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Total Synthesis of (±)-Baphicacanthcusine A Enabled by Sequential Ring Contractions

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Abstract

Reported herein is the first total synthesis of the *poly*-pseudoindoxyl natural product baphicacanthcusine A. The synthesis leverages the oxidative rearrangement of indoles to pseudoindoxyls to install vicinal pseudoindoxyl heterocycles in a diastereoselective manner. Key steps include an acid-mediated cyclization/ indole transposition, two diastereoselective oxidative ring contractions, and a site-selective C–H oxygenation. The synthesis of the oxidation precursors was guided by recognition of an element of hidden symmetry. This work provides a foundation for the chemical synthesis of other *poly*-pseudoindoxyl alkaloids.

Keywords

total synthesis; ring contractions; oxidations; rearrangements; alkaloids

The flowering plant *Baphicacanthus cusia* (Nees) Kuntze or *Strobilanthes cusia* (Nees) Bremek has been used for centuries as an ingredient in traditional medicines throughout East Asia.[1] The utility of the leaves, stems, and roots of *B. cusia* to treat a wide variety of diseases such as psoriasis, leukemia, and the common cold has led to a search for the specific compounds responsible for this range of pharmacological activity. Recently, these studies have yielded a number of *poly*-pseudoindoxyl alkaloids (**1**–**5**, Figure 1)[1–5] that are characterized by a central five-membered ring that bears two or three pseudoindoxyl heterocycles. Despite this shared structural motif, the *poly*-pseudoindoxyl alkaloids exhibit significant structural and pharmacological diversity, providing ample opportunities for both synthetic and biological exploration. None of the members of the *poly*-pseudoindoxyl alkaloid family has been synthesized to date.

Several strategies have been developed for the synthesis of the pseudoindoxyl motif,[6] the most common of which is the oxidative rearrangement of indoles to pseudoindoxyls.[6–7] Generally, this transformation involves oxidation of an indole (see, e.g., **6**, Figure 2A) to a hydroxyindolenine (**7**), followed by an acid- or base-mediated stereospecific rearrangement to the pseudoindoxyl (**9**) (Figure 2, Path A). Despite its efficiency, this strategy for

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Conflict of Interest

The authors declare no conflict of interest.

pseudoindoxyl formation often proceeds with poor diastereoselectivity for the oxidation and poor selectivity in the rearrangement step (i.e., to give either an oxindole or pseudoindoxyl; see Figure 2A, Path B).[18–21] Notably, while the oxidative rearrangement approach has been successfully applied in many total syntheses,[6,9–19] the use of biindole substrates is exceedingly rare. To date, this strategy has been employed only on 2,2'-biindoles (**11**, Figure 2A), and there are no reports of 3,3'- or 2,3'-biindoles (**12** and **13**, respectively) being used.[11–14] Moreover, there are only two examples of non-symmetric substrates (i.e., $R^1 \neq R^2$ or $R^3 \neq R^4$). We recognized that the family of *poly*-pseudoindoxyl natural products would provide an intriguing platform for the use of non-symmetric 2,3'- or 3,3'-biindoles in the oxidative ring contraction methodology, thereby expanding the utility and applicability of this rearrangement protocol.

On the basis of these considerations, we chose baphicacanthcusine A (**1**), a cytotoxic alkaloid isolated by Liu et al. in 2020,[2] as a synthetic target. Baphicacanthcusine A (**1**) contains the central five-membered ring and vicinal pseudoindoxyl rings characteristic of the secondary metabolites of *B. cusia*. In addition, **1** bears a lactam ring fused to one of the pseudoindoxyls, which, along with the three contiguous stereocenters and oxidation-sensitive catechol unit, pose a formidable synthetic challenge. In our key synthetic recognition, we sought to take advantage of the oxidative rearrangement of indoles (*vide supra*) to install the vicinal pseudoindoxyl motif in a regio-, chemo-, and stereoselective manner.

We envisioned that **1** could arise from **14** through a C–H hydroxylation to install the catechol unit (Figure 2B). The spiro-fused pseudoindoxyl motifs would originate from fused hexacycle **15** through two iterative oxidative rearrangements in the forward sense. This sequence would constitute two ring contractions, transforming the central seven-membered ring of **15** into the characteristic five-membered ring of **1**. The single embedded stereocenter of **15** was anticipated to impart diastereoselectivity in the indole oxidation/rearrangement reactions. Recognizing an element of symmetry, we identified the 3,3'-biindole structural motif in **15** as an easily accessible starting point. In the forward sense, a highly convergent coupling of an enoate fragment (**16**) and a biindole fragment (**17**) would forge the central seven-membered ring in **15**.

Our synthesis of **1** began with known 3,3'-biindole **18**, which was synthesized on decagram scale (see the Supporting Information for details).[22–23] Bis-*tert*-butoxycarbonyl (Boc) protection of the indole nitrogen atoms was critical for mono-bromination of the dimer to afford **19** (Scheme 1A).[24] Notably, attempts to brominate **18** resulted only in decomposition, presumably because of the excess electron density in the resulting brominated product, which may have led to polymerization. Suzuki coupling between bromide **19** and pinacol boronate ester **20**—prepared in two steps from commercial materials—proceeded smoothly to give cyclization precursor **21**, setting the stage for formation of the key seven-membered-ring intermediate. We hypothesized that the use of Brønsted acids would cleave the Boc groups of **21** and subsequently promote conjugate addition of the northern indole into the α,β-unsaturated ester moeity.[25] However, while treatment of **21** with excess hydrochloric acid in ethanol did effect cleavage of the Boc protective groups and cyclization to form a seven-membered ring, an unexpected

indole transposition to give hexacycle **22** ensued. This rearrangement might occur through conjugate addition of the nucleophilic C3 carbon of the northern indole to give spirocyclic iminium ion **24** (Scheme 1A). Migration of the C3–C3' bond at that stage (through transition state **25**) would give cation **26**, which can aromatize to give the rearranged framework (**22**). The selectivity for migration of the indole unit might arise from anchimeric assistance of the southern indole π-system in the 1,2 (or 1,5–) suprafacial shift of the C3–C3' bond as shown in **25**.

Upon further analysis, we recognized that desired ring contraction product **28** might be even more readily accessed from transposed hexacycle **22** compared to the originally proposed substrate (i.e., **29**, Scheme 1B). This convergence in product outcome arises because formation of the spiro-fused bicycle is only dependent on the stereoselectivity of the indole oxidation and the regioselectivity of the migration, not the connectivity of the starting fused indole (see **27**→**28** and **30**→**28**). Furthermore, we hypothesized that high levels of diastereo- and site-selectivity would be achieved in the oxidation of **22** because the nucleophilic C3 position is a) proximal to the existing stereocenter and b) in conjugation with both the northern and southern indole groups. Upon subjecting **22** to *meta*-chloroperoxybenzoic acid (*m*-CPBA, **31**; 1 equiv) at room temperature, hydroxyindolenine **36** was formed, albeit with low conversion. Stronger oxidants, such as Davis' oxaziridine (**33**), dimethyl dioxirane (DMDO, **34**)[21] or singlet oxygen (**35**),[26–27] resulted only in complex mixtures of products (see Insert A, Scheme 2). However, performing the oxidation with saccharin-derived oxaziridine **32** (2.5 equiv) proved optimal,[28] proceeding completely (99% conversion) to hydroxyindolenine **36** as a single diastereomer, albeit in low isolated yields (<50%) (Scheme 2). Presumably, the increased steric hinderance of oxaziridine **32** relative to Davis' oxaziridine (**33**) tempers its reactivity and slows the rate of over-oxidation pathways. The relative configuration of the C3 and C10 groups in **36** was confirmed through X-ray crystallographic analysis.[29] We propose that the anti-configuration arises from the pseudo-axial disposition of the ester group of **22** (see Insert B in Scheme 2) blocking the bottom face and directing oxidation to the top face of the molecule.

Despite the relatively low isolated yields of hydoxyindolenine **36**, we turned our attention to investigating the first ring contraction. While basic conditions failed to effect the desired transformation, the use of scandium(III) trifluoro-methanesulfonate ($Sc(OTf)_3$) as a Lewis acid promoted the rearrangement and subsequent lactam formation to give desired pseudoindoxyl **37**. We hypothesized that the low isolated yield of **36** could arise from its instability on silica gel, so we chose to use **36** without purification. This two-step protocol proved superior, increasing the isolated yield of **37** dramatically (82% over two steps). The lactamization (i.e., **28**→**37**) likely serves to trap the pseudoindoxyl, which may be in equilibrium with the corresponding oxindole.

Having installed the first pseudoindoxyl moiety, we next investigated the oxidative rearrangement of the southern indole group. Oxidants that had proven effective for oxidation of the northern indole group (e.g., *m*-CPBA or **32**) were not reactive enough to oxidize **37**. However, DMDO (**34**)—which can be generated *in situ* from acetone and Oxone®—cleanly oxidized the southern indole, which rearranged spontaneously to give pseudoindoxyl **38** as

a single diastereomer (Scheme 3).[21] Notably, dropwise addition of the Oxone® solution to the reaction mixture proved to be pivotal for achieving high levels of diastereoselectivity. On the basis of the report from Houk and co-workers that epoxidations of polarized olefins occur asynchronously through an approximately perpendicular approach of the oxidant,[30] we hypothesized that oxidation from the top face of **37** would lead to a pronounced "eclipsing" interaction with the C3 carbonyl (Insert A in Scheme 3). On the other hand, approach of the oxidant from the bottom between C10 and N1 could proceed through a more favorable staggered-type conformation. With **38** in hand, only the cleavage of the methyl ether and C–H oxygenation at C13 remained to complete the synthesis of **1**. Demethylation of **38** was accomplished using boron tribromide (BBr_3) to give phenol **39**. At this stage, however, all attempts at installing the C13 oxygenation resulted in returned starting material (see Insert B in Scheme 3 for representative examples of C–H oxidation methods tried).[31–36] Hypothesizing that the free aniline-type group in **39** negatively impacts productive reactivity, we redesigned the route so that this group was introduced at the end of the synthesis. Cleaving the methyl protecting group in **37** using BBr_3 prior to oxidation of the southern indole gave phenol **40**. Inspired by the work of Pettus,[36] we found that 2-iodoxybenzoic acid (IBX)-mediated oxidation of phenol **40** to the corresponding ortho-quinone followed by *in situ* reduction with sodium dithionite ($Na_2S_2O_4$) afforded the desired catechol, which was subsequently bis-acetylated with acetic anhydride to give **47**. Application of our previously successful Oxone®-mediated oxidation of indoles to pseudoindoxyls (see **37**→**38**) converted **47** in excellent diastereoselectivity but required warming to room temperature to achieve full conversion. The resulting product was directly subjected to methanolysis of the acetyl groups to afford baphicacanthcusine A (**1**) in 40% yield over the final two steps.

In summary, we have developed a concise route to the complex bis-pseudoindoxyl alkaloid baphicacanthcusine A (**1**; 11 steps from known biindole **18**). Our synthesis was enabled by rapid construction of a key seven-membered ring intermediate that was then rearranged through sequential oxidations and ring contractions with remarkable substrate-controlled diastereo- and chemoselectivities. Our synthesis of **1** takes advantage of a symmetry inspired convergent coupling of biindole and enoate fragments, which preceded an unexpected acid-mediated transposition of the northern indole group. Notably, this transposition set the stage for a highly selective oxidative rearrangement by placing the site of the initial oxidation proximal to the existing stereocenter. Overall, this work provides a strategy for the installation of vicinal pseudoindoxyls that may inform the syntheses of other members of the bis-pseudoindoxyl family of natural products.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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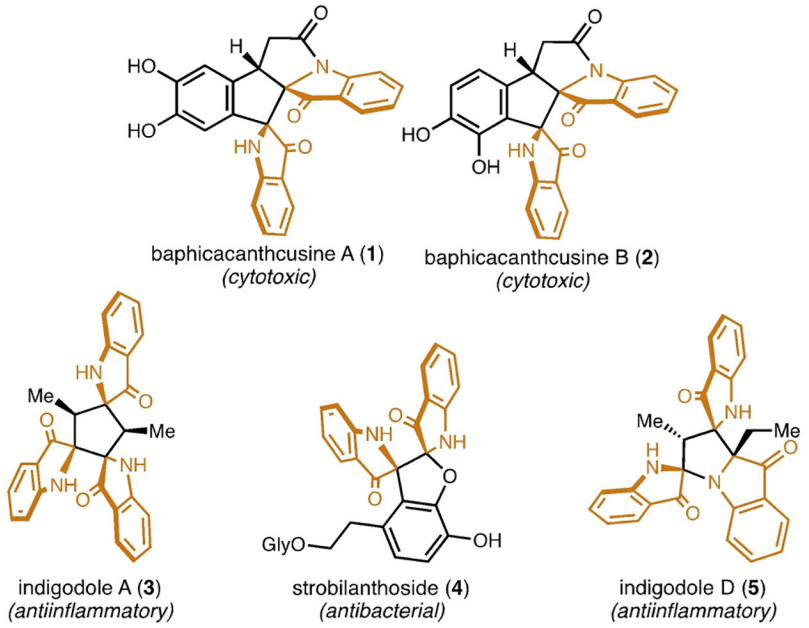


Figure 1.
Structures of *poly*-pseudoindoxyl alkaloids isolated from *B. cusia*.

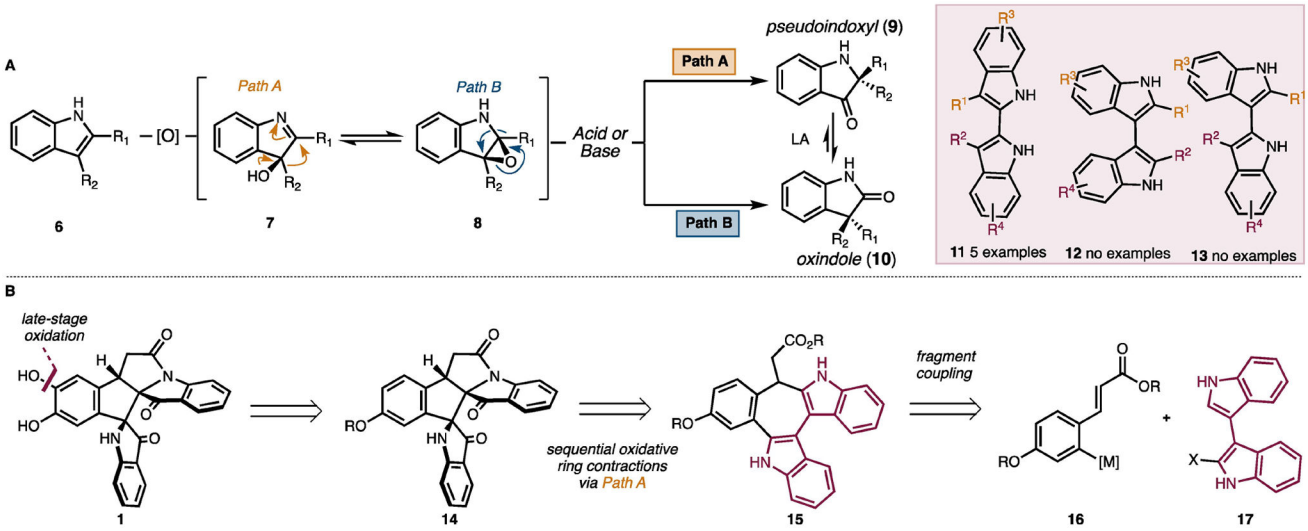
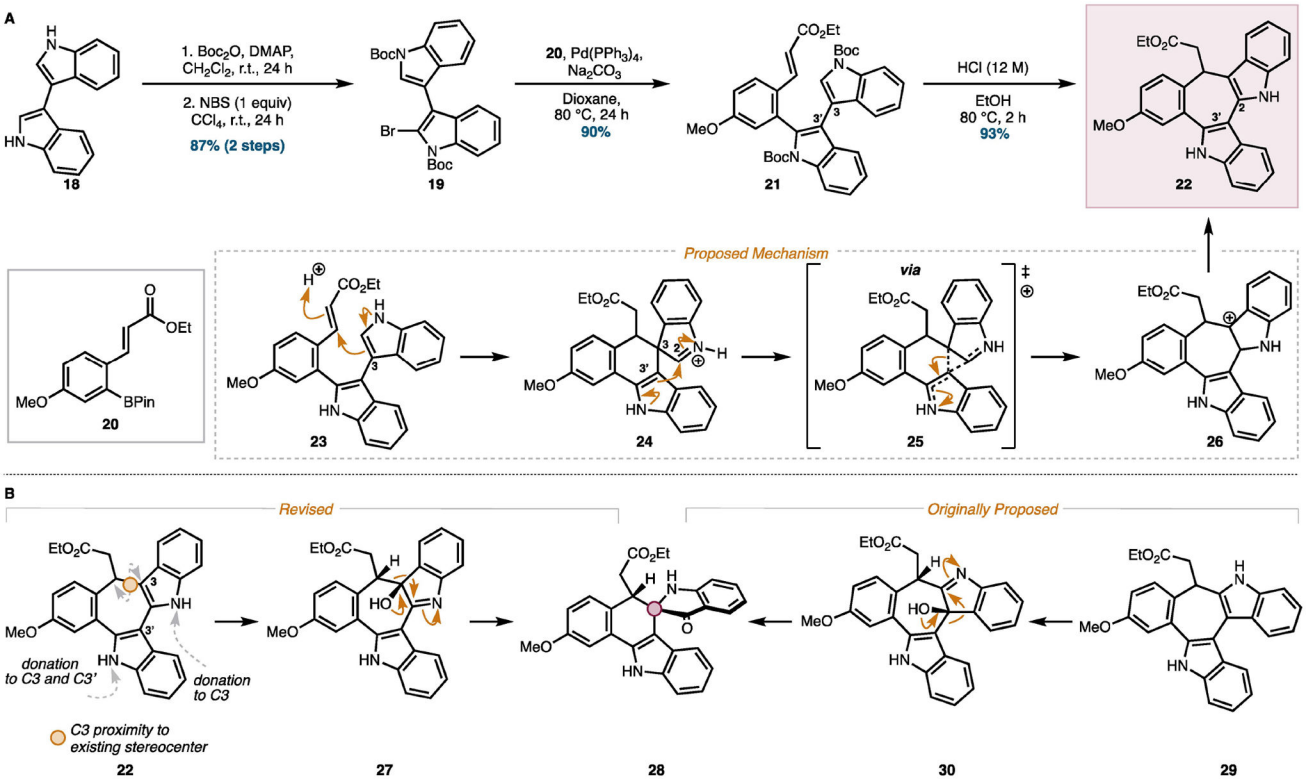


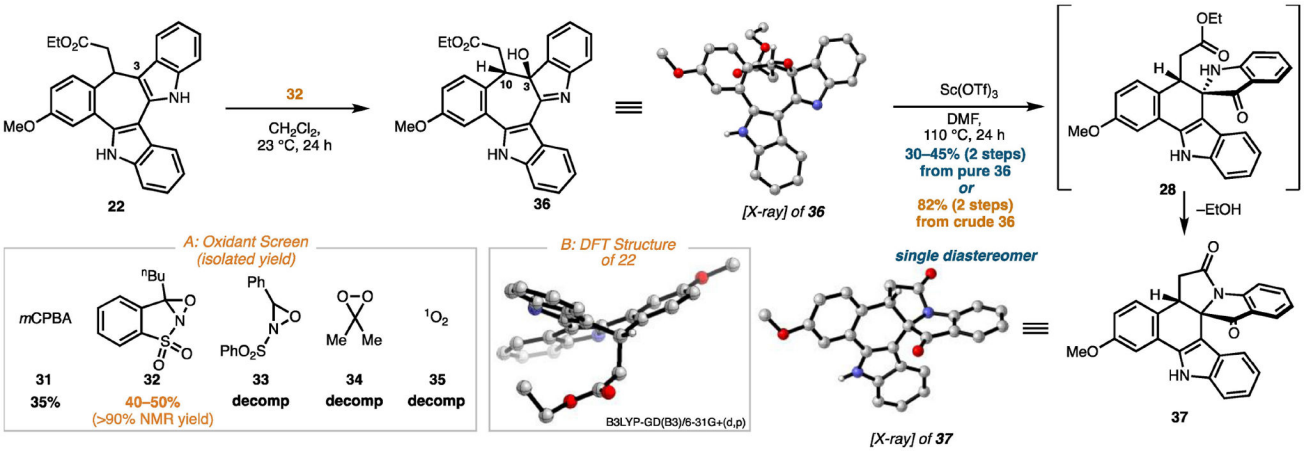
Figure 2.

(A) Oxidative rearrangement of indoles and use of biindoles as substrates. (B) Proposed retrosynthesis of baphicacanthcusine A.



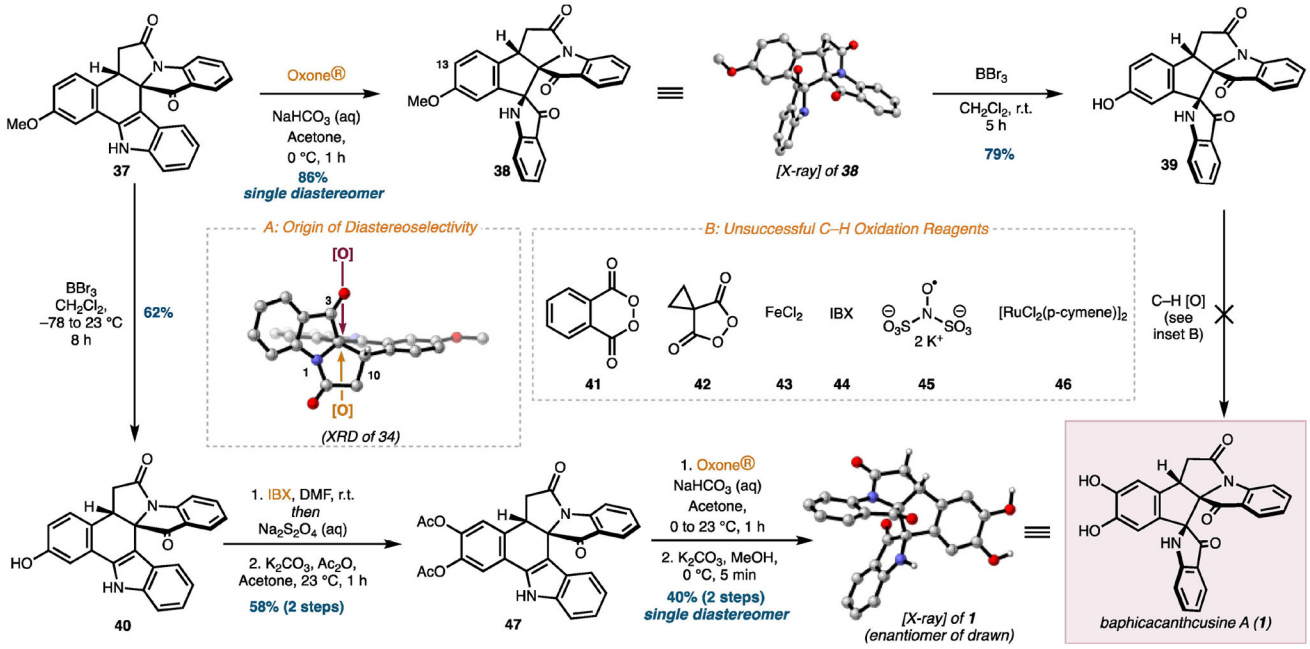
Scheme 1.

(A) Construction of oxidation precursor **22** featuring an unexpected rearrangement. (B) Analysis of the oxidative rearrangement of structures with different indole connectivity.



Scheme 2.

First oxidative ring contraction to access **37**.



Scheme 3.

Completion of the synthesis of baphicacanthcusine A (**1**).