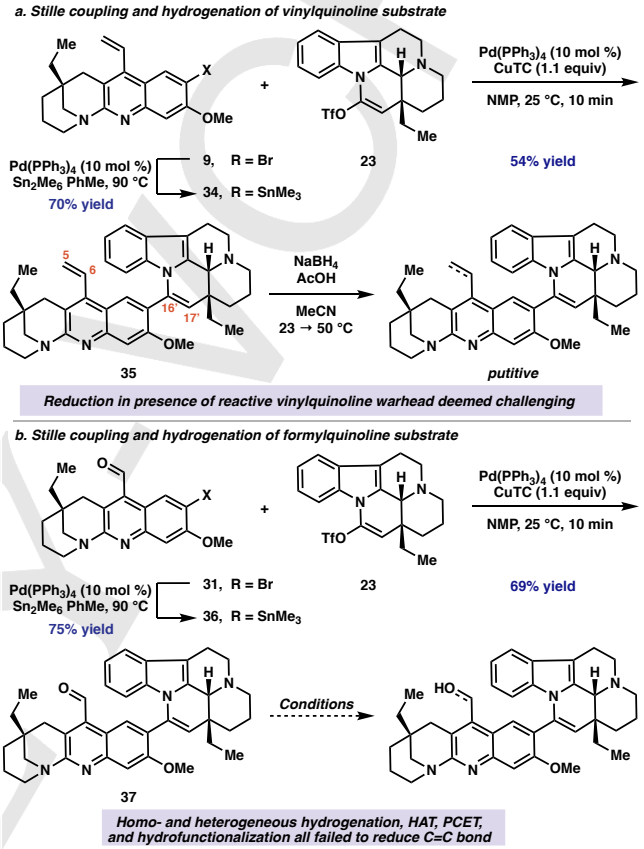


Scheme 4. Enantioselective formal synthesis of eucophylline.

Tetracycle **29** is subsequently exposed to photoredox-mediated Minisci conditions [29] to generate hydroxymethyl quinoline **30**. After performing control experiments, we were delighted to observe an Ir-photocatalyst was not required for this transformation, and the bromoquinoline motif is believed to act as its own photocatalyst. Similar reactivity has been observed in related electron-deficient heteroarenes [29,30] and aryl bromides[31] have been shown to exhibit prolonged excited state lifetimes. Further studies are underway to elucidate the reaction mechanism of this transformation.

To complete the synthesis, alcohol **30** is oxidized to aldehyde **31**, then a Julia–Kocienski olefination with tetrazole **32** generates vinylquinoline **9** in 87% yield.[32] Proto-debromination with *n*-BuLi then affords *O*-methyl eucophylline **33**, which could be advanced to eucophylline **(5)** under conditions described by Landais,[10] thus completing the formal synthesis in 11 steps from divergent intermediate **10**.

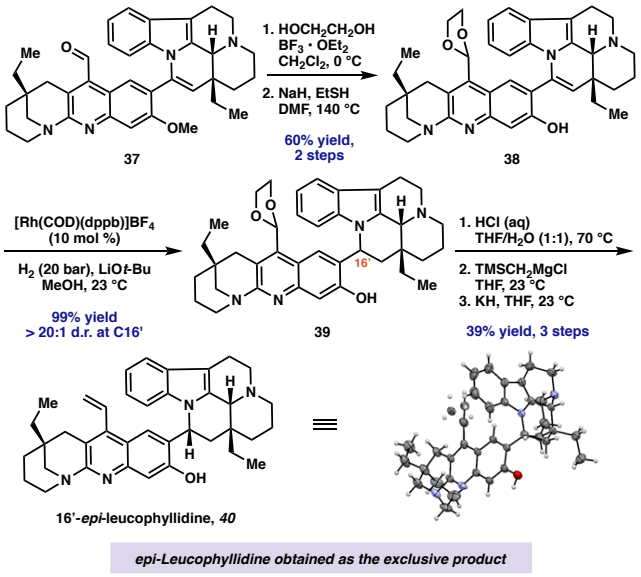
To avoid regioselectivity concerns associated with biomimetic couplings, we elected to forge the central C–C bond through a Stille coupling.[33] Vinylquinoline **9** is first advanced to the trimethylstannane **34** in good yield (Scheme 5a). After brief optimization, we found that efficient cross-coupling with triflate **23** could be obtained using $Pd(PPh_3)_4$ and copper (I) thiophene-2-carboxylate (CuTC) to afford dimer **35** as a mixture of atropisomers in 54% yield after only 10 minutes.[34] Initially, we hypothesized that the trisubstituted Δ16',17'-olefin would be more electron-rich than the monosubstituted Δ5,6-vinyl group, enabling chemoselective reduction with mild hydride sources under acidic conditions. Unfortunately, a complex mixture of products was observed, likely due to 1,6-reduction of the vinylquinoline motif.



Scheme 5. Stille coupling and attempted reductions.

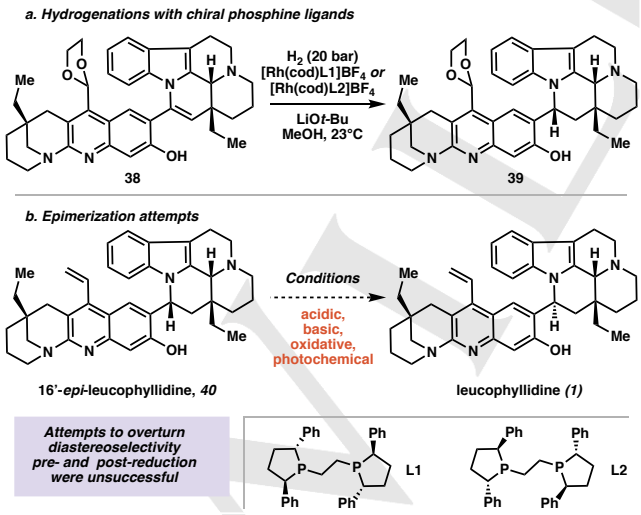
We then elected to use the formylquinoline substrate **31** as any over-reduction would still produce synthetically tractable material (Scheme 5b). Gratifyingly, we discovered that both stannane **36** and dimer **37** were obtained in higher yields than the respective vinyl intermediates. Despite employing a number of different reaction manifolds to saturate this Δ16',17'-olefin, we were unable to obtain any desired olefin-reduced products.

Given the steric encumbrance of this alkene, we hypothesized that the phenolic oxygen of the natural product might be employed as a directing group to facilitate this otherwise intractable hydrogenation.[35] To this end, dimeric aldehyde **37** is first protected as the acetal and demethylated to furnish phenol **38** (Scheme 6). We were delighted to observe that hydrogenation with $[Rh(COD)(dppb)]BF_4$ afforded smooth and quantitative reduction of the trisubstituted alkene as a single diastereomer **39**.[36] Acetal cleavage then unmasks the aldehyde, which is homologated with a Peterson olefination.[37] At this point, we obtained X-ray quality crystals of **40** and we were dismayed to find that the reduction had occurred with the undesired stereochemistry to provide 16'-*epi*-leucophyllidine.



Scheme 6. Completion of 16'-*epi*-leucophyllidine

Despite this unexpected result, we remained optimistic that the desired stereochemistry could be installed. We first attempted to perform the hydrogenation with a chiral Rh-complex, hypothesizing that we could overturn substrate bias once again through catalyst control. Employing asymmetric phenol-directed hydrogenation conditions, we observed exclusive formation of the undesired C16' stereocenter (**38** → **39**, Scheme 7a), when either enantiomer of BPE-phos ligand (**L1** and **L2**) was used. Given the difficulty in overriding the inherent diastereoselectivity of this reduction, we then attempted a late-stage epimerization using various conditions including acidic, basic, oxidative and photochemical manifolds. Unfortunately, in all cases, we observed either no reaction or decomposition of the substrate (Scheme 7b; see SI for more details).



Scheme 7. Attempted asymmetric hydrogenation and epimerization.

In summary, we report the enantioselective synthesis of eburnamonine, eucophylline, and 16'-*epi*-leucophyllidine through a convergent-divergent strategy. An enantioenriched lactam building block, accessible through Pd-catalyzed enantioselective allylic alkylation, is advanced to eburnamonine and eucophylline in ten and sixteen steps respectively, marking the shortest asymmetric synthesis of either natural product to date. A highly efficient Stille coupling unites the two polycyclic hemispheres and a directed hydrogenation is used to advance to the epimeric natural product. We believe that further investigations of $C(sp)^3$-$C(sp)^2$ coupling strategies could ultimately provide access to this natural product and other related heterodimeric bisindole alkaloids.

Acknowledgements

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Keywords: alkaloids • convergence • cross-coupling • divergence • total synthesis

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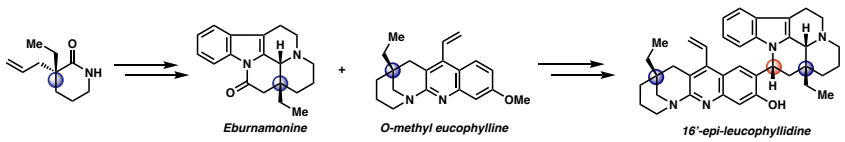

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A strategy to synthesize the dimeric natural product leucophyllidine is described using a “convergent-divergent” approach. An enantioenriched lactam building block is advanced in divergent fashion to complete syntheses of both eburnamonine and eucophylline in 10 and 16 steps respectively. A convergent cross-coupling and hydrogenation sequence is then employed to afford 16’-*epi*-leucophyllidine.

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