Prayogik Rasayan

Synthetic Approaches to Potent Bioactive Natural Product Haouamine A: A Key Ascidian Diterpenoid from Aplidium haouarianum

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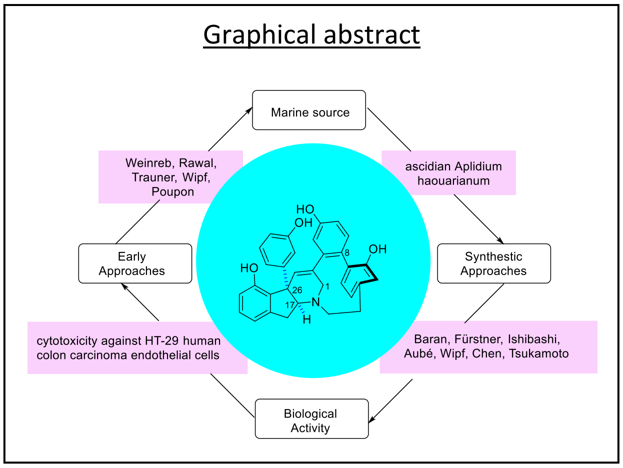
Abstract

Haouamine A, a structurally unique ascidian diterpenoid isolated from the marine tunicate *Aplidium haouarianum*, exhibits potent cytotoxicity against HT-29 colon carcinoma cells (IC_{50} = 0.1 μg/mL). Its unprecedented 3-aza-[7]-paracyclophane core, featuring planar chirality and severe ring strain (14–15.6 kcal/mol), poses significant synthetic challenges due to dynamic isomerism (nitrogen inversion) and a congested quaternary centre. This review chronicles two decades of synthetic campaigns, showcasing a diversity of strategic solutions to the formidable challenges posed by haouamine A's architecture. Key breakthroughs include Baran's pyrone-alkyne Diels–Alder macrocyclization (8-step racemic synthesis), Fürstner's asymmetric Heck cascades, and Chen's strain-accelerated late-stage oxidation. Modular approaches (e.g., Tsukamoto's Pd-catalyzed "anti-Wacker" cyclization) and biomimetic insights further enriched the synthetic toolbox. Despite these achievements, the biosynthetic origin of haouamine A remains enigmatic, with proposed unconventional tyrosine modifications or unknown enzymatic pathways. Synthetic advances enabled the gram-scale production, configurational assignment (8R,17S,26S), and biological validation of this compound, underscoring its potential as an anticancer scaffold. This work exemplifies how complex natural products drive methodological innovation, offering a paradigm for targeting strained architectures in drug discovery. Future directions include the elucidation of biosynthesis and the development of analogs to optimize bioactivity.


Graphical abstract

Keywords: Marine natural product, Anticancer activity, 3-aza-[7]-paracyclophane, Ring strain, Dynamic isomerism, Structure-activity relationship (SAR).

1. Introduction

Total synthesis is a dynamic and continually evolving discipline within organic chemistry, centred on the strategic construction of complex molecular architectures from simple precursors. Its primary objective is to develop efficient, reproducible, and often innovative synthetic methodologies for assembling structurally intricate molecules, many of which possess significant biological and pharmaceutical relevance. The advancement of such synthetic protocols not only pushes the boundaries of organic synthesis but also plays a crucial role in the discovery and development of novel therapeutic agents. A considerable number of pharmaceuticals and bioactive molecules are either natural products themselves or are structurally derived from, or inspired by, naturally occurring scaffolds.[1] In this context, heterocycles represent a dominant class of targets and intermediates, as they form the core of countless natural products and therapeutic agents, with applications spanning anticancer, antimicrobial, antiviral, and

CNS-active drugs.[2] Among these, natural products featuring highly strained cyclophane frameworks are of particular interest due to the synthetic challenges they pose and their unique bioactivities. Although natural products from ascidians were first reported in the mid-1970s, it wasn't until a decade later that they became the focus of growing chemical research. Marine ascidians (tunicates) have emerged as prolific sources of structurally unique, bioactive natural products, particularly nitrogen-containing metabolites with anticancer potential. Among these, the genus Aplidium has yielded diverse alkaloids, nucleosides, and peptides, including the clinically significant antitumor agent aplidine. In 2003, a groundbreaking study by Zubía and co-workers[3] unveiled the isolation of a new class of alkaloids, haouamines A (**1**) and B (**2**), from the marine tunicate *Aplidium haouarianum*, collected off the coast of Tarifa in southern Spain. Here, researchers studied a marine organism from the Polyclinidae family, *Aplidium haouarianum* species (a type of sea squirt) and discovered two new nitrogen-containing alkaloids (**1**) (Major) and (**2**) (Minor), which are part of a previously unknown class of alkaloids. These molecules exhibit unprecedented molecular architectures, with haouamine A demonstrating potent and selective cytotoxicity against HT-29 human colon carcinoma endothelial cells (IC_{50} = 0.1 μg/mL). This significant bioactivity, coupled with its unique structure, has made haouamine A, as focal point of interest in synthetic organic chemistry. Haouamine A exists in solution as a mixture of two rapidly interconverting isomers that can switch back and forth, which could be atropisomers or nitrogen-inverted forms, which cannot be separated. Its most striking structural feature is a rare and highly strained, 3-aza-[7]-paracyclophane macrocycle, which exhibits planar chirality and is the key to its uniqueness. The pronounced ring strain in the paracyclophane core of **(1)** is further evidenced by the remarkable upfield chemical shifts of the C1-attached proton in its ^{1}H NMR spectrum. This proton, which occupies both an allylic and α-position relative to the nitrogen, appears as a doublet at **0.84 ppm** and **0.43 ppm** for the two interconverting isomers. Such extreme shielding is a hallmark[4] of highly strained small cyclophanes, where the methylene bridge protons experience strong anisotropic effects due to their enforced proximity to the aromatic π-system. This phenomenon aligns with established observations in cyclophane chemistry, where steric compression induces significant upfield shifts in NMR spectra. The structure of (**1**) was confirmed using advanced techniques, including NMR (for example, 2D techniques like HSQC-TOCSY and HMBC), X-ray crystallography. The molecule's unique topology features a nitrogen atom that is connected across the structure, creating a bridge between non-adjacent parts, forming a strained cyclophane ring. Four aromatic rings are arranged in a flexible "clamshell" – like shape. One side features a trisubstituted anti-Bredt's double bond, the other a hydroxylated aromatic system, combined with a congested quaternary centre at C-26. An indeno-tetrahydropyridine ring is fused to an 11-membered paracyclophane, conferring both conformational rigidity and synthetic complexity. This motif represents the smallest cyclophane, identified in any natural product to date, and induces significant distortion of the rightmost phenol ring, pulling it out of planarity due to the inherent strain. The synthesis of haouamine A has proven particularly challenging because of this strain. The macrocyclic ring may be formed *via* oxidative coupling or other enzyme-catalysed cyclisation, but the details remain speculative. Haouamine A stands as a rare example where molecular architecture, biosynthetic intrigue, and synthetic innovation intersect to yield a compelling target for chemical biology and drug discovery. Advanced modeling suggests[5] the isomerization arises from constrained nitrogen pyramidal inversion coupled with tetrahydropyridine conformational changes, although atropisomeric contributions remain theoretically plausible. Structural analysis of (**1**) reveals substantial angular deformation[6] within its cyclophane core, characterized by two critical distortion angles (α and β) that serve as key metrics for quantifying strain in small[7] [n]-paracyclophane systems (n ≤ 8). For (**1**), these parameters were measured at α = 13.9°/13.6° and β = 17.9°/17.3°, values which starkly contrast with the ideal planar geometry of unstrained phenol (α = β = 0°) (Fig. 1). This pronounced distortion is visually evident when comparing the bent arene moiety in (**1**)'s crystal structure with conventional planar phenolic systems. The foundational syntheses of [n]-paracyclophane systems incorporating an all-carbon quaternary centre were first established through Friedel-Crafts methodologies by Rawal[8] (2005) and Trauner[9] (2006). Subsequently, Weinreb and colleagues[10] (2006) pioneered an innovative approach employing an intramolecular [3+2] nitrone-olefin cycloaddition, which simultaneously installed both the quaternary centre and nitrogen functionality. This elegant sequence, followed by aldol condensation and reductive amide transformation, efficiently furnished the crucial indeno-tetrahydropyridine core structure. In a complementary approach, Wipf's[11] research group (2006) developed the sole successful strategy for constructing the strained macrocycle featuring the characteristically distorted aromatic system. Their methodology uniquely employed a non-aromatic cyclic precursor, which was subsequently elaborated to form the bent arene motif, demonstrating the feasibility of this challenging structural transformation in model systems. Notably, Poupon and co-workers[12] (2011) later retracted their initial findings when subsequent investigations revealed that their reported cyclocondensation of amines with phenylacetaldehyde to form substituted pyridinium derivatives proved irreconcilable with Baran's established synthetic work, highlighting the importance of rigorous validation in complex natural product synthesis.

Biosynthetic Mystery

The biosynthesis of (**1**) and (**2**) (how they are made naturally), is not yet understood, and their hydroxylation pattern (meta vs para position), seems to involve unusual pathways not typical for similar compounds. The authors proposed two possible explanations for this, both highly unconventional, Tyrosine could undergo enzymatic removal of its para- OH group during biosynthesis- a reaction with no known precedent in nature, or haouamine A might derive from a hypothetical, undiscovered amino acid that is meta hydroxylated (e.g. "meta- tyrosine") but no such amino acid has been identified in living organisms. Non-tyrosine precursors (e.g., shikimate pathway intermediate or polyketides) could be involved, but no evidence supported this. This suggests an unusual or unknown biosynthetic origin. It seems that these compounds are related to aromatic amino acids like tyrosine, phenylalanine biosynthetically or dopamine-like building blocks or precursors, but how they are assembled into such a strained macrocycle is not known. The absence of similar structures as (**1**) limits comparative genomic approaches. Understanding the biosynthesis of (**1**) could reveal new enzymatic chemistry, possibly involving enzymes that bend aromatic rings or catalyse rare pericyclic reactions. It also enables biosynthetic engineering to produce analogs for drug development and helps in total synthesis efforts by offering biomimetic strategies. So, (**1**) remains a biosynthetic enigma. It challenges our understanding of natural product biosynthesis due to its highly strained and distorted aromatic system, the unclear origin of its unusual macrocyclic core. It stands as a fascinating example of how nature's chemistry can surpass current synthetic and enzymatic paradigms- and why exploring such mysteries is crucial in natural product chemistry.[3] (**Figure 1**)

Baran's Total Synthesis of (±)-Haouamine A:

In 2006, Baran and Burns reported a concise and highly innovative total synthesis of racemic haouamine A (**1**) in eight steps from a commercially available indanone derivative (**3**) and allylic iodide (**4**).[13] (**Scheme 1**) The synthesis overcame two central challenges: construction of the indeno-tetrahydropyridine ring and formation of the highly strained macrocyclic aza-paracyclophane. Their approach was inspired by a hypothesized biosynthetic pathway involving oxidative condensation of meta-hydroxylated phenylacetaldehydes. They designed a cascade annulation beginning with an oxime intermediate (**5**), which underwent a series of reactions including nitrone cyclization with electrophilic Br source (**6**), stereoselective reduction with $NaBH_4$ to form (**8**), which on heating at 50° C gave aziridinium formation (**9**), and ring

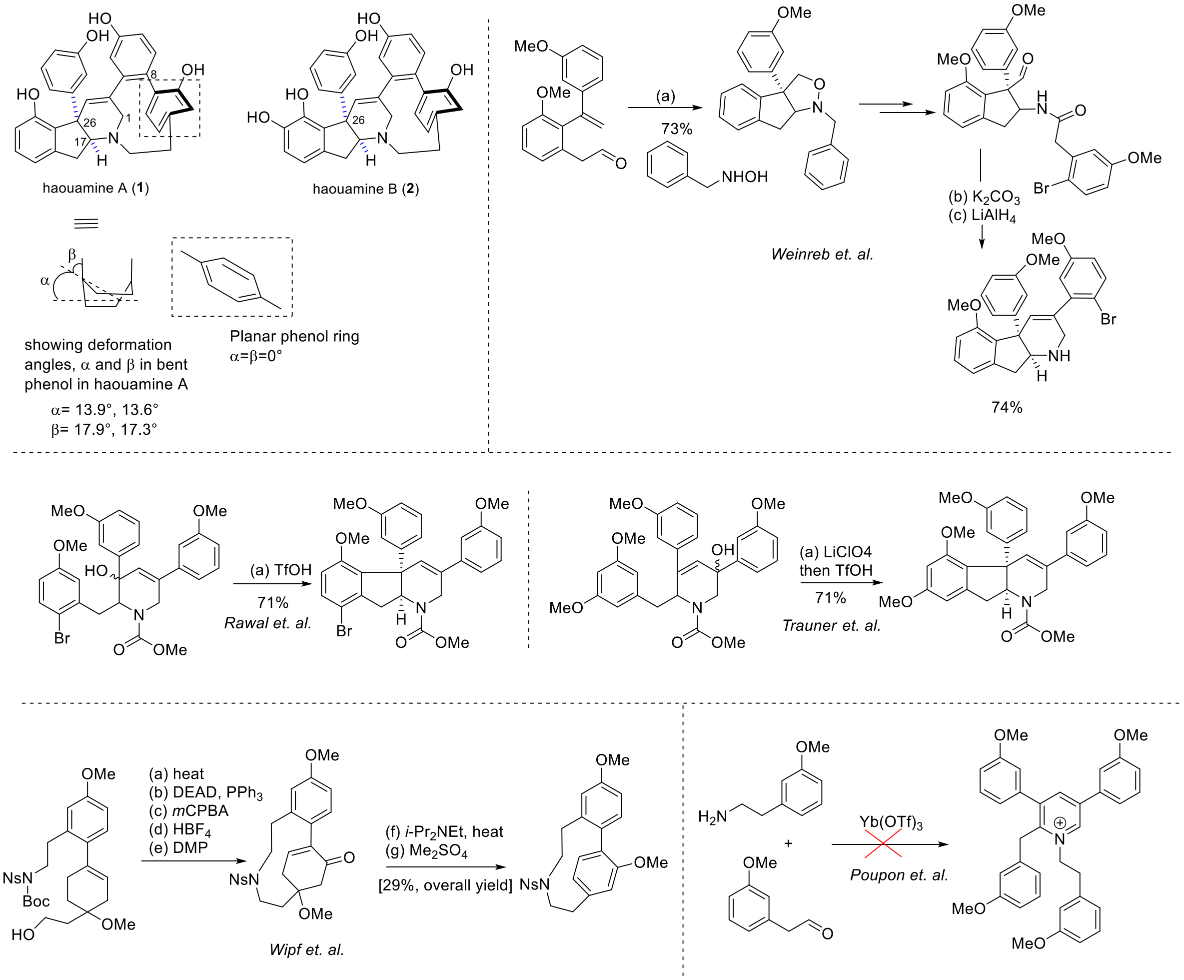
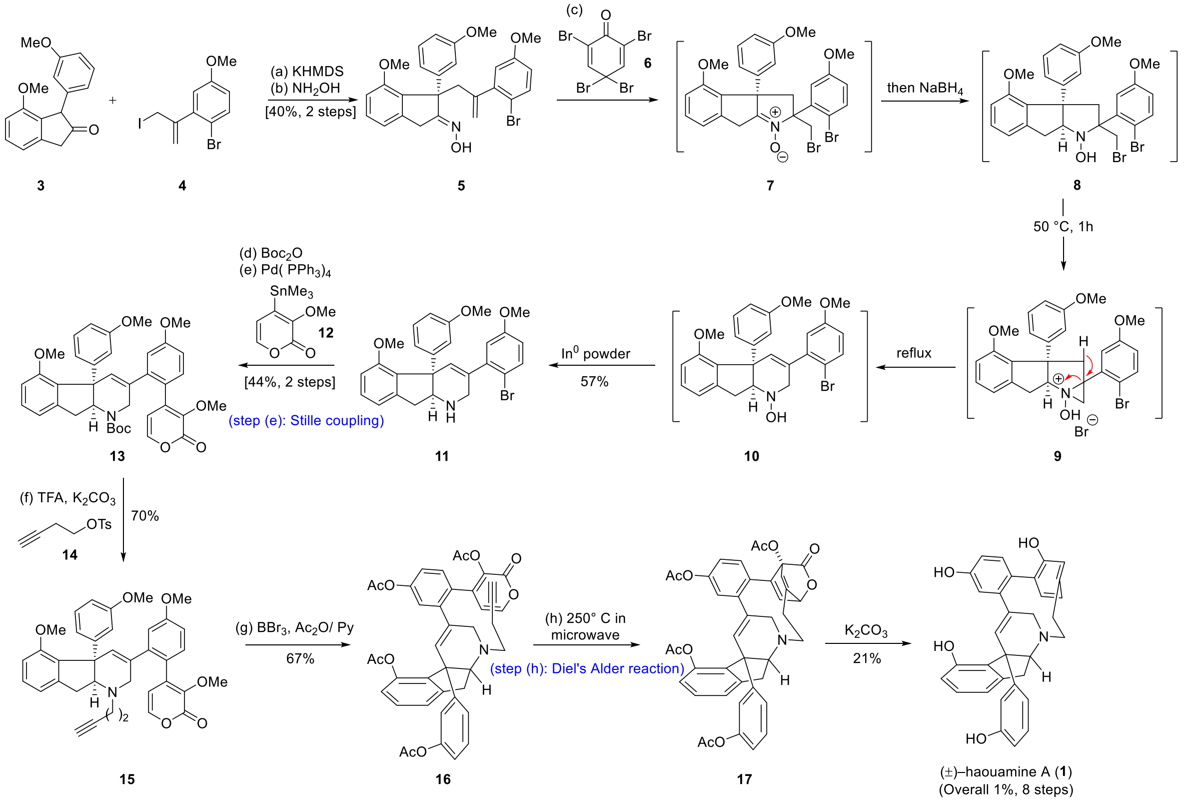


Figure 1: Isolated structures of haouamine A (**1**) and B (**2**) and some early synthetic strategy to haouamine A core.

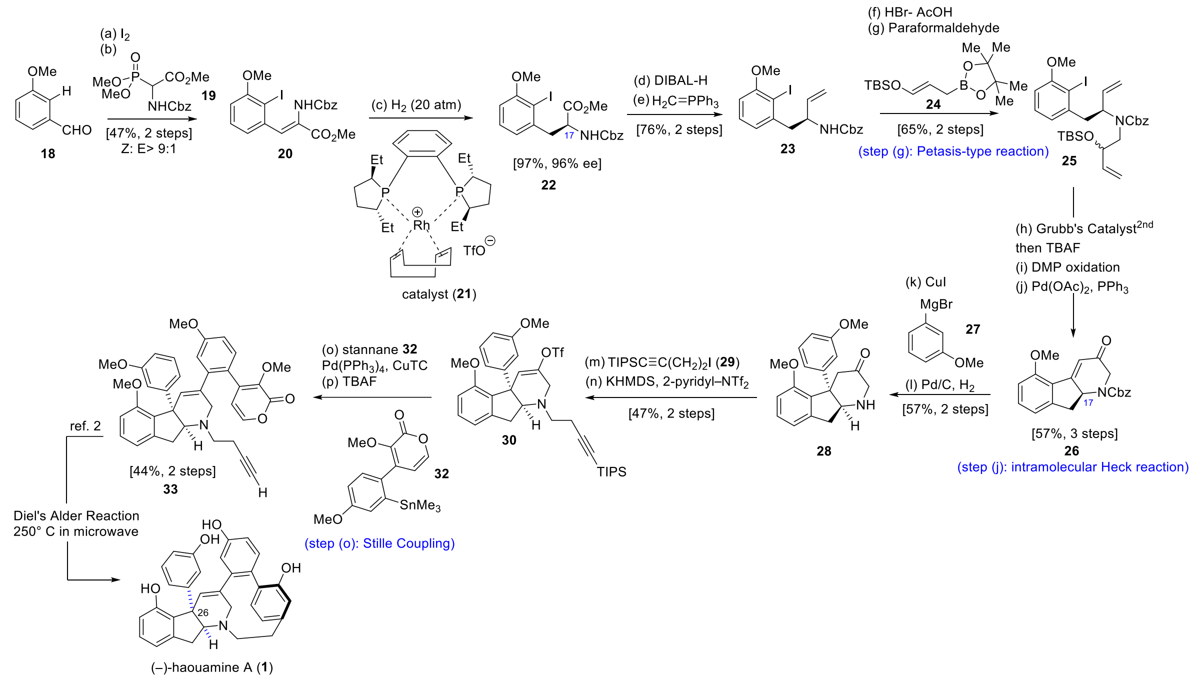
expansion to yield the *N*-hydroxypiperidine core (**10**). Subsequent reduction of the N–O bond with In^0 and further Boc protection yielded the key intermediate required for macrocyclization, which underwent Stille coupling with pyrone (**12**) to afford (**13**). Then, deprotection and N-alkylation with (**14**) gave (**15**), which immediately underwent a universal demethylation and acetylation process and afforded (**16**). Then, a novel pyrone-alkyne Diels–Alder macrocyclization was developed to construct the bent aromatic ring. This strategy used a pyrone-piperidine conjugate which, upon microwave heating at 250 °C, underwent a clean macrocyclization with high atropselectivity and gave (**17**). Final deacetylation delivered haouamine A (**1**) in (10:1) atropselectivity, which was spectroscopically identical to the natural product. The synthesis allowed complete control over chemo-, stereo-, and position-selectivity and enabled access to gram-scale quantities of (±)-haouamine A (**1**).

Fürstner's Formal Total Synthesis of (-)-Haouamine A:

In 2008, Fürstner and co-workers developed a scalable asymmetric route to Baran's hexacyclic intermediate (**34**), enabling the formal total synthesis of (-)-**1**.[14] (**Scheme 2**) Their strategy relied on using 3-methoxybenzaldehyde (**18**), which underwent iodination followed by reaction with phosphonate (**19**) in base, afforded (**20**) in high diastereoselectivity. A Rhodium-catalyzed (**21**) asymmetric hydrogenation took place to set the C-17 stereocentre (**22**), DIBAL-H reduction and treatment with Wittig reagent gave (**23**), followed by a Petasis-type multicomponent reaction to form (**25**). The ring-closing metathesis, DMP oxidation, and for the tricyclic core, an intramolecular Heck reaction were then employed to close the third ring with careful control of conditions to form (**26**). The annulated product (**28**) was completed by stereoselective 1,4-conjugate addition of a Grignard reagent (**27**) mediated by CuI. Subsequent manipulations in (**28**) with (**29**) and 2-pyridyl-NTf_2 gave *N*-alkylated product (**30**) because, after alkylation now, N won't allow an unwanted enol triflate to form. Now (**30**), upon Stille coupling with a stannane-derived pyrone fragment (**32**), provided a precursor to the Baran macrocyclization substrate (**33**) to afford (-)-haouamine A.



Scheme 1: Baran's approach to (±)-haouamine A in 8 steps starting from indanone (**3**).

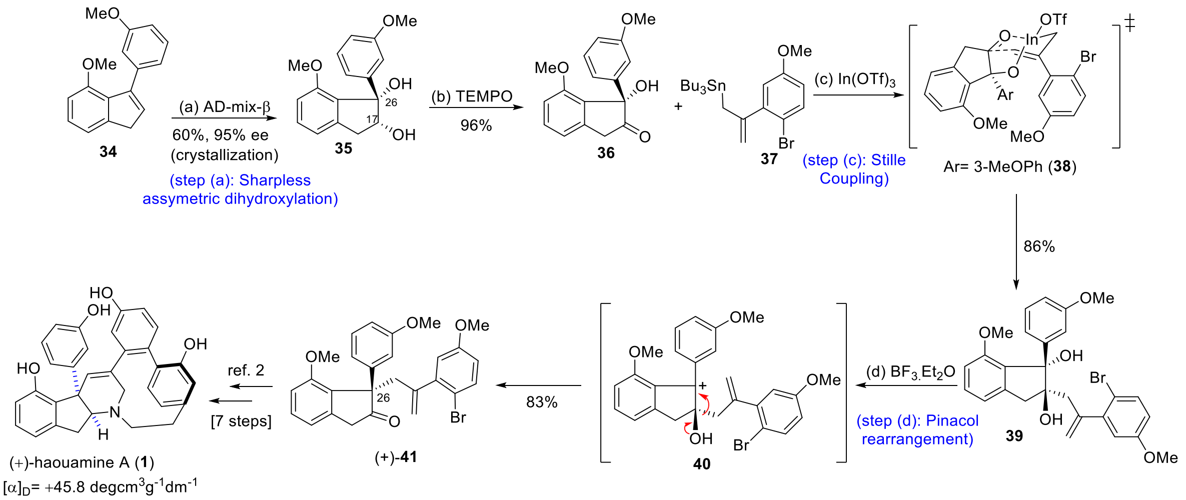


Scheme 2: Fürstner's formal total synthesis of (-)-haouamine A.

Baran's Enantioselective Formal Synthesis of (+)-Haouamine A (non-natural enantiomer):

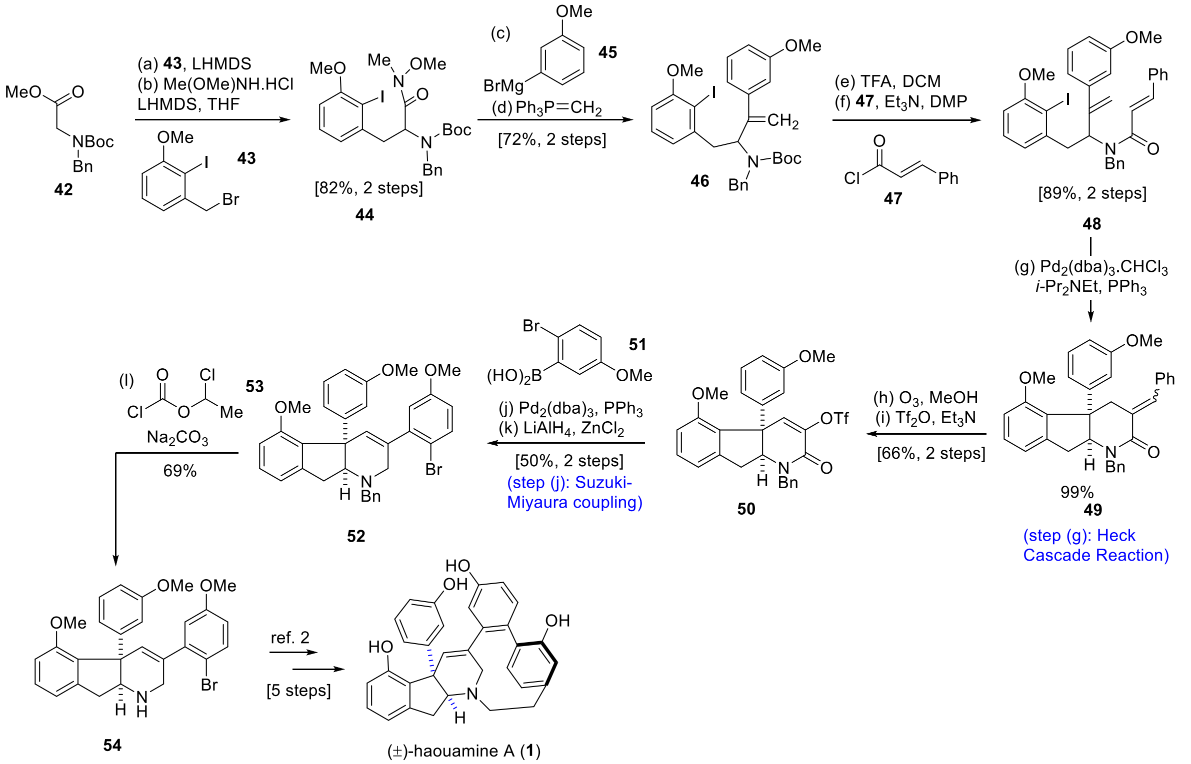
In 2008, Baran's group pursued an enantioselective total synthesis that resolved the absolute configuration of the natural product.[15] (**Scheme 3**) This was achieved through a Sharpless asymmetric dihydroxylation, where Indene (**34**) was transformed to diol (**35**), enriched by crystallization, a novel In(OTf)$_3$-catalyzed addition of allylstannane (**37**) to *α*-hydroxy ketone (**36**) (formed by chemoselective oxidation from (35) *via* TEMPO), delivered (**39)** (*via* an allylindium species (**38**)) which was generated as a result of Stille coupling and was formed with high selectivity to install a crucial quaternary centre. A selective pinacol rearrangement, where BF$_3$.Et$_2$O-induced rearrangement of (**39)** established the C-26 quaternary centre in (+)-**41** (26*R*), confirmed by X-ray analysis, which is the precursor for (+)-haouamine A.

Ishibashi's Formal Total Synthesis of (±)-Haouamine A:



Scheme 3: Baran's enantioselective formal synthesis of non-natural (+)-haouamine A.

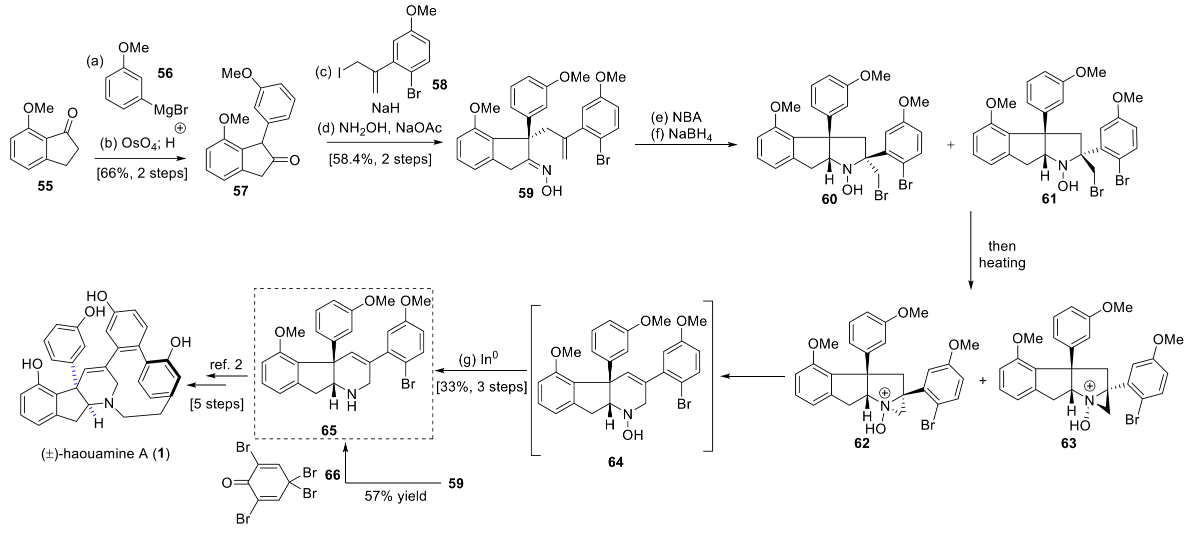
In 2009, Ishibashi and co-workers presented a concise formal synthesis of (±)-haouamine A (**1**).[16] (**Scheme 4**) The work focused on constructing Baran's key intermediate (**54)** through an innovative palladium-catalyzed cascade Mizoroki–Heck reaction, addressing the challenge of forging the molecule's congested diaryl quaternary centre and tricyclic core. The synthesis began with glycine methyl ester derivative (**42**), which was alkylated to introduce a 2-iodo-3-methoxybenzyl group (**43**), then converted to Weinreb amide (**44)** for Grignard addition, yielding ketone, subsequent, Wittig olefination produced (**46**) and Boc deprotection and treatment with acetylating agent cinnamyl chloride (**47**) furnished alkene (**48**), designed to undergo an intramolecular Heck cascade. Optimization revealed $Pd_2(dba)_3.CHCl_3$ with diisopropylethylamine in DMF (100 °C, 2.5 h) as optimal, delivering tricycle (**49)** in 99% yield. The reaction proceeded *via* sequential aryl–alkene couplings, forming two rings and the quaternary centre in one step in a Heck Cascade Reaction. The cinnamyl group in (**49**) ensured alkene stability to prevent undesired alkene isomerization post-cyclization. Ozonolysis of (**49)** and triflation produced enol triflate (**50**), enabling Suzuki–Miyaura coupling with 2-bromo-5-methoxyphenylboronic acid (**51**) to install the aryl group. Further, reduction with $ZnCl_2/LiAlH_4$ gave aryl-alkene (**52**), and N-deprotection completed the synthesis of (**54)**, matching Baran's intermediate for (±)-haouamine A. The Heck cascade showcased efficient, atom-economic construction of polycyclic frameworks, avoiding stepwise ring formations.



Scheme 4: Ishibashi's concise formal total synthesis of (±)-haouamine A.

Baran's Formal Synthesis of Haouamine A:

This study, in 2009, by Baran and co-workers builds on Baran's prior work, addressing unresolved synthetic hurdles through a cascade annulation strategy and enantioselective route.[17] (**Scheme 5**) Their successful route begins with applying indanone-based approaches, where indanone (**55**) reacted with 3-methoxyphenylmagnesium bromide (**56**), followed by hydrolysis and OsO_4-based dihydroxylation and subsequent dehydration, to form (**57**). The enolate formed from ketone (**57**) reacted with aryl-allyl iodide (**58**), then treatment with NH_2OH formed oxime (**59**), which contains an all-carbon quaternary centre. A pivotal cascade sequence transformed oxime (**59)** into the core structure of nitrones (**60/61)** by giving *N*-bromoacetamide (NBA), which underwent reduction in $NaBH_4$ to *cis*-pyrroloindolines (**62/63)**, together with aziridinium ion formation. Then, the ring expansion to (**64**), and indium-mediated reduction to amine (**65)** (33% overall yield) that is their protocol for bromooxime (**59**), does not worked well, so, (**59**), treating with tetrabromocyclohexadienone (**66**) after optimization as the electrophilic bromine source yielding (**65)** in 57% yield. Enantioselective synthesis for (**1**) has already been reported in Baran's 2008 paper. The 14-step route (gram-scale) to (**69)** compares favourably with prior syntheses, emphasizing scalability and catalytic efficiency. It resolved the absolute configuration of haouamine A (8*R*, 17*S*, 26*S*) and supported an L-phenylalanine biosynthetic origin. It also

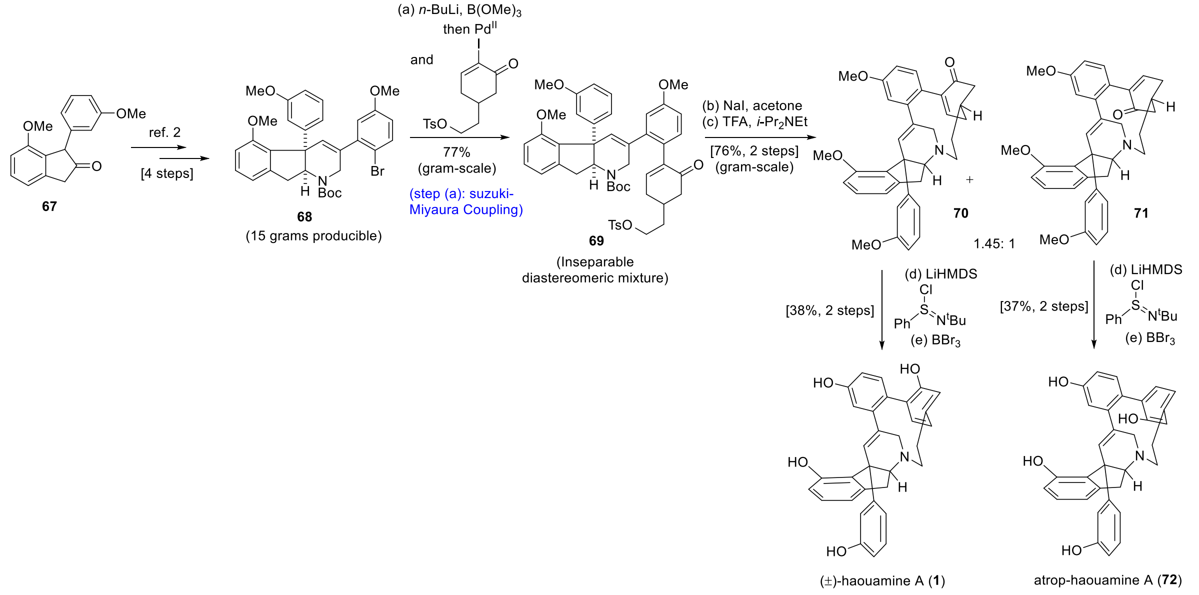


Scheme 5: Baran's approach to (±)-haouamine A (**1**) starting from (**55**).

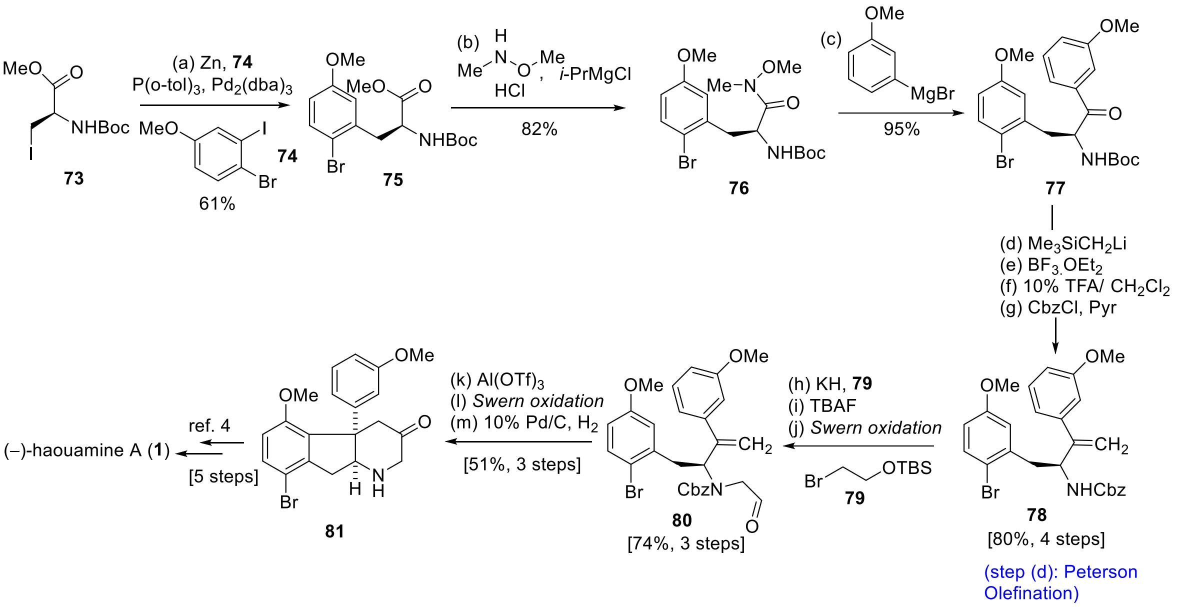
highlighted the utility of cascade reactions and transition-metal catalysis in complex alkaloid synthesis.

Baran's Scalable Synthesis of Haouamine A and its Biological Evaluation:

This study in 2009, by Baran's and co-workers, addressed the long-standing structural ambiguity of haouamine A (**1**), which gave the synthetic evidence that confirmed that observed solution-state isomerism of (**1)** arises from slowed pyramidal inversion at nitrogen coupled with tetrahydropyridine conformational dynamics, not atropisomerism.[18] (**Scheme 6**) A *point-to-planar chirality transfer* approach was employed, leveraging a cyclohexenone intermediate to program macrocycle strain. Key steps involved are Gram-scale Suzuki–Miyaura coupling of bromo-indenopyridine (**68)** with **cyclohexenone** to achieve (**69**) (77% yield), macrocyclization *via* amine-TFA salt activation (79% yield, (**70):(71)** = 1.45:1), chemoselective aromatization using *N-tert*-butylbenzenesulfinimidoyl chloride to forge the bent phenol (60–61% yield), a novel application for strained systems. The route enabled production of >550 mg of (±)**-1**, with all steps (except final demethylation) conducted on a gram-scale.



Scheme 6: Baran's synthesis of (±)-haouamine A (**1**) and atrop-haouamine A (**72**) in 9 steps from starting ketone (**67**).



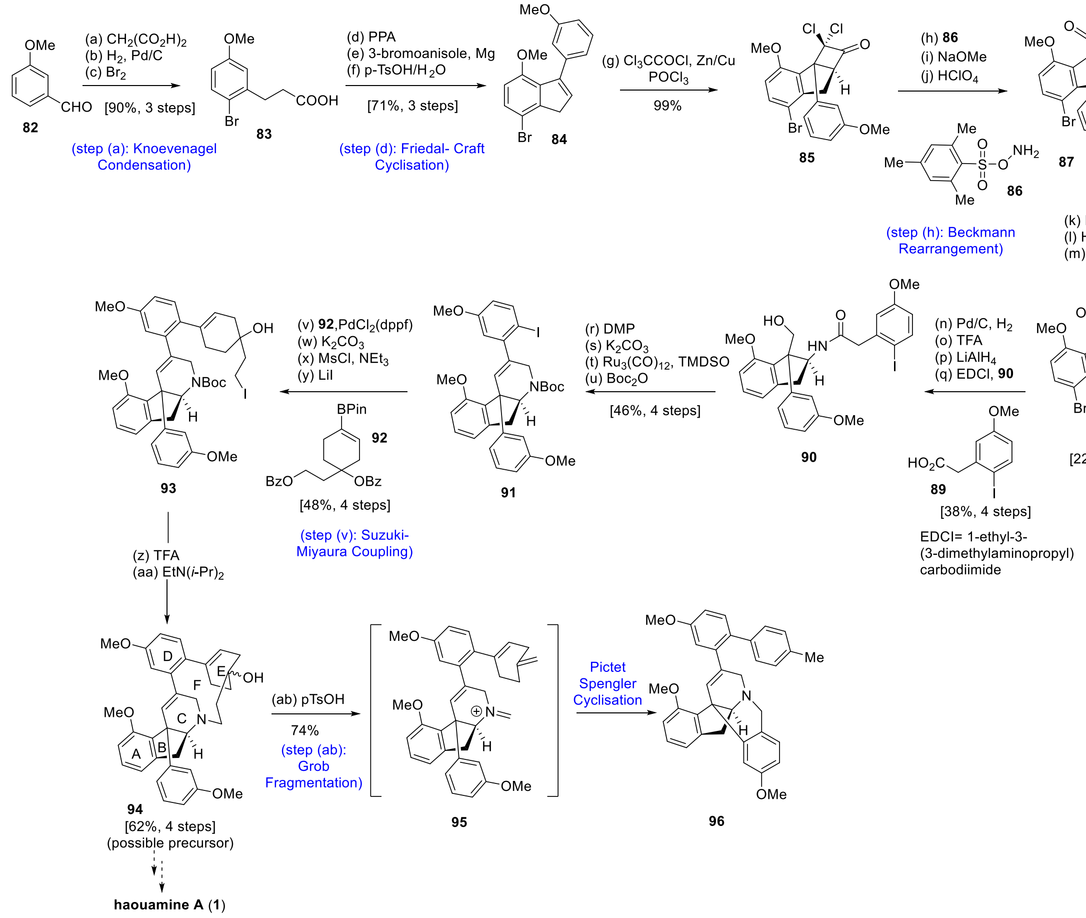
Scheme 7: Aubé's formal synthesis of (-)-haouamine A.

Aubé's Formal Synthesis of (-)-Haouamine A:

This study in 2011, presented a concise formal synthesis of (-)-haouamine A, leveraging a tandem Prins/Friedel-Crafts reaction to construct its indeno-tetrahydropyridine core.[19] (**Scheme 7**) The synthesis of (**1**) started with the formation of an *N*-protected ester (**75**) from (**73**) in presence of a substituted anisole (**74**), further arylation was done *via* the formation of a Weinreb amide (**76**) and additional treatment with aryl magnesium bromide afforded (**77**) which then underwent Peterson Olefination under the given conditions and yielded N-Boc protected olefin, then, switching to a Cbz group produced (**78**) in 80% over 4 steps. Further, reaction with TBS-protected alcohol and subsequent deprotection and oxidation protocol enabled the desired aldehyde (**80**). Critical to success was the use of "non-nucleophilic" Lewis acids (BF_3, $Al(OTf)_3$) in nitromethane, suppressing halide addition and delivering the fused tricycle, which on oxidation formed a ketone, followed by hydrogenolysis, afforded tricycle (**81**), which is identical to Fürstner's intermediate, thus completing the formal synthesis in 13 steps from serine derivative. So, this approach highlighted the importance of protecting group choice (Cbz > Boc).

Wipf's Analysis of Paracyclophane Ring Strain in the Synthesis of Haouamine A:

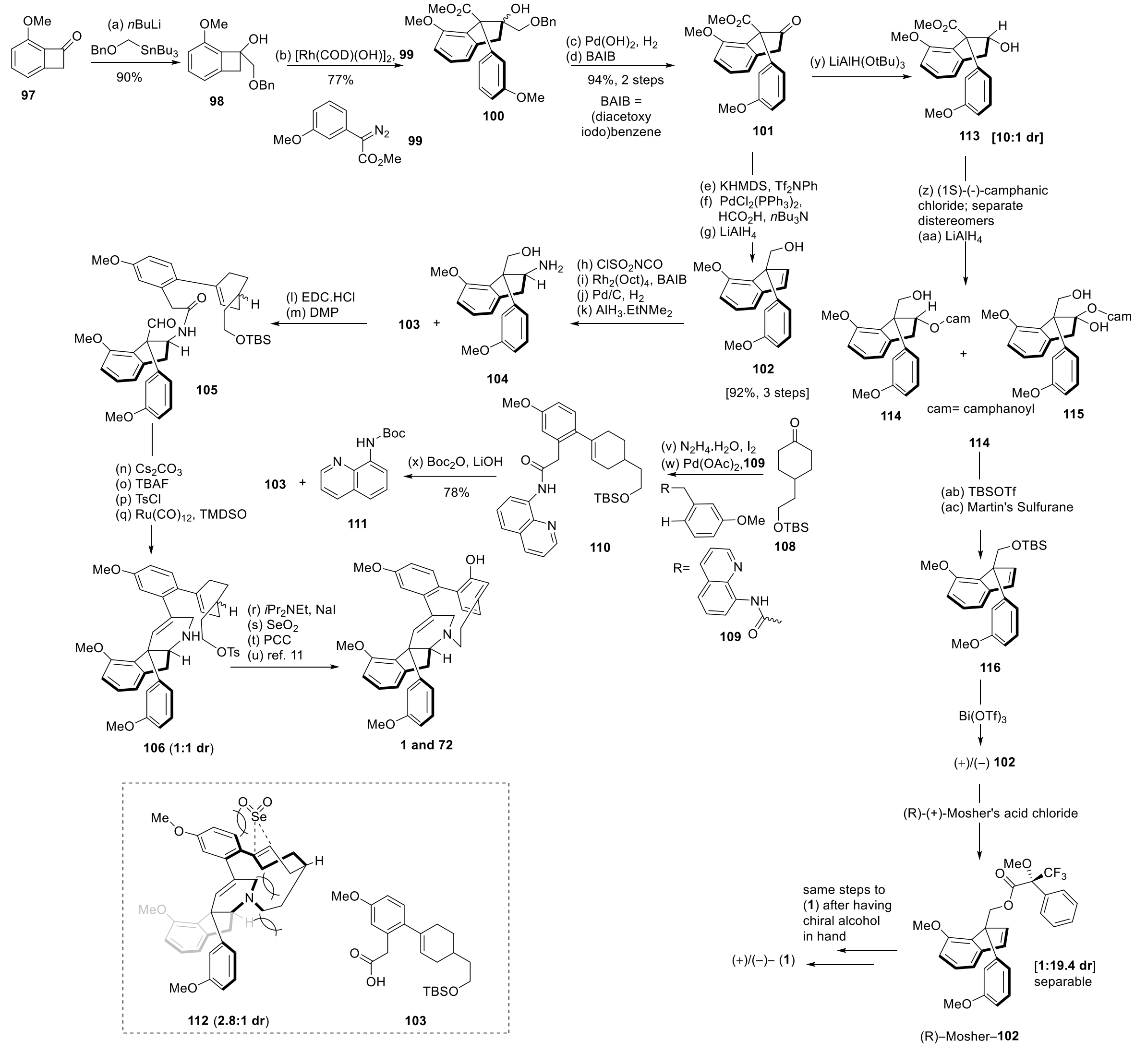
This study by Wipf's and co-workers, in 2019, involved a multi-step strategy to construct the strained 3-aza[7]paracyclophane core and adjacent rings.[20] (**Scheme 8**) The authors employed a sequence of key reactions, including Construction of the Indene Scaffold, by Knoevenagel Condensation of 3-Methoxybenzaldehyde (82) which was extended to cinnamic acid derivative, then, the hydrogenation followed by bromination yielded (83), setting the stage for a Friedel-Crafts cyclization, Polyphosphoric acid (PPA)-mediated cyclization of (83) gave indanone, which was converted to indene (84) *via* Grignard addition of 3-bromoanisole and dehydration (71% over 3 steps). Dichloroketene (generated *in situ*) reacted with indene (84) to form cyclobutanone (85) (quantitative yield) *via* a [2+2] Cycloaddition. Then, treatment with mesitylene sulfonyl hydroxylamine (86) inserted nitrogen regioselectively, yielding dichlorolactam, *via* a Beckmann rearrangement combined with Methanolysis/hydrolysis converted (85) to α-ketolactam (87), avoiding competing side reactions under harsh conditions. For the formation of C-Ring assembly, Oxidative decarboxylation of Boc-protected (87) gave β-amino ester (**88**), then, Reduction of (88) to the amino alcohol, followed by amide coupling with acid EDCI (**90**), formed amide (90) in 38% yield over 4 steps. Dess–Martin oxidation of (90) formed an aldehyde, and an intramolecular aldol reaction closed the C-ring, yielding lactam. Chemoselective reduction of lactam produced (Ru-catalyzed with TMDSO) and Boc protection afforded (91) (in 46% yield over 4 steps). **E**/F-Ring Formation involved Suzuki–Miyaura Coupling, where, Iodide (91) reacted with boronate (92) to form a styrene, which on Saponification, mesylation and substitution with LiI generated (**93**), besides, Boc deprotection, and amine alkylation closed the 11-membered F-ring, yielding (94), which is the late stage precursor for (1). Acid treatment of (94), underwent a Grob fragmentation, where, (94) unexpectedly triggered paracyclophane ring cleavage via iminium ion (95), followed by Pictet–Spengler cyclization to form (96) (74% yield), a novel polycyclic structure. This unexpected cascade highlights the reactivity of strained systems and suggests potential implications for the natural product's bioactivity, possibly involving iminium ion intermediates akin to DNA-alkylating agents like ecteinascidin. The revised structure of haouamines, initially misassigned, features a cis-indenotetrahydropyridine (rings A–B–C) and a distorted 3-aza[7]paracyclophane (rings D–E–F), with DFT calculations estimating a ring strain of 14.0–15.6 kcal/mol. The synthetic strategy leveraged a macrocyclization-aromatization protocol to alleviate strain.



Scheme 8: Wipf's formal synthesis of haouamine A (**1**).

Chen's Strain Accelerated Synthesis of Haouamine A:

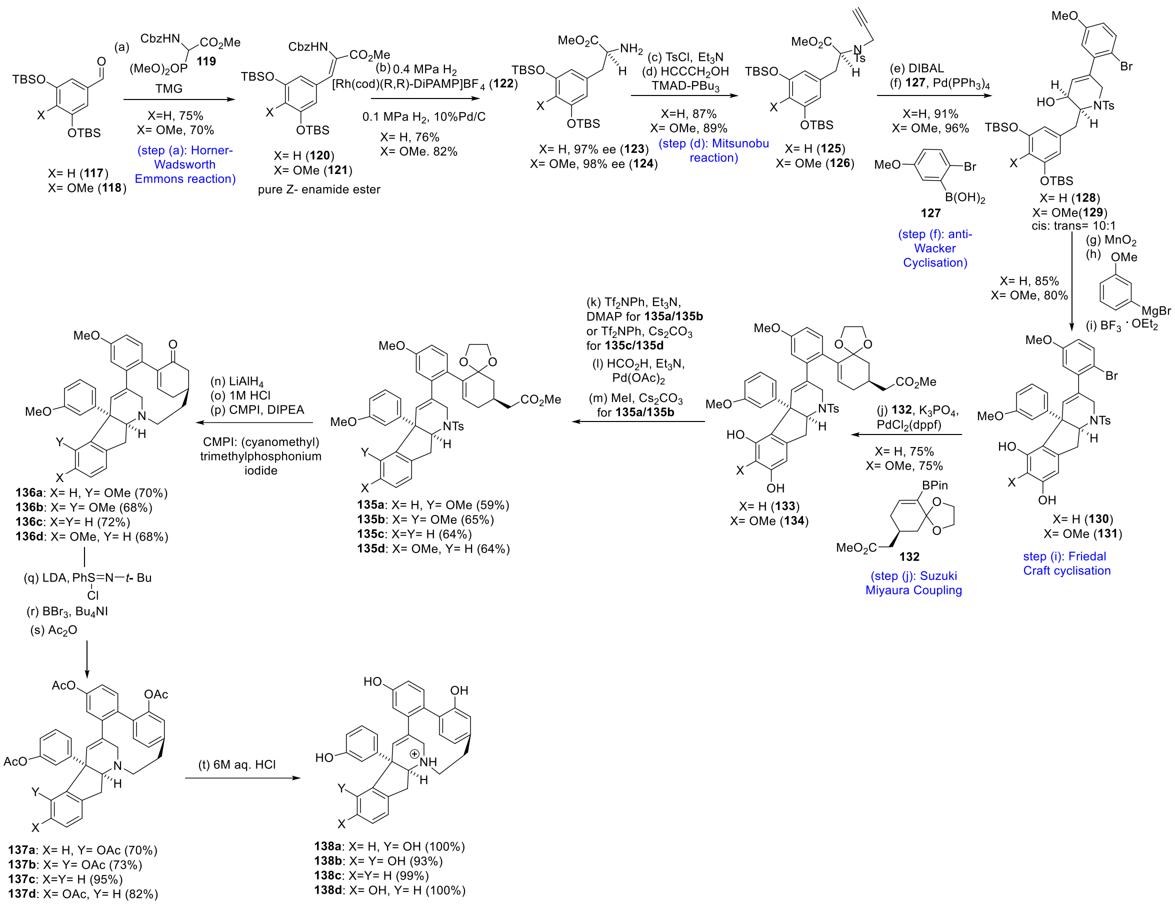
In 2020, Chen's and co-workers, reported a novel synthetic route to haouamine A, leveraging late-stage oxidation and rhodium-catalyzed transformations to address the challenges posed by its distorted biphenol cyclophane core.[21] (**Scheme 9**) The strategy hinges on a "deoxygenated" macrocyclic precursor (**112**) formed by treatment of (**107**) with amine and NaI, whose strain facilitates selective oxidation to install the critical phenolic oxygens- a departure from conventional aromatization approaches. So, the key innovations included are, Rh-Catalyzed C–C Bond Formation, where a room-temperature diazo-insertion between benzocyclobutanol (**98**) (from benzo-cyclobutanone (**97**)) and diazoester (**99**) constructed a quaternary centre containing 3˚-alcohol (**100**), optimized for scalability (0.8 mol% catalyst, multi-gram yields). Furthermore, oxidative cleavage of diol gave rise to β-ketoester (**101**) ensued by deoxygenation and $LiAlH_4$ mediated reduction to form olefinic alcohol (**102**). Sulfamate derived from alkenyl alcohol (**102**), after treating with $ClSO_2NCO$ underwent Rh-catalyzed intramolecular aziridination, which is reductively opened to amino-alcohol (**104**)- a validated intermediate for haouamine's core. Biaryl carboxylic acid (**103**) was prepared from a substituted cyclohexanone (**108**), then an EDC-mediated coupling and DMP oxidation yielded an aryl amide (**105**). Intramolecular Aldol Condensation of (**105**) and further conversion of the silyl protecting group to tosylate and Ru metal-mediated reduction constructed a 2˚-amine (**106**). This tosylate containing 2˚-amine (**106**) cyclizes under high-dilution conditions (NaI additive) to yield strained macrocycle (**112**), with diastereoselectivity influenced by conformational dynamics. Notably, alternative Suzuki macrocyclization failed, underscoring the necessity of sp³-hybridized flexibility for ring closure. Then, a strain accelerated oxidation included, SeO_2-mediated allylic oxidation of N- alkylated product proceeds selectively at 45°C, followed by PCC oxidation to enones-advanced intermediates in prior syntheses. Computational studies suggest alkene twist in (**128)** enhances reactivity. The optically active alkenyl alcohol (+)/(−)-(**102**) was efficiently obtained through a resolution process, providing an asymmetric route to haouamine A. Initially, compound **(101)** was selectively reduced to afford **(103)**, which was subsequently derivatized with chiral camphanic chloride followed by LiAlH4 reduction, yielding diastereomeric alcohols **(114)** and **(115)**. These intermediates were readily separable, allowing for further elaboration. The primary alcohol **(114)** was then subjected to TBS protection, followed by olefination using Martin's Sulfurane to furnish alkene **(116)**. Deprotection with $Bi(OTf)_3$ cleanly delivered racemic (+)/(−)**-**(**102**), which was ultimately resolved into its enantiomerically pure forms via derivatization with chiral Mosher's acid chloride. The work highlighted strain as a strategic tool for late-stage functionalization, offering a streamlined route to haouamine A and analogues.



Scheme 9: Chen's approach to (±)**-**haouamine A (**1**) and atrop-haouamine A (**72**) and chiral haouamine (**1**).

Tsukamoto's Modular Synthesis of Haouamine A:

Tsukamoto *et al.* in 2020 presented a scalable and modular synthesis of haouamines A (**1**) and B (**2**), leveraging innovative cyclization strategies to address the challenges posed by their strained aza-paracyclophane core and indeno-



Scheme 10: Tsukamoto *et. al.* modular synthesis of haouamine A.

tetrahydropyridine scaffold.[22] (**Scheme 10**) The synthesis initiated with Horner-Wadsworth-Emmons reaction of Substituted benzaldehydes (**117**) and (**118**) with N- Cbz aminophosphonoacetate (**119**). (**120**) and (**121**) formed underwent assymmetric reduction with the Rh-catalyst (**122**), followed by deprotection to attain an amine (**123**) and (**124**) with all C- quaternary centre with great enantioselectivity. Further, tosylation and propargylation with Mitsunobu reaction conditions afforded (**125**) and (**126**), further key transformation included a Pd(0)-catalyzed "anti-Wacker"-type arylative cyclization of alkyne-aldehydes (formed by DIBAL-H reduction) with 2-bromoarylboronic acid (**127**) to construct the tetrahydropyridine ring, where using Pd(0) avoids competing side reactions, preserving optical purity (cis/trans >10:1) which afforded (**128**) and (**129**), oxidation of allylic alcohol (**128**) and (**129**) with MnO_2 and treatment with Grignard reagent yielded tertiary alcohol, then, a $BF_3{\cdot}OEt_2$-promoted Friedel-Crafts cyclization of tertiary alcohols to form the indeno-tetrahydropyridine skeleton (**130**) and (**131**), where $BF_3{\cdot}OEt_2$ outperforming Brønsted acids for silyloxy groups. A Suzuki-Miyaura coupling with cyclohexenylboronate (**132**) to append the E-ring i.e. (**133**) and (**134**), then their triflation of sterically more favourable phenol in presence of Tf_2NPh and amine without and with DMAP took place for (**133**) and (**134**) respectively, then Pd catalysed reduction of mono-/di-triflate intermediates formed and methylation with MeI and $CsCO_3$ enables (**135a**), (**135b**), (**135c**) and (**135d**) respectively, further treated them with $LiAlH_4$ reduces the ester group and detosylation. After acetal hydrolysis, a novel (cyanomethyl)trimethylphosphonium iodide (CMPI)-mediated macrocyclization of amino alcohols formed to forge the strained aza-paracyclophane, where direct dehydration of amino-alcohol under high dilution achieves 11-membered ring closure in excellent yield (Baran's intermediates (**136a**) and (**136b**), surpassing Mitsunobu or metal-catalyzed alternatives. Further, oxidative aromatisation and substituting Me groups with acetyl group yielded (**137a**) and (**137b**) followed by acidic removal of acetate group yielded haouamine salts (**138a**) and (**138b**). Similar procedures were followed to prepare (**136c**), (**136d**), (**137c**), (**138d**), (**139c**), (**139d**).

To provide a clear overview of the synthetic strategies toward Haouamine A, we have compiled a summary table comparing each approach in terms of total steps, overall yield, key innovative steps, enantioselectivity, and scalability. This table allows readers to quickly assess the efficiency and strategic

Synthesis (Group, Year)	Total Steps	Overall Yield	Key Innovative Step	Enantioselective	Gram-Scale synthesis
Baran (2006)	8	1%	Pyrone-Diels-Alder Macrocyclization	No (Racemic)	Yes
Fürstner (2008)	17	Formal synthesis	Asymmetric Heck Cascade	Yes (to (-)-enantiomer)	Yes
Baran (2008)	111	Formal synthesis	Diastereoselective Pinacol rearrangement	Yes (to (+)-enantiomer)	No
Ishibashi (2009)	17	Formal synthesis	Intramolecular cascade Mizoroki-Heck reaction	No (Racemic)	Yes
Baran (2009)	12	Formal synthesis	Cascade annulation sequence	No (Racemic)	Yes
Baran (2009)	9	22.1%	Chemo-selective aromatization	No (Racemic)	Yes
Aubé (2011)	18	Formal synthesis	Tandem Prins/ Friedel-Crafts reaction	Yes (to (-)-enantiomer)	No
Wipf (2019)	31	Formal synthesis	Formation of the strained framework via the macrocyclization	No (Racemic)	Yes
Chen (2020)	23	Not Predictable	Strain-accelerated SeO_2 mediated allylic oxidation	Yes (to (-)-enantiomer)	Yes
Tsukamoto (2020)	20	<1%	"Anti-Wacker" Cyclization and Direct Dehydration	Yes (to (-)-enantiomer) salt form	Yes

Figure 2: Short summary of all the strategies towards haouamine A.

innovations of different synthetic campaigns over the past two decades.

2. Conclusions

The total synthesis of Haouamine A, a structurally complex and biologically potent ascidian diterpenoid, represents a landmark achievement in organic chemistry, showcasing innovative strategies to overcome its highly strained 3-aza-[7]-paracyclophane core and indeno-tetrahydropyridine scaffold. Pioneering work by Baran, Fürstner, Ishibashi, and others has demonstrated diverse synthetic approaches, including cascade annulations, asymmetric catalysis, and strain-accelerated macrocyclizations, to address the molecule's unique challenges. These efforts have not only resolved its absolute configuration (8*R*, 17*S*, 26*S*) but also provided gram-scale access for biological evaluation, confirming its potent cytotoxicity against HT-29 colon carcinoma cells (IC_{50} = 0.1 μg/mL). Key advancements, such as late-stage oxidation, Heck cascades, and biomimetic cyclizations, have expanded the synthetic toolbox for strained cyclophanes, while computational and experimental studies have elucidated the molecule's dynamic isomerism and ring strain (~15 kcal/mol). Despite these synthetic triumphs, the biosynthetic origin of Haouamine A remains enigmatic, with proposed pathways involving unconventional tyrosine modifications or undiscovered amino acids. The collective work underscores the intersection of synthetic innovation and natural product complexity, offering insights into enzymatic mechanisms and potential drug development. Future research may leverage these methodologies to explore analogs with enhanced bioactivity or reduced synthetic complexity. Ultimately, haouamine A (**1**) stands as a testament to the power of total synthesis in unraveling nature's most intricate architectures and advancing therapeutic discovery.

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