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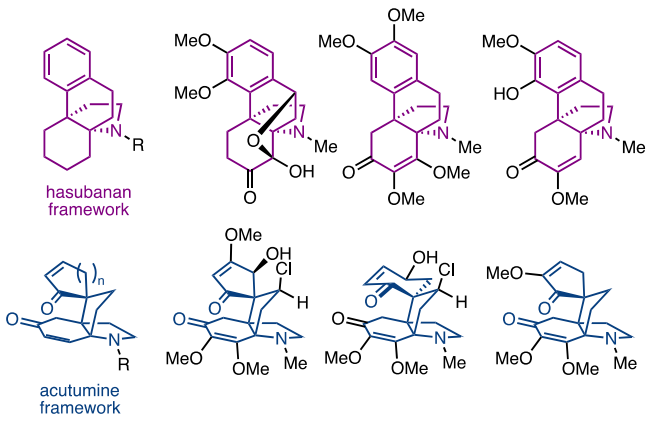


Isolation, Biosynthesis, and Chemical Syntheses of the Hasubanan and Acutumine Alkaloids: A Historical Perspective

Denise C. Grünenfelder,[1] Sarah E. Reisman,[1] Raul Navarro[2]*

[1]Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States

[2]Department of Chemistry, Occidental College, Los Angeles, California 90041, United States

Corresponding author email address: rnavarro@oxy.edu

Corresponding author mailing address: 1600 Campus Road; Mail Code M-5, Norris Hall of Chemistry; Los Angeles, CA 90041

Abstract

The hasubanan and acutumine alkaloids comprise a large collection of aza-propellane natural products that possess varying degrees of structural complexity and biological activity. Since their initial structural elucidation in the 1960s, these alkaloids have garnered considerable attention from the synthetic community and have remained the subject of numerous studies aimed toward understanding their biosynthetic origins and synthesizing their complex architectures. Herein, we review the rich history associated with their isolation, characterization, biosynthetic origins, and chemical synthesis, with an emphasis on the range of synthetic strategies that have been implemented to access their aza-propellane framework. The unique features and history of each class of aza-propellanes are discussed in two separate sections of this account.

Keywords: hasubanan, acutumine, propellanes, alkaloids, total synthesis

1. The Hasubanan Alkaloids

1.1. Introduction

The hasubanan alkaloids represent a large collection of natural products isolated from the *Menispermaceae* family of plants, which have long been used in traditional Chinese medicine for the treatment of pain, arthritis, fever, and many other illnesses.[1] Since their initial discovery in the 1920s, over 80 members of this collection of alkaloids have been isolated to date.[2–4] Each of these compounds can be structurally characterized by the presence of a densely functionalized [4.4.3] aza-propellane framework (**3**, rings B/C/D, Figure 1), and can be further organized based on the oxidation pattern that adorns their propellane core. Cepharamine (**1**) and 8-demethoxyrunanine (**2**) constitute the least oxidized hasubanan alkaloids, due to their lack of a functional group at the C8 carbon. Introduction of a C8 oxygen functionality leads to natural products bearing the hasubanonine oxidation pattern, such as hasubanonine (**4**), aknadinine (**5**), runanine (**6**), and delavayine (**7**). Additional oxidation at the C10 carbon is characteristic of the oxo-bridged propellane alkaloids, including metaphanine (**8**), longanine (**9**), periglaucine A (**10**), and stephanaberrine (**11**).

Since their initial structural elucidation in the 1960s, the hasubanan alkaloids have garnered considerable attention from the synthetic community in part due to their resemblance to morphine. Indeed, the hasubanan and morphinan frameworks differ primarily in their D ring composition: whereas **3** contains a C14-N bond to form a pyrrolidine, the morphine backbone presents the analogous C9-N-linked piperidine ring. Additionally, these natural products are of opposite enantiomeric series; as a result, it has been speculated that the unnatural enantiomers of the hasubanan alkaloids might exhibit analgesic activity.[5] Although studies aimed at assessing this hypothesis have yet to be reported, several naturally occurring hasubanans display promising biological properties. For instance, the oxo-bridged propellanes periglaucine A (**10**) and longanine

(**9**) were found to demonstrate anti-hepatitis B virus activity and selective δ-opioid receptor binding affinity, respectively.[6]

As a result of their unique molecular architecture and potential biological applications, the hasubanans have been the subject of numerous synthetic endeavors for nearly 60 years. Herein, we take a comprehensive look at the diverse array of strategies employed over the last six decades to target their propellane framework. Preceding the discussion of these reports, a brief history of the hasubanan family of natural products is presented, including their isolation and biosynthetic origins.[7]

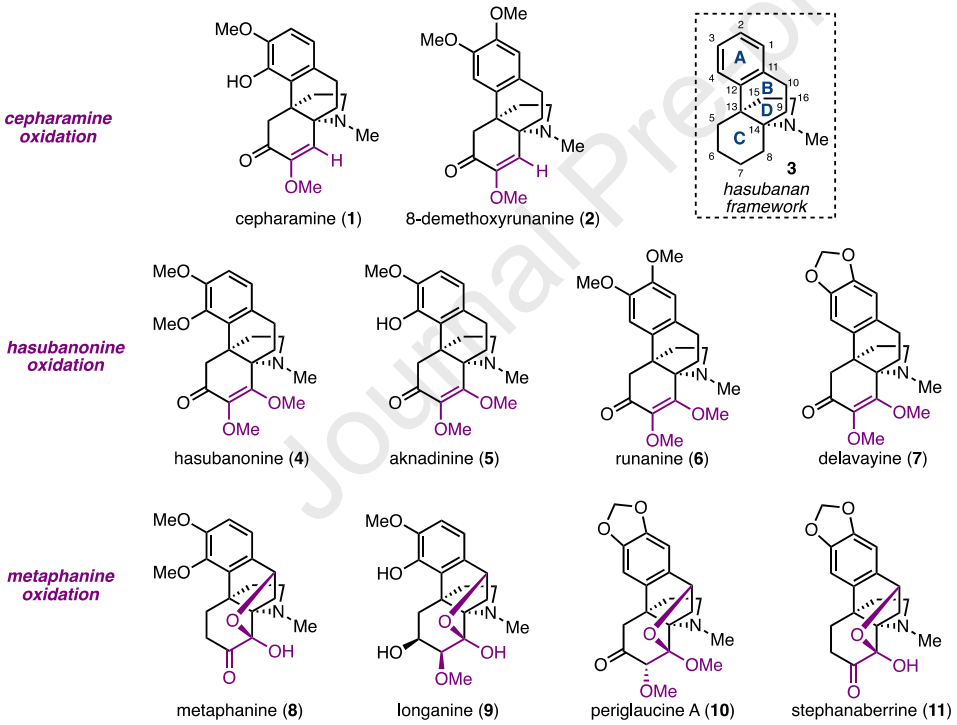
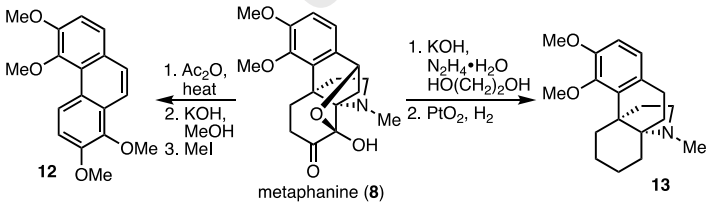


Figure 1. Representative members of the hasubanan alkaloids.

1.2. Isolation

In 1924, Kondo and coworkers described the isolation of metaphanine (**8**), an oxo-bridged hasubanan alkaloid.[8] Its structure was not elucidated until 1964, when Takeda and coworkers characterized the compound by infrared (IR) and 1D nuclear magnetic resonance (NMR)

spectroscopy, as well as through a number of derivatization studies.[9] Specifically, degradation of **8** under reducing conditions delivered anthracene derivative **12**, a structural motif observed to arise from the degradation of morphine alkaloids (Scheme 1). In addition, sequential reduction of **8** afforded hasubanan **13**, a known compound whose enantiomer had previously been prepared from a codeinone intermediate. Using these spectroscopic techniques and synthetic derivatizations, Tomita and coworkers determined the structures of cepharamine (**1**)[10] and hasubanonine (**4**).[11] Tomita's assignments were validated in 1968, when Kupchan and coworkers obtained an X-ray crystal structure of the brosylate derivative of aknadinine (**5**).[12] As novel hasubanan alkaloids began to emerge, 2D NMR techniques and mass spectrometry became important tools for more efficient structural determination. For example, the structure of runanine (**6**) was ascertained by extensive NOE experiments. Additionally, the most abundant ion peak observed in the mass spectrum of **6** was *m*/*z* = 315, which corresponds to loss of its ethylamine chain.[13] This type of fragmentation is characteristic of propellane alkaloids bearing the hasubanonine framework.[4] Taken together, these pioneering studies laid the foundation for the characterization of subsequently discovered hasubanan alkaloids.



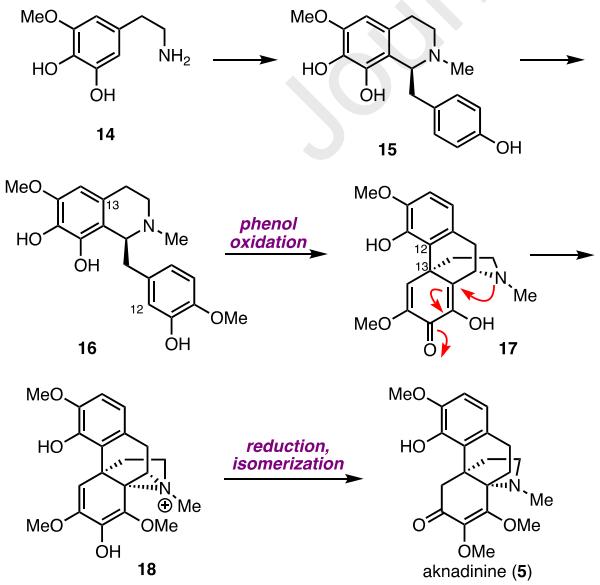
Scheme 1. Structural elucidation of metaphanine (**8**).

In more recent years, a significant number of natural products comprising the metaphanine oxidation pattern have been discovered: nearly 30 oxo-bridged hasubanans have been reported in the last 20 years alone.[6,14–18] Interestingly, members of the metaphanine-type alkaloids are the only hasubanans reported to demonstrate medicinal properties (*vide supra*). Moreover, the recent

emergence of oxo-bridged hasubanans in the literature raises numerous questions regarding their biosynthetic relationship to their less oxidized congeners.

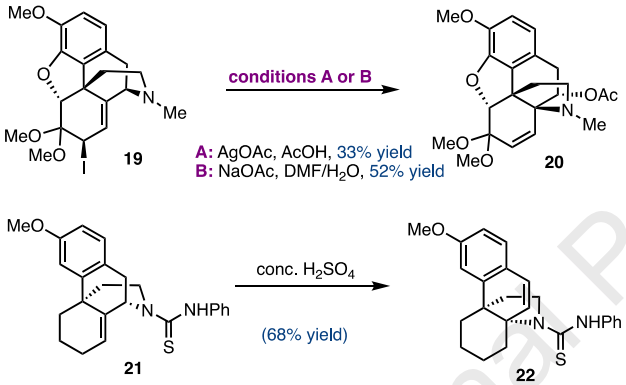
1.3. Biosynthesis

The structural similarities between the morphinan and hasubanan alkaloids have been exploited to examine the biosynthesis of hasubanonine (**4**). Specifically, it is known that morphine is derived from the coupling of two tyrosine building blocks, which initially generates an isoquinoline intermediate.[19] With these considerations in mind, Battersby and coworkers conducted feeding experiments with ^{14}C-labeled tyrosine and isoquinoline derivatives bearing an array of arene oxidation patterns,[20] which revealed that the hasubanan framework is indeed derived from two different tyrosine-based building blocks. Moreover, Battersby concluded that the C ring of **5** originates from trioxygenated intermediate **14** (Scheme 2). Importantly, the oxidation of tyrosine occurs prior to isoquinoline formation: feeding studies using analogous mono- and dioxygenated isoquinolines determined that these precursors are not elaborated to the natural product.



Scheme 2. Proposed biosynthesis of the hasubanan alkaloids.

Based on these findings, amine **14** is believed to undergo condensation with a tyrosine derivative to deliver **15**, which upon oxidation affords **16**.[4] In analogy to morphinan biosynthesis, an intramolecular oxidative coupling between the C12-C13 carbons is proposed to deliver piperidine **17**. At this point, the propellane backbone can arise from an initial intramolecular conjugate addition of the basic amine into the enone system, giving rise to aziridinium ion **18**. Reduction of this intermediate generates the corresponding pyrrolidine, which can then undergo isomerization of the C ring to give **5**.



Scheme 3. Conversion of morphinans to propellane intermediates.

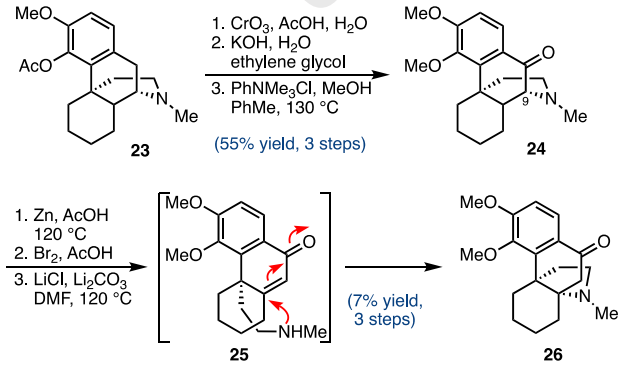
Although the proposed skeletal rearrangement of **17** to **5** has not been validated in a biosynthetic context, researchers have successfully converted a morphine derivative to a propellane alkaloid. In one example, Kirby and coworkers facilitated the conversion of thebaine-derived iodide **19** to propellane **20** by exposure to Ag- or NaOAc (Scheme 3);[21] this reaction may proceed via displacement of the allylic iodide. In a similar transformation, treatment of morphinan **21** with concentrated H_2SO_4 gives pyrrolidine **22** in 68% yield.[22] While these examples remain limited, they provide credence for the biosynthetic relationship between the hasubanan and morphinan family of alkaloids.

1.4. Previous Synthetic Studies

Over the last six decades, the hasubanan alkaloids have been the subject of numerous synthetic studies. While a number of syntheses of the hasubanan core as a racemate have been described, there are fewer enantioselective total syntheses. Nevertheless, collectively these studies highlight the diverse array of strategies that have been developed to prepare the hasubanan framework. The discussion below is intended to highlight the key features of these synthetic endeavors, and is divided into two sections: core syntheses and total syntheses.

1.4.1 Core Syntheses

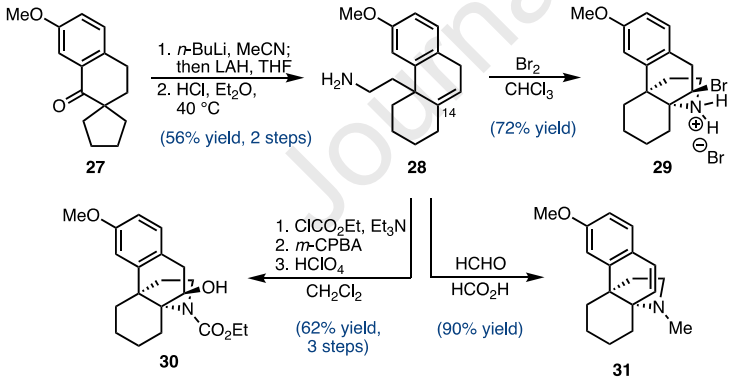
Of the existing approaches to access the hasubanan framework, several rely on late-stage intramolecular aminocyclization to establish the D ring of the natural product (see **3**, Figure 1). The earliest example of this strategy was presented by Ibuka and Kitano in 1966.[23] Benzylic oxidation of sinomenine-derived alkaloid **23** gave ketone **24** after protecting group manipulations (Scheme 4). Reductive cleavage of the C9-N bond of **24** with zinc dust, followed by treatment with bromine, provided the corresponding α-bromo ketone. Exposure of the bromide to LiCl and Li_2CO_3 in DMF at 120 °C promoted the formation of enone **25**, which spontaneously cyclizes to yield propellane **26**, albeit in poor yield.



Scheme 4. Synthesis of **26** from a sinomenine derivative.

In their efforts to prepare more effective morphine analgesics, the Bristol-Myers group reported the synthesis of a number of morphinan and hasubanan derivatives. In the context of

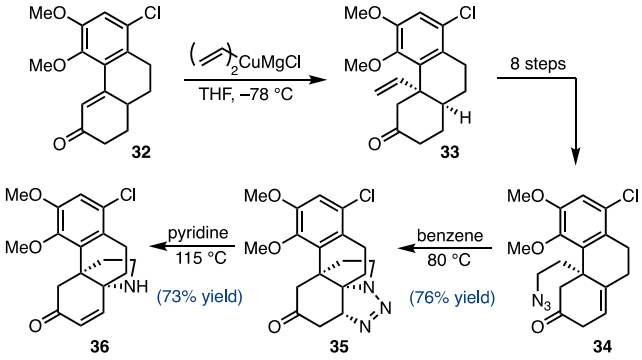
propellane alkaloids, the authors targeted the synthesis of amine **28** from α-tetralone-derived tricycle **27** (Scheme 5).[24] Exposure of **27** to the lithium anion of MeCN afforded the cyanomethyl adduct, which could be reduced in situ with LAH to give the corresponding amino alcohol. Wagner-Meerwein rearrangement of this intermediate was triggered under acidic conditions to yield amine **28** in 56% yield over two steps. At this point, an aminocyclization reaction was effected by treatment of **28** with bromine to generate hydrobromide salt **29** in 72% yield. The authors were able to extend this aminocyclization protocol to an epoxide-bearing substrate, providing access to alcohol **30** in good yield.[25] Concomitant to the studies by Bristol-Myers, Shiotani and Kometani reported the direct aminocyclization reaction of amine **28**.[26] In the event, propellane **31** was obtained in 90% yield by exposure of **28** to paraformaldehyde and formic acid. It is hypothesized that cyclization of the pendant amine occurs via the intermediacy of a C14 carbocation, and the resulting pyrrolidine then undergoes an Eschweiler-Clark methylation.



Scheme 5. Bristol–Myers' and Kometani's aminocyclization approaches.

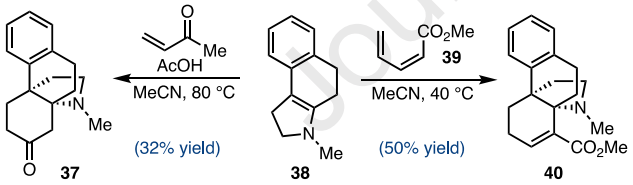
The Mulzer group also developed an aminocyclization approach to the hasubanan core. Their synthetic endeavors commenced with tricyclic enone **32**, which is available in three steps from commercially available 4-(3,4-dimethoxyphenyl)butyric acid (Scheme 6).[27] Vinylcuprate addition to the enone yields olefin **33**, which in eight steps can be elaborated to azide **34**. To form the requisite pyrrolidine ring, a thermal (3+2) dipolar cycloaddition reaction of **34** was used to access

triazene **35** in 76% yield. Decomposition of the triazene was achieved by heating **35** in refluxing pyridine to give propellane **36**.



Scheme 6. Mulzer's (3+2) cycloaddition approach to the propellane alkaloids.

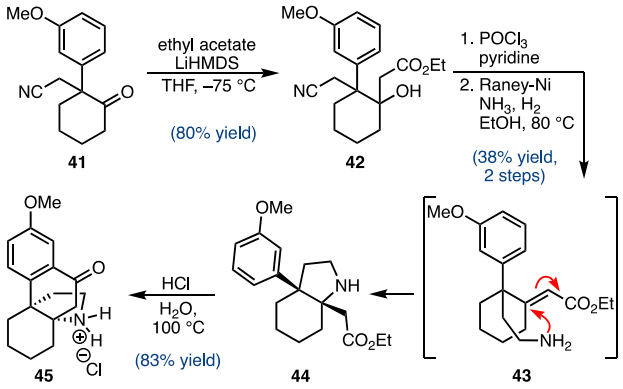
An alternative approach for propellane synthesis exploits the reactivity of tetrahydrobenzindoles. In 1969, Evans and Tahk independently disclosed the Robinson annulation of enamine **38** with methyl vinyl ketone (Scheme 7).[28,29] However, this reaction promotes the formation of **37** in modest yield.[30] Evans observed an improvement in the yield when methyl pentadienoate (**39**) was used as the electrophile, thereby furnishing **40** in 50% yield.[31]



Scheme 7. Preparation of the hasubanan core via enamine **38**.

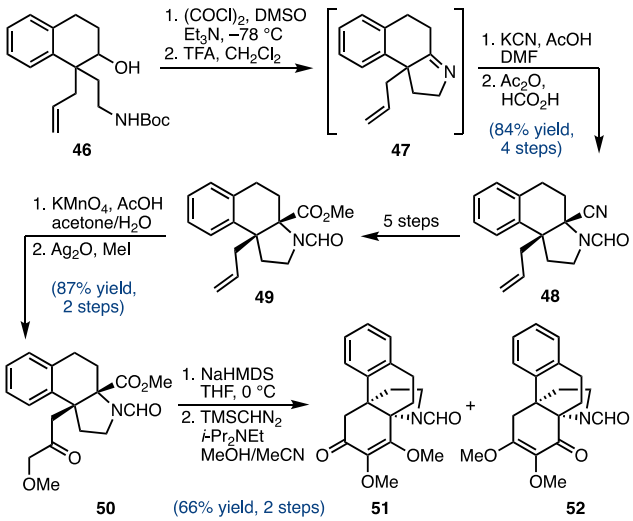
The Hoffman-La Roche group devised an approach to the hasubanan framework starting from cyclohexanone derivative **41** (Scheme 8).[32] Aldol reaction between **41** and ethyl acetate provided alcohol **42**, which was then subjected to $POCl_3$ in pyridine to yield a 2:1 mixture of α,β and β,γ-unsaturated esters. Treatment of this mixture of products with Raney-Ni, NH_3, and H_2 unveiled primary amine **43**, which undergoes intramolecular conjugate addition to produce *cis*-fused

pyrrolidine **44**. Installation of the B ring was accomplished by an acid-mediated Friedel-Crafts reaction of the arene with the ester moiety of **44**, providing tetracycle **45** in 83% yield.



Scheme 8. Synthesis of **45** from cyclohexanone **41**.

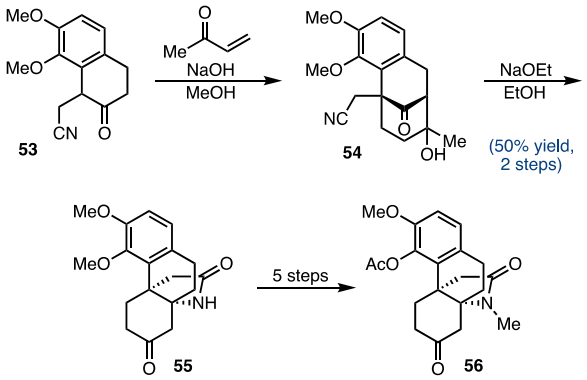
In contrast to the previously discussed core syntheses, the Kobayashi group pursued an approach that focused on a late-stage C-ring formation. To this end, β–tetralone was readily converted to alcohol **46**, which upon Swern oxidation and cleavage of the Boc group generated unstable imine intermediate **47** (Scheme 9).[33] To circumvent decomposition of **47**, the crude product was immediately treated with KCN in AcOH and DMF to give the hydrocyanation product. The resulting amine was *N*-formylated with formic acid and acetic anhydride to afford tricycle **48**. Conversion of the nitrile to its methyl ester proved nontrivial; the authors accomplished this transformation in five steps from **48** via the intermediacy of an *N*-acylbenzotriazole. Permanganate oxidation of **49** followed by methylation generated ketone **50** in 87% yield. Completion of the propellane backbone was realized by a Dieckmann condensation reaction and methylation with $TMSCHN_2$; however, the desired alkaloid (**51**) was obtained as a 1:1 mixture with its enol tautomer (**52**). Unfortunately, attempts to convert the undesired regioisomer to **51** were unsuccessful.



Scheme 9. Kobayashi's synthesis of hasubanan congener **51**.

1.4.2 Total Syntheses

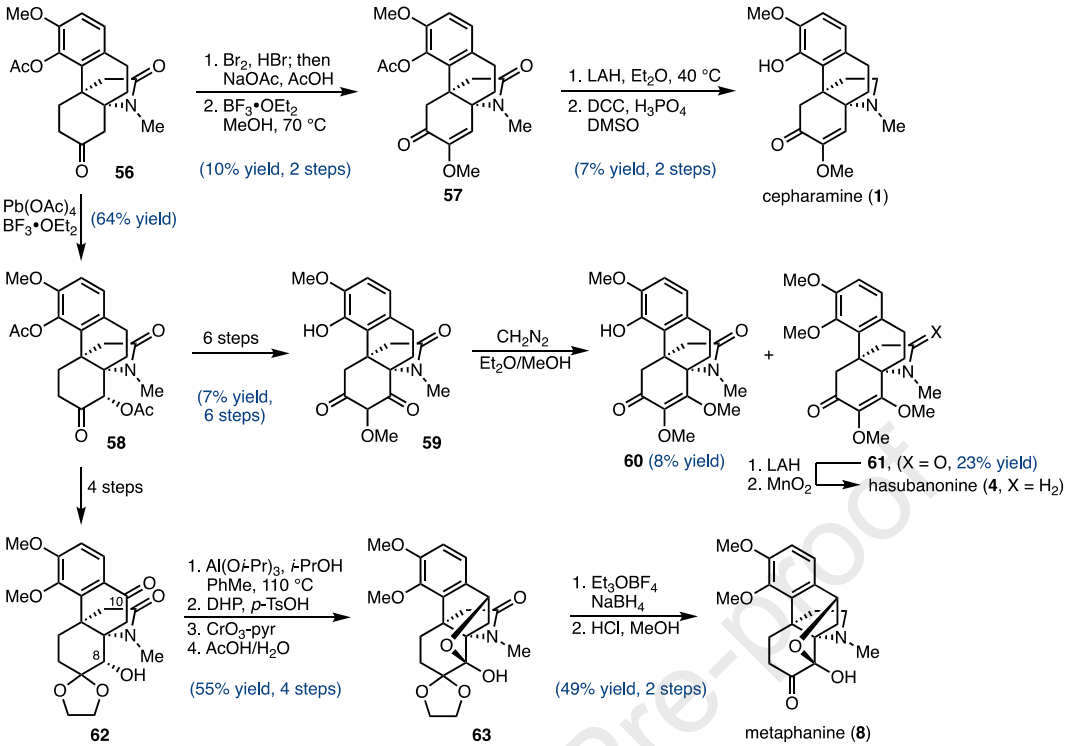
Shortly after the structure of hasubanonine was confirmed, Ibuka and coworkers embarked on a campaign aimed at preparing several hasubanan alkaloids. Their synthetic strategy was highly dependent on the preparation and differential oxidation of propellane **56** (Scheme 10). Beginning with tetralone derivative **53**, an interrupted Robinson annulation with methyl vinyl ketone furnished bridged ketone **54**.[34,35] Exposure of this intermediate to NaOEt in EtOH facilitated a retro-aldol/aldol reaction followed by a nitrile hydrolysis/conjugate addition cascade to give **55** in 50% yield over two steps. Further functional group manipulations allowed access to differentially protected propellane **56**.



Scheme 10. Ibuka's synthesis of tetracycle **56**.

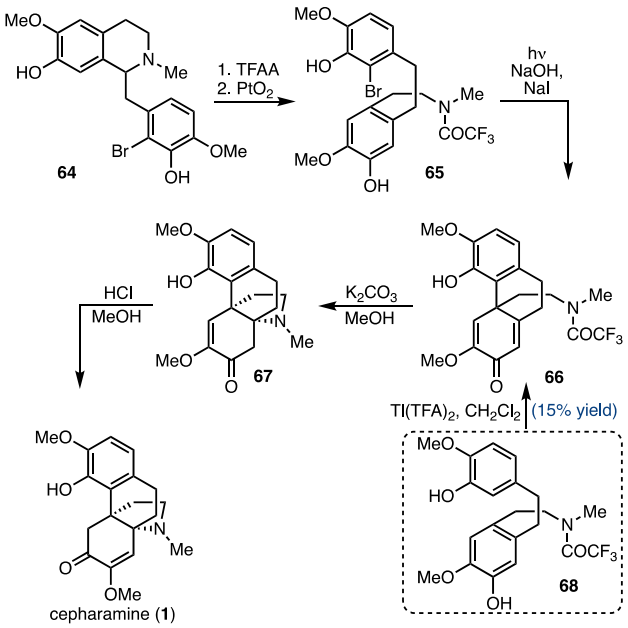
With ketone **56** in hand, the authors initially pursued a synthesis of (±)–cepharamine (**1**, Scheme 11). Methoxy enone **57** was prepared from **56** via oxidation to the diketone followed by methylation with $BF_3{\cdot}OEt_2$ in MeOH. Global reduction of the carbonyl moieties with LAH and subsequent oxidation of the resulting allylic alcohol delivered the natural product (**1**), albeit in low yield. Alternatively, **56** could be elaborated to the hasubanonine oxidation pattern by an initial α-acetoxylation to give acetate **58**.[36,37] A series of oxidative manipulations provided diketone **59**, an intermediate that was treated with diazomethane to give aknadilactam (**60**)[38] and **61** in 8 and 23% yield, respectively. In this methylation reaction, the authors observe the formation of **60**, **61**, and each of their corresponding enol ether regioisomers in a 1:1:1:1 ratio, which accounts for the low isolated yields. Reduction of lactam **61** was effected by LAH reduction and MnO_2 oxidation to afford (±)–hasubanonine (**4**).

As a testament to the divergent nature of Ibuka's strategy, acetate **58** was also advanced to metaphanine (**8**). In this case, benzylic ketone **62** could be prepared from **58** after a series of steps including benzylic oxidation.[39,40] After an exhaustive screen of reducing conditions, the authors found reduction of the ketone with $Al(O\textit{i}\text{-}Pr)_3$ in PhMe/*i*-PrOH to be optimal, delivering the corresponding alcohol in good yield and excellent diastereoselectivity (>20:1). Protection of the benzylic alcohol as its THP ether and oxidation of the C8 alcohol provides the corresponding ketone, which spontaneously underwent intramolecular ketalization after deprotection of the THP group to furnish oxo-bridged intermediate **63**. To complete the synthesis, the amide functionality of **63** was reduced using Meerwein's salt and $NaBH_4$, and the ketal was hydrolyzed under acidic conditions.



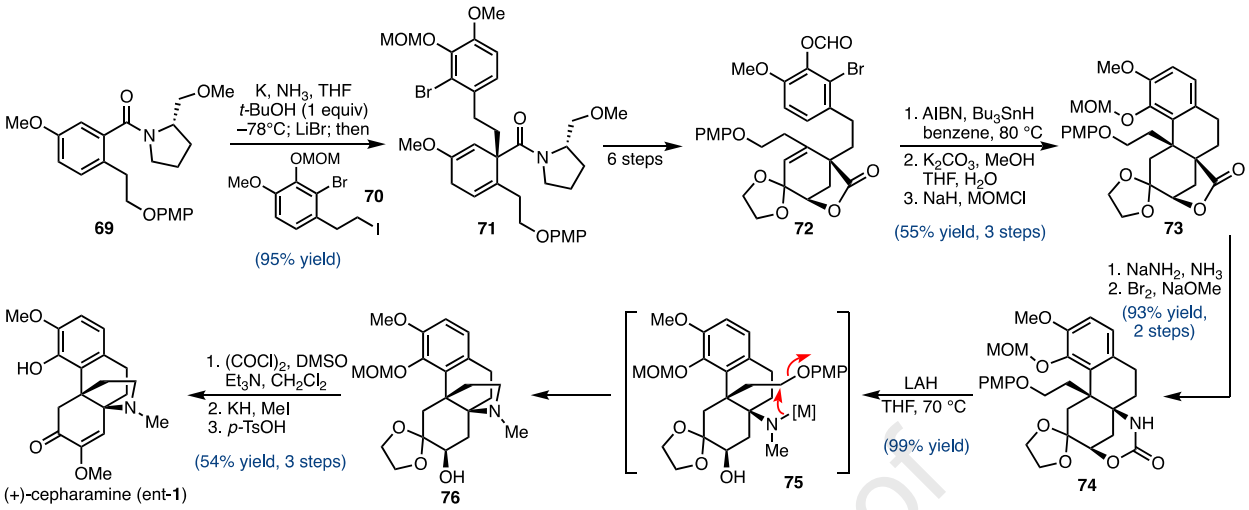
Scheme 11. Ibuka's syntheses of hasubanan alkaloids.

Soon after the publication of Ibuka's studies, Kametani and coworkers reported their efforts toward (±)–cepharamine (**1**, Scheme 12). In this biomimetic approach, the authors sought to construct the hasubanan backbone from simple isoquinoline precursors.[41,42] To this end, reticuline-derived isoquinoline **64** was sequentially subjected to TFAA and Adam's catalyst to access intermediate **65**. In the key step, photoexcitation of **65** with a mercury lamp promoted an intramolecular biaryl coupling to afford dienone **66**. Hydrolysis of the trifluoroacetamide group under basic conditions facilitated addition of the amine to the more electron poor enone to selectively give tetracycle **67**. Acid-mediated isomerization of the methoxyenone then delivered the natural product (**1**). More recently, Schwartz and Wallace described the direct oxidative coupling of **68** in the presence of thallium (III) trifluoroacetate, thereby completing a formal synthesis of cepharamine.[43]



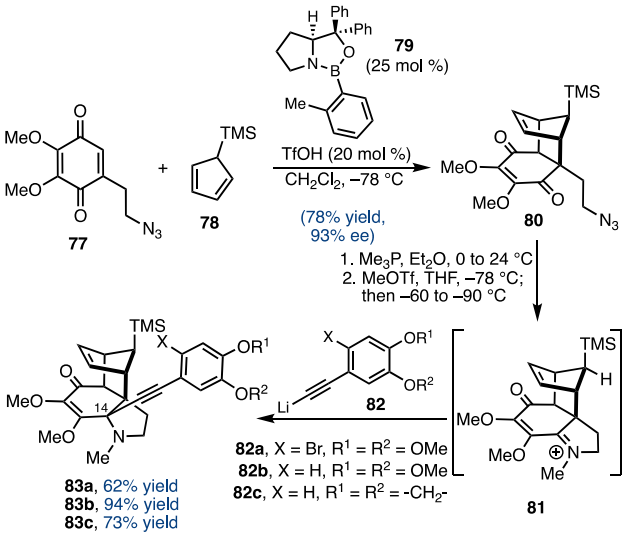
Scheme 12. Kametani's and Schwartz's approach to cepharamine (**1**).

The synthetic endeavors of Ibuka and Kametani represented the sole completed syntheses of the hasubanans for over 20 years. The subsequent total synthesis of a propellane alkaloid was not reported until 1998, when Schultz and Wang disclosed their preparation of (+)–cepharamine (ent-**1**).[5] Starting with chiral benzamide **69**, Birch reduction followed by in situ alkylation with alkyl iodide **70** provided cyclohexadiene **71** in excellent yield and as a single diastereomer (Scheme 13). In an additional six steps, the authors could access lactone **72**. Exposure of **72** to AIBN and Bu_3SnH in refluxing benzene facilitated an intramolecular radical cyclization, which following protecting group manipulations delivered hydrophenanthrene **73** in 55% yield over 3 steps. Introduction of the amine was effected via a Hoffman rearrangement to give carbamate **74**, which upon LAH reduction and cyclization furnished propellane **76**. Finally, oxidation of the alcohol, methyl enol ether formation, and ketal hydrolysis yielded the unnatural antipode of the natural product (**1**). With a longest linear sequence of 21 steps, this represented the first enantioselective preparation of any member of the hasubanan alkaloids.



Scheme 13. Schultz's enantioselective synthesis of (+)–cepharamine (ent-**1**).

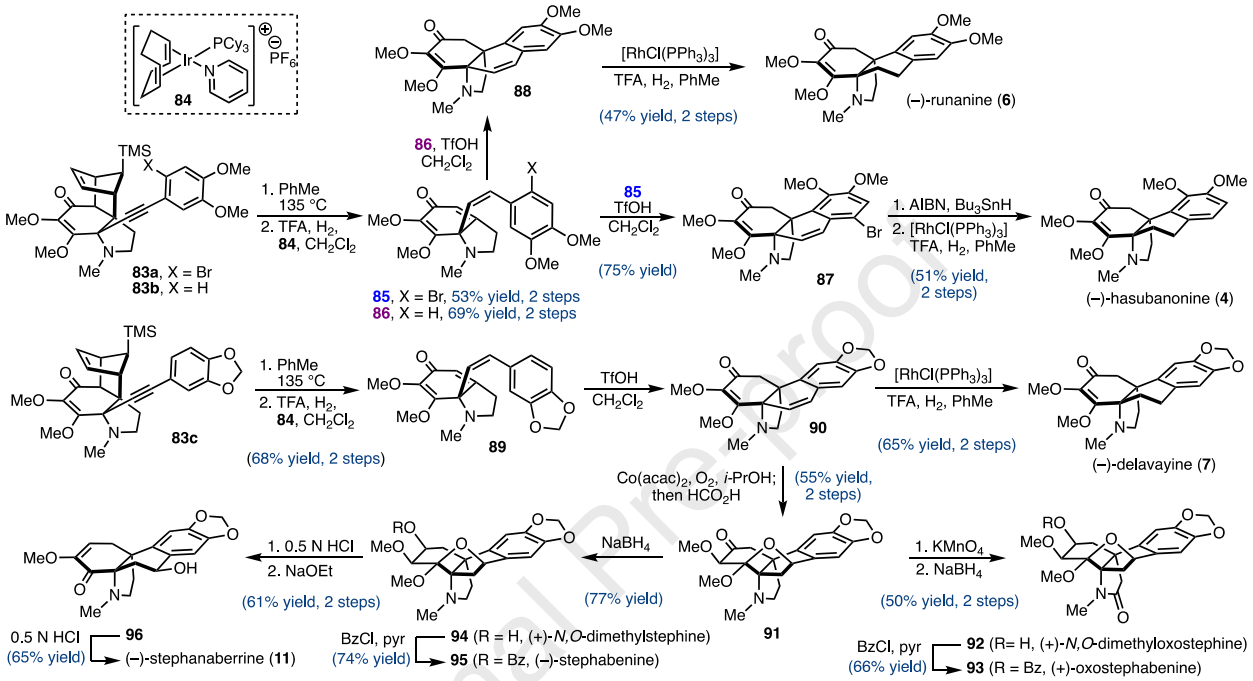
In 2011, Herzon and coworkers reported the development of a unified strategy for the enantioselective synthesis of several hasubanan alkaloids.[44] In contrast to Schultz's report, this synthetic approach relied on an early-stage installation of the C14 stereocenter. To this end, an oxazaborolidine-catalyzed Diels-Alder reaction between quinone **77** and cyclopentadiene **78** afforded enedione **80** in 78% yield and 93% ee (Scheme 14). Staudinger reduction of **80** generated the corresponding quinone imine, which was activated toward nucleophilic attack by treatment with methyl triflate. The resulting iminium salt (**81**) was found to undergo a highly diastereoselective addition of an alkynyllithium reagent (e.g., **82**) to access pyrrolidine **83**. Using this 1,2-addition strategy, the authors could efficiently access an array of hasubanan frameworks by modifying the nature of the acetylide nucleophile employed.



Scheme 14. Herzon's general approach to the hasubanans.

To prepare (–)-hasubanonine (**4**), addition of acetylide **82a** to iminium ion **81** afforded **83a** in 62% yield (Scheme 14). Thermolysis of the cyclopentenyl group and monoreduction of the alkyne with Crabtree's catalyst provided dienone **85** (Scheme 15), an intermediate found to undergo a highly regioselective triflic-acid mediated cyclization. Hydrodebromination of propellane **87** with AIBN and Bu_3SnH followed by hydrogenation with Wilkinson's catalyst delivered **4**. Using a similar reaction sequence, the authors were also able to access (–)-runanine (**6**) and (–)-delavayine (**7**) from alkynyl pyrrolidines **83b** and **83c**, respectively. Alternatively, hydration of alkene **90** with $Co(acac)_2$ under an atmosphere of oxygen followed by addition of formic acid gave (+)-periglaucine B (**91**) in 55% yield. To further demonstrate the versatility of their approach, Herzon's team successfully elaborated **91** to six additional hasubanan alkaloids.[45,46] For example, $KMnO_4$-mediated oxidation to the lactam followed by diastereoselective ketone reduction delivered (+)-*N,O*-dimethyloxostephine (**92**), which was converted to its acylated derivative (+)-oxostephabenine (**93**). This reduction/acylation sequence was used to prepare (+)–*N,O*-dimethylstephine (**94**) and (–)-stephabenine (**95**) from **91**, while exposure of ketal **94** to aqueous

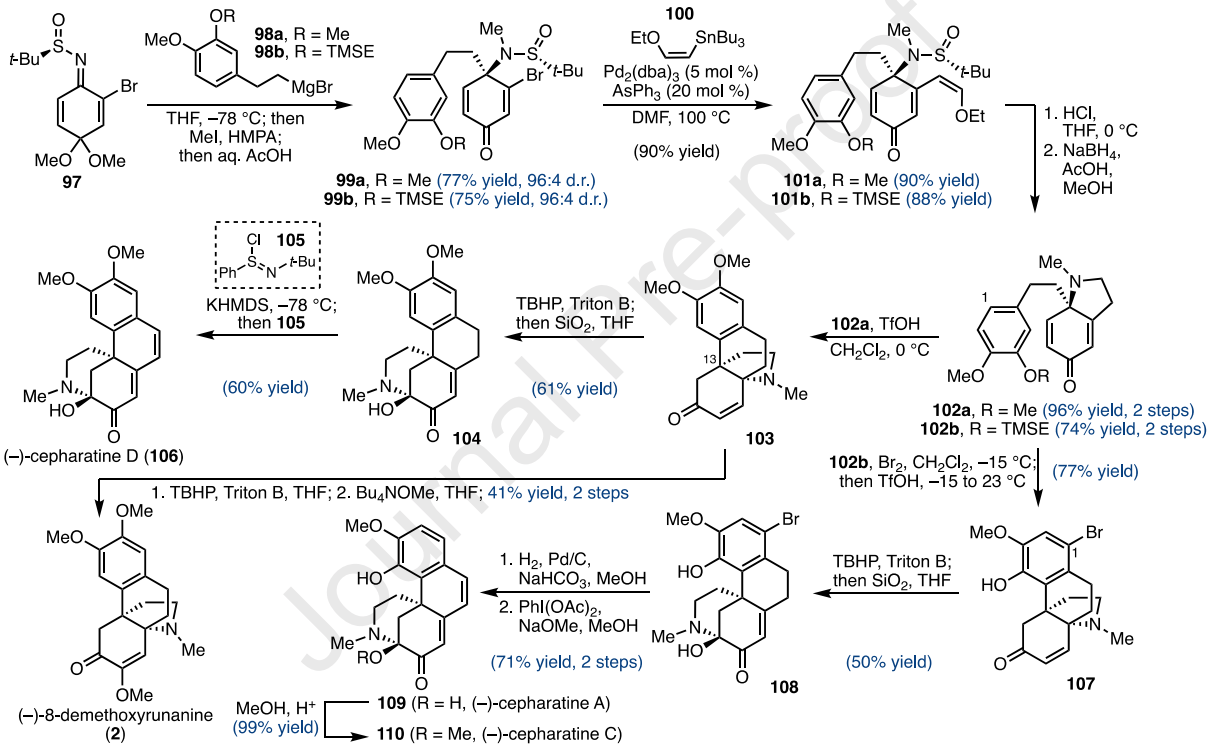
HCl followed by catalytic NaOEt facilitated the formation of (–)-prostephanaberrine (**96**). Finally, elaboration of enone **96** to (–)–stephanaberrine (**11**, see Figure 1) was accomplished under acidic conditions.



Scheme 15. Herzon's enantioselective synthesis of hasubanan alkaloids.

In the same year, Reisman and coworkers disclosed a synthetic approach to the hasubanan alkaloids,[47] which relied on a highly diastereoselective 1,2-addition to quinone-derived *N*-tert-butanesulfinimes[48] to set the C14 stereocenter (Scheme 16). Specifically, exposure of sulfinimine **97** to Grignard reagent **98a** at – 78°C followed by in situ methylation afforded sulfinamide **99a** in 96:4 dr and 77% yield. Installation of the pyrrolidine ring was accomplished using a 3-step sequence involving Pd-catalyzed cross-coupling to vinyl stannane **100**, acid-mediated sulfinamide cleavage and intramolecular condensation to give the corresponding indolone, and chemoselective reduction of the enamine moiety with $NaBH_4$ and acetic acid. Treatment of dihydroindolone **102a** with excess triflic acid promoted intramolecular Friedel-Crafts reaction exclusively at the C13-position, delivering propellane **103** in excellent yield. The authors successfully prepared (–)-8-

demethoxyrunanine (**2**) from enone **103** via epoxidation with TBHP/Triton B followed by Bu_4NOMe-mediated epoxide-opening. Interestingly, it was observed that exposure of the crude epoxide to silica gel facilitated a rearrangement to afford hemiaminal **104**, an intermediate bearing the skeletal framework of the closely related cepharatine alkaloids (e.g., **106**). Desaturation of **104** was carried out by deprotonation with excess KHMDS at –78 °C followed by addition of **105**, thereby delivering cepharatine D (**106**) in 31% yield from quinone imine **97**.

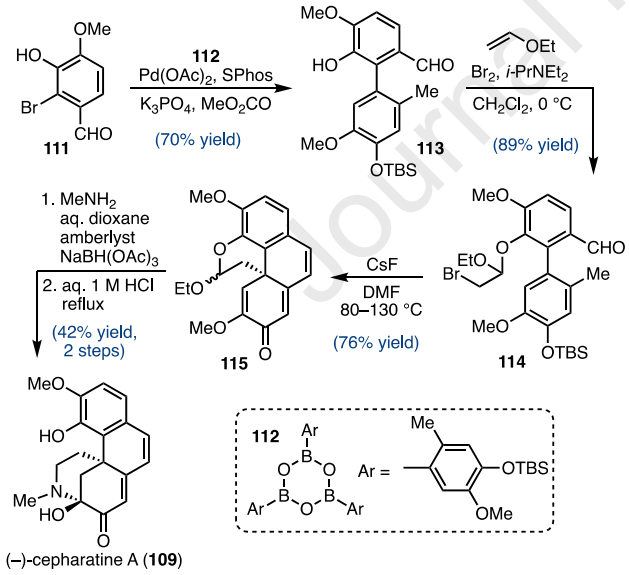


Scheme 16. Reisman's asymmetric synthesis of hasubanan and cepharatine alkaloids.

To access the cepharamine framework, sulfinimine **97** was exposed to orthogonally protected Grignard reagent **98b**. The resulting sulfinamide was subjected to the aforementioned cross-coupling / cyclization / reduction protocol to furnish dihydroindolone **102b**, an intermediate that was elaborated to azapropellane **107** via chemoselective bromination at C1 followed by in situ TfOH-mediated cyclization. Although conversion of **107** to cepharamine (**1**) proved unsuccessful, treatment with the tandem epoxidation/rearrangement conditions delivered the corresponding

hemiaminal in 50% yield. Hydrodebromination of **108** followed by treatment with $PhI(OAc)_2$ and NaOMe in methanol delivered cepharatine A (**109**), which was readily converted to cepharatine C (**110**) using methanol and mildly acidic reaction conditions.

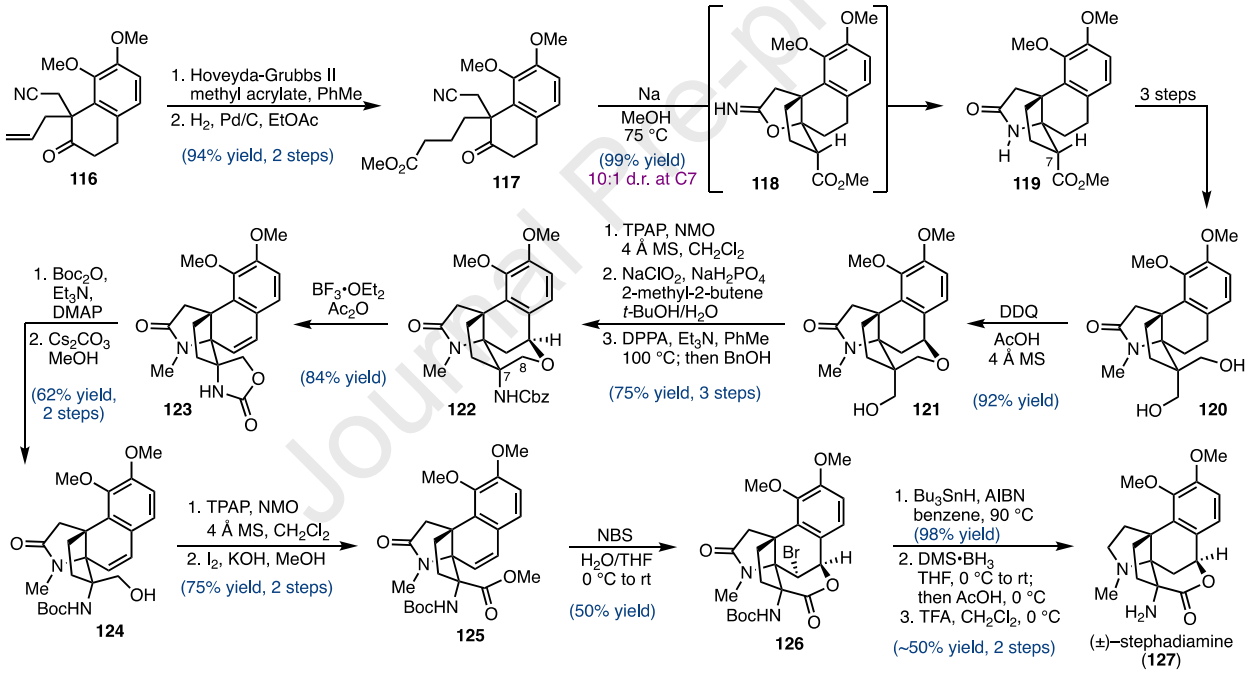
A concise synthesis of (±)–cepharatine A (**109**) was also developed by Magnus and coworkers (Scheme 17).[49] Starting with aryl bromide **111**, Suzuki cross-coupling with boroxine derivative **112** afforded biaryl phenol **113** in 70% yield, an intermediate that was elaborated to acetal **114** upon exposure to ethyl vinyl ether and Br_2 in the presence of *i*-$PrNEt_2$. In a key step in the synthesis, treatment of **114** with CsF at elevated temperatures promoted desilylation, intramolecular cyclization of the resulting phenoxide with the tethered bromide, and a vinylogous aldol reaction to deliver dienone **115** in good yield. Reductive amination of acetal **115** followed by acid-mediated enol ether hydrolysis and cyclization delivered cepharatine A (**109**).



Scheme 17. Magnus' synthesis of cepharatine A (**109**).

More recently, Trauner and coworkers reported the first total synthesis of (±)–stephadiamine (**127**), a hasubanan alkaloid bearing an unusual 5-membered C-ring (Scheme 18).[50] Their synthetic studies begin with β-tetralone derivative **116**, which was subjected to cross-metathesis with methyl

acrylate followed by hydrogenation to deliver alkyl ester **117**. Exposure of this intermediate to in situ-generated NaOMe in methanol triggered a cyclization cascade involving intramolecular aldol reaction between the ester enolate and ketone, addition of the resulting alkoxide to the nitrile, and an elimination / conjugate addition sequence of intermediate imidate **118**. Notably, this key step efficiently installs the propellane core of the natural product in near quantitative yield and good diastereoselectivity. Tetracycle **119** was then elaborated to diol **120** in 3 steps involving *N*-methylation, chemoselective reduction of the ester to its corresponding aldehyde, and a tandem base-mediated aldol reaction / Cannizzaro reaction.

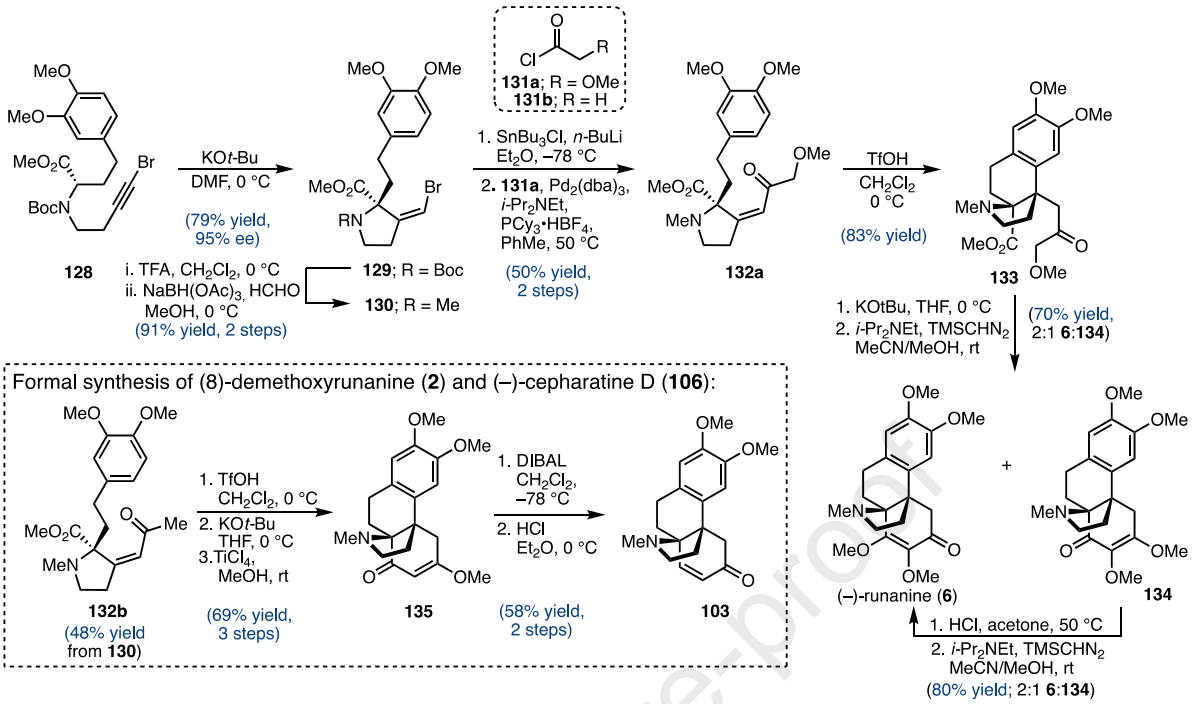


Scheme 18. Trauner's Total Synthesis of Stephadiamine (**127**).

At this point, completion of the synthesis required oxidation of the B ring to form the requisite lactone and installation of the C7 amine. To this end, treatment of diol **120** with DDQ and AcOH enabled formation of benzylic ether **121** in 92% yield. The remaining hydroxymethyl group was converted to Cbz-protected amine **122** via a 3-step protocol involving alcohol oxidation to the corresponding acid followed by acyl azide formation and a Curtius rearrangement. While attempts

to chemoselectively oxidize the C8 ether to its corresponding lactone proved unsuccessful, the authors found that elimination of the benzyl ether and concomitant condensation of the intermediate alkoxide with the pendant carbamate could be accomplished under Lewis acidic conditions. The resulting spirocycle **123** was converted to Boc-protected amine **124**, which then underwent a 2-step oxidation to afford methyl ester **125** in good yield. Exposure of ester **125** to NBS in wet THF delivered bromolactone **126** in 50% yield. Reductive cleavage of the C-Br bond, reduction of the lactam, and acid-mediated cleavage of the Boc group furnished (±)–stephadiamine (**127**). The authors also achieved an enantioselective synthesis of allyl ketone **116** via asymmetric allylation chemistry, thereby establishing a viable route to prepare (+)-stephadiamine.

In 2019, Kim and coworkers disclosed a "memory of chirality" (MOC)–based approach to the asymmetric synthesis of (–)-runanine (**6**, Scheme 19).[51] Their synthetic endeavors begin with bromo alkyne **128**, which is available in 4 steps from commercially available (*R*)-3,4-dimethoxy-homophenylalanine. Exposure of alkyne **128** to KO*t*-Bu in DMF at 0 °C promoted 5-*exo*-dig cyclization of the in situ-generated ester enolate with the tethered alkyne, delivering pyrrolidine **129** in 79% yield and excellent enantioselectivity. Deprotection of the Boc group and *N*-methylation afforded vinyl bromide **130**, which was found to undergo transmetallation to its corresponding stannane and subsequent Stille coupling with acid chloride **131a** to furnish enone **132a** in 50% yield over two steps. To access the propellane backbone of **6**, a TfOH-mediated Friedel-Crafts-type reaction was employed to install the B ring (i.e., **133**) followed by a base-promoted Dieckmann cyclization to furnish the C ring. The resulting 1,3-diketone underwent etherification with TMS-diazomethane to afford a 2:1 mixture of (–)-runanine (**6**) and its regioisomer **134** in 70% yield. Fortunately, the undesired regioisomer could be recycled via acid-mediated hydrolysis of the vinylogous ester and resubjection to the etherification conditions.

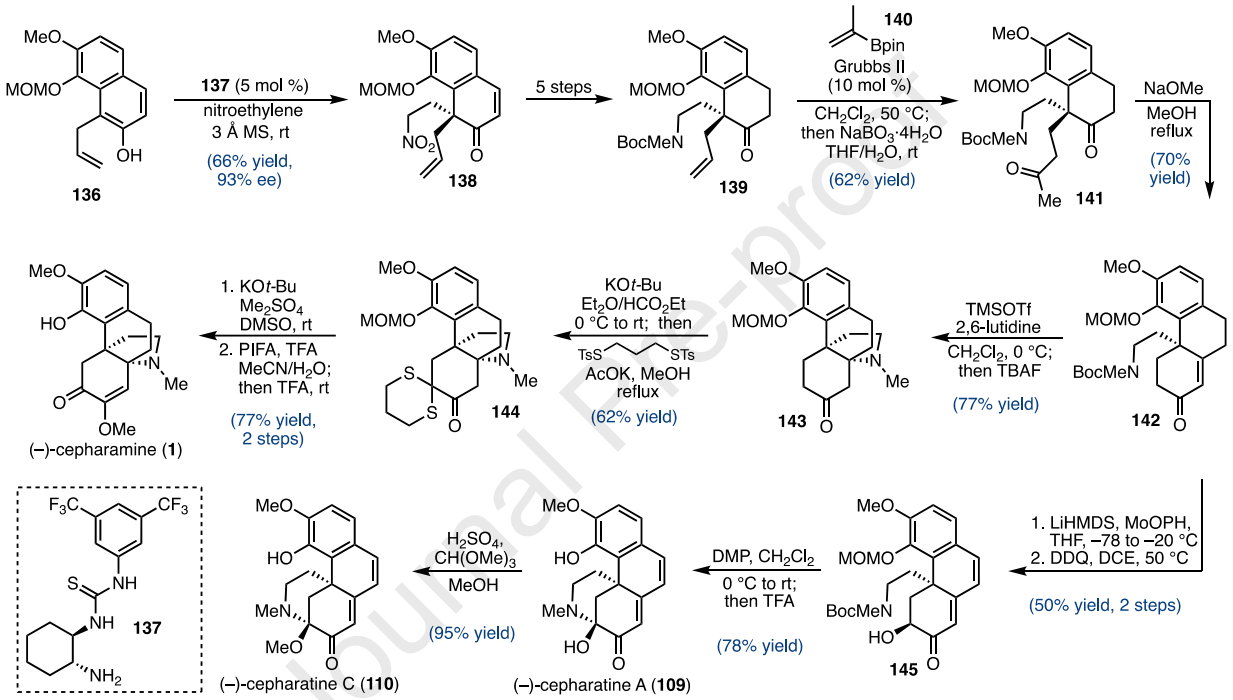


Scheme 19. Kim's memory of chirality approach to access (–)-runanine.

The divergent nature of the MOC-based approach enabled efficient syntheses of several other hasubanan frameworks. For example, coupling of the vinyl stannane derived from **130** with acetyl chloride (**131b**) delivered enone **132b** in 48% yield over 2 steps, and application of the Friedel-Crafts-type / Dieckmann cyclization sequence to this intermediate afforded the corresponding 1,3-diketone. The crude diketone was subjected to $TiCl_4$ in MeOH to give vinylogous ester **135**, and a Stork-Danheiser transposition protocol enabled the synthesis of enone **103**, thereby intercepting Reisman's propellane intermediate and establishing a formal synthesis of (8)-demethoxyruninane (**2**) and cepharatine D (**106**).

As part of their efforts to develop divergent syntheses of structurally diverse alkaloids, Zhu and coworkers recently reported a unified strategy to prepare three sub-classes of hasubanan natural products.[52] In contrast to previous enantioselective syntheses, Zhu's team relied on the catalytic installation of the C13 stereocenter to facilitate their synthetic endeavors (Scheme 20).

To this end, naphthol **136** was subjected to an asymmetric dearomatization with nitroethylene in the presence of 5 mol % thiourea **137** to deliver Michael addition product **138** in 66% yield and 93% ee. In 5 additional steps, **138** was converted to Boc-protected amine **139**, a versatile intermediate that was used to access four natural products: (–)-cepharamine (**1**), (–)-cepharatines A and C (**109** and **110**), and (–)-sinoracutine (not shown).

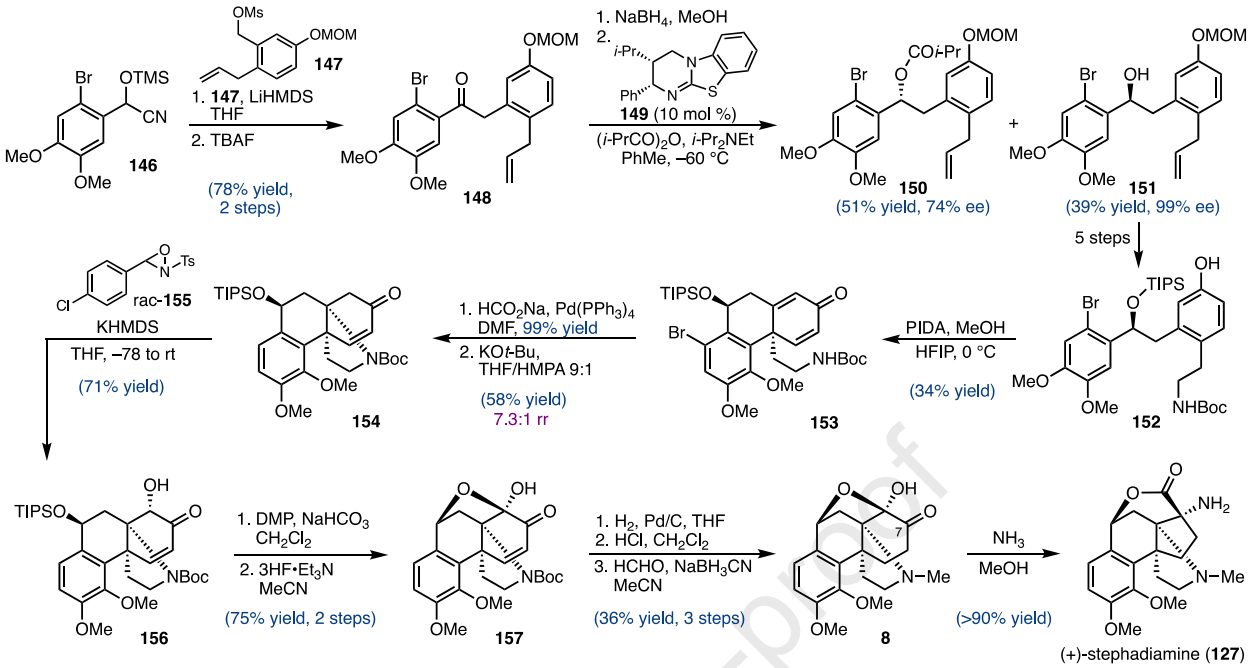


Scheme 20. Zhu's enantioselective strategy to prepare several hasubanan alkaloids.

To prepare **1**, cross-metathesis of allyl ketone **139** with boronic ester **140** in the presence of Grubbs 2nd generation catalysts followed by an oxidative workup furnished homologated ketone **141**. The C-ring was then installed using a base-mediated intramolecular aldol reaction to afford cyclohexanone **142** in 70% yield. Treatment of enone **142** with TMSOTf and 2,6-lutidine followed by TBAF promoted *N*-deprotection and concomitant aza-Michael addition to deliver propellane **143**. To convert the southern ketone to the requisite methoxyenone, a regioselective α-thioketalization of ketone **143** was effected using trimethylene dithiotosylate and KO*t*-Bu followed

by methyl enol ether formation and hydrolysis of the dithioketal. The acidic nature of the final deprotection step (PIFA and TFA) also facilitated cleavage of the MOM ether, thereby delivering (–)-cepharamine (**1**) in 48% yield over 3 steps. Alternatively, access to the cepharatines was accomplished by oxidation of **142** using LiHMDS and MoOPH, then treatment of the resulting α-hydroxy enone with DDQ to afford conjugated dienone **145**. Oxidation to the diketone with DMP and concomitant acid-mediated cleavage of the MOM ether and *N*-Boc group delivered (–)-cepharatine A (**109**) in 78% yield. Cepharatine A was readily converted to (–)-cepharatine C (**110**) under mildly acidic reaction conditions.

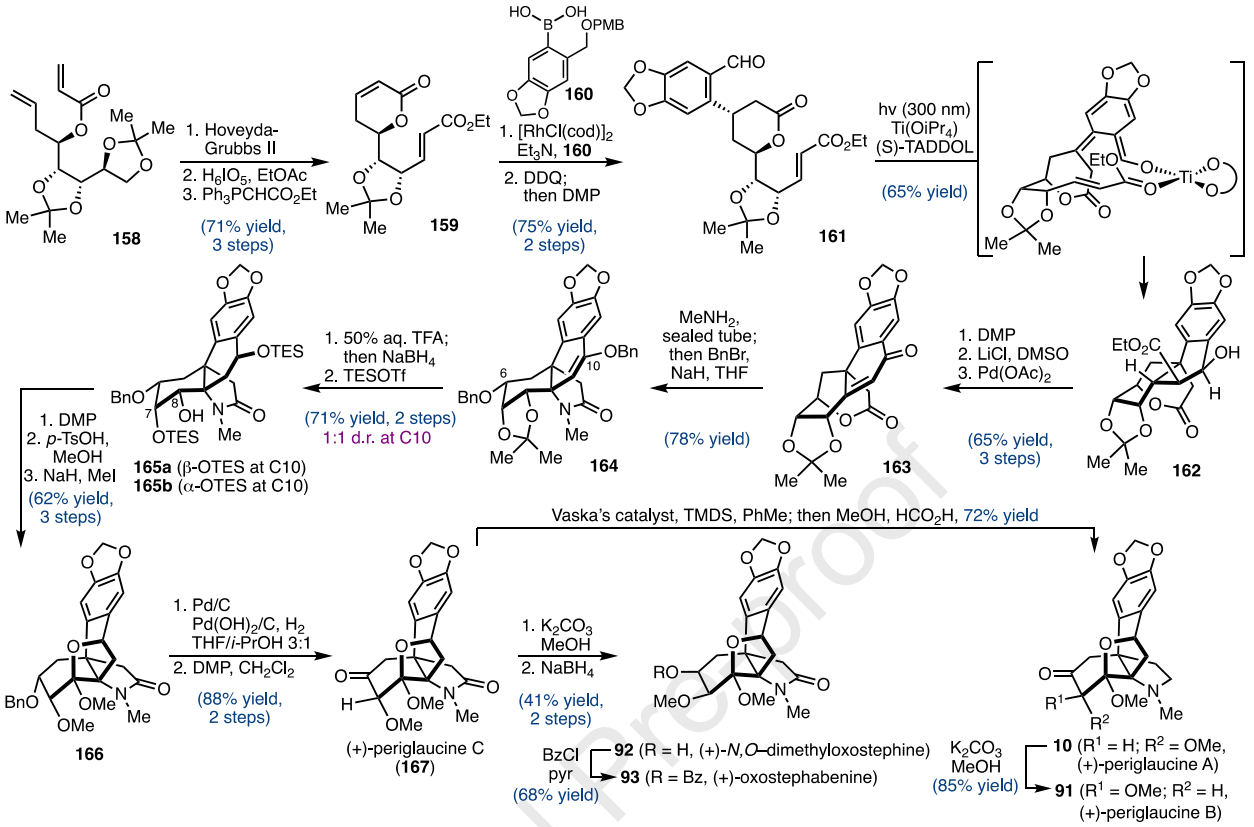
The first enantioselective synthesis of (+)-stephadiamine (**127**) was achieved by Nagasawa and coworkers in 2021.[53] As part of their synthetic strategy, Nagasawa's team relies on formation of the stereogenic C13-N bond via an aza-benzylic acid-type rearrangement of (–)-metaphanine (**8**), a reaction that the authors propose as a plausible biosynthetic pathway to **127** (Scheme 21). Beginning with TMS-protected cyanohydrin **146**, LiHMDS-mediated alkylation with mesylate **147** and desilylation afforded aryl ketone **148**. Sodium borohydride reduction of the aryl ketone delivered the corresponding alcohol, which was subjected to an NHC-catalyzed acylative kinetic resolution to give enantioenriched **151** in 39% yield and 99% ee. Importantly, the undesired acylated alcohol (**150**) could be recycled through this protocol via a base-mediated deacylation and oxidation to regenerate **148**. In five additional steps, alcohol **151** was converted to phenol **152**, an intermediate found to undergo a PIDA-mediated intramolecular oxidative phenolic coupling to furnish tricycle **153** in 34% yield as a single diastereomer.



Scheme 21. Nagasawa's Bioinspired Total Synthesis of (+)–Stephadiamine (**127**).

To install the requisite pyrrolidine ring, aryl bromide **153** was subjected to Pd-catalyzed hydrodebromination followed by an intramolecular aza-Michael addition, delivering propellane **154** in 58% yield and in 7.3:1 rr. Interestingly, the use of KO*t*-Bu in THF/HMPA was uniquely effective in promoting regioselective addition to the more substituted enone; acidic and other basic conditions skewed the product ratio toward the undesired regioisomer. Enone **154** was oxidized to α-hydroxy ketone **156** using Davis oxaziridine *rac*-**155**, and subsequent DMP-mediated oxidation and silyl ether cleavage triggered formation of hemiacetal **157**. Hydrogenation of the enone olefin, removal of the Boc group, and reductive methylation afforded (–)–metaphanine (**8**) in 36% yield over 3 steps, thereby setting the stage to evaluate the proposed aza-benzylic acid rearrangement. In the event, exposure of **8** to ammonia in methanol promoted the formation of (+)–stephadiamine (**127**) in excellent yield, a reaction that is postulated to proceed via the intermediacy of the C7 imine.

The following year, Gao and coworkers disclosed their synthetic approach to access a variety of hasubanans, including periglaucines A-C, *N*,*O*-dimethyloxostephine, and oxostephabenine (Scheme 22).[54] Beginning with *L*-ribose-derived diene **158**, ring-closing metathesis delivered the corresponding lactone, which then underwent chemoselective acetonide deprotection, oxidative cleavage with periodic acid and Wittig olefination to afford ester **159**. A diastereoselective conjugate addition of arylboronic acid **160** was achieved via a Rh-catalyzed Hiyashi-Miyaura reaction, and subsequent deprotection and oxidation of the benzyl ether delivered aldehyde **161** in 75% yield over 2 steps. After significant optimization, the authors found that irradiation of **161** with UV light in the presence of Ti(O*i*Pr)$_4$ and (S)-TADDOL promotes a tandem photoenolization/intramolecular Diels-Alder (PEDA) reaction to give **162** in 65% yield. Notably, this key transformation simultaneously installs the C and D rings of the hasubanan framework in a single step. Alcohol **162** was elaborated in 3 steps to enone **163**, an intermediate found to undergo a methylamine-mediated aminolysis of the lactone and subsequent intramolecular conjugate addition of the resulting amide. Aza-propellane **164** was accessible in 78% yield after in situ benzylation of the C6 hydroxyl group and trapping of the ketone as its enol ether.

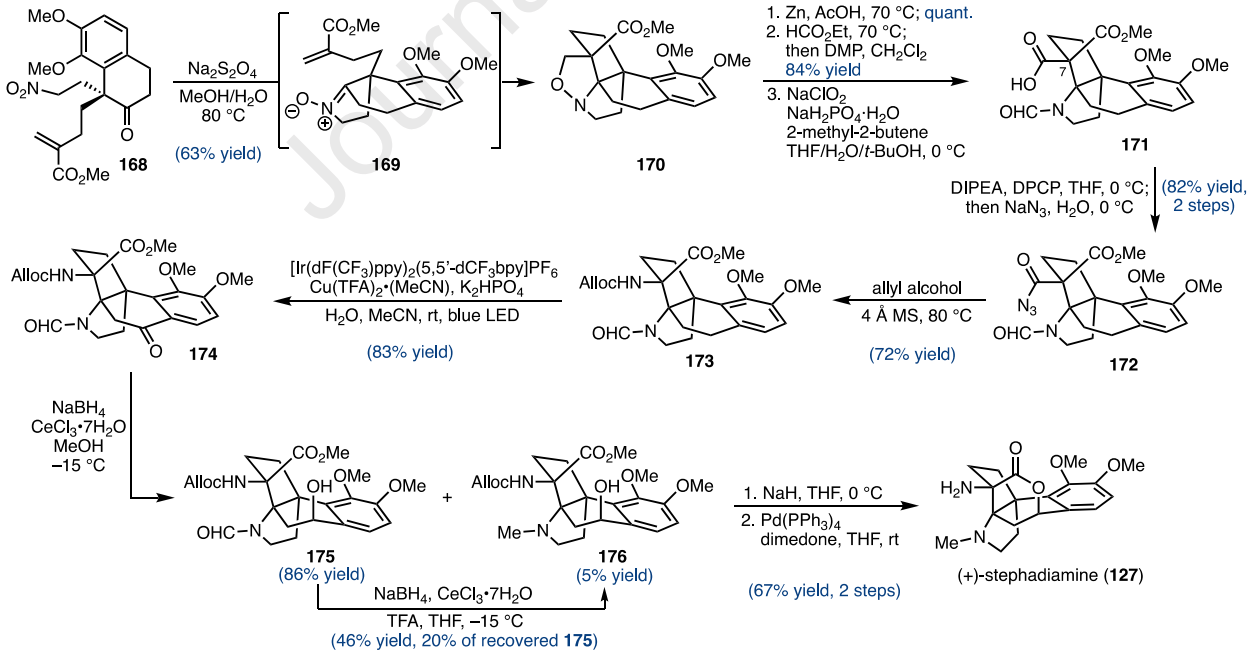


Scheme 22. Gao's asymmetric total synthesis of periglaucines A-C, *N,O*-dimethyloxostephine, and oxostephabenine.

Having established access to a functionalized aza-propellane intermediate, the authors were poised to access several highly oxidized hasubanan congeners. To this end, exposure of **164** to aqueous TFA promoted hydrolysis of the enol ether and acetonide moieties, and reduction of the resulting ketone with $NaBH_4$ followed by treatment with TESOTf afforded **165a** and **165b** as a 1:1 mixture of C10 diastereomers. The requisite β-epimer (**165a**) was elaborated to oxo-bridged intermediate **166** following oxidation of the C8 alcohol, global desilylation and acid-catalyzed methyl ketal formation, and base-mediated methylation of the C7 alcohol. Hydrogenolysis of the benzyl ether and subsequent DMP-mediated oxidation afforded (+)–periglaucine C (**167**) in 88% yield over 2 steps. Epimerization of the α-methoxy ketone and diastereoselective ketone reduction

afforded (+)-*N*,*O*-dimethyloxostephine **92**, a hasubanan alkaloid that was readily converted to benzoylated derivative (+)-oxostephabenine (**93**). Alternatively, catalytic reduction of the lactam in **167** using Vaska's complex and TMDS delivered periglaucine A (**10**) in 72% yield, and subsequent isomerization of its C7 methoxy group furnished periglaucine B (**91**).

Zhu's team leveraged the success of their previous synthesis of hasubanan alkaloids to facilitate an enantioselective total synthesis of (+)–stephadiamine (**127**, Scheme 23).[55] Specifically, enantioenriched β-tetralone derivative **168** was accessible from its corresponding naphthol using a thiourea-catalyzed asymmetric dearomative Michael addition.[51] Exposure of **168** to sodium dithionite facilitated the chemoselective reduction of the γ-nitro ketone to nitrone **169**, which engages the pendant olefin in a highly regio- and stereoselective [3+2] cycloaddition reaction. Notably, this transformation affords pentacycle **170** in 63% yield as a single diastereomer, and installs 2 vicinal quaternary stereocenters in a single step.



Scheme 23. Zhu's enantioselective total synthesis of (+)–stephadiamine (**127**).

With aza-propellane **170** in hand, introduction of the C7 amine was pursued via reductive cleavage of the *N*,*O*-bond, *N*-formylation, and sequential oxidation of the hydroxymethyl group to the corresponding carboxylic acid (**171**). The acid was converted to acyl azide **172**, which underwent a Curtius rearrangement in the presence of allyl alcohol to deliver Alloc-protected amine **173** in good yield. At this point, completion of the synthesis required a benzylic oxidation to construct the requisite lactone. While several oxidants failed to promote this transformation, the authors found that treatment of **173** under photocatalytic benzylic C–H alkoxylation conditions enabled the formation of ketone **174** in good yield. Diastereoselective reduction of the ketone under Luche conditions ($NaBH_4$, $CeCl_3$•$7H_2O$, MeOH) delivered alcohol **175** in 86% yield as a single diastereomer as well as overreduction product **176** in ~5% yield. Interestingly, chemoselective reduction of the *N*-formyl group was achieved by subjecting **175** to sodium borohydride in THF in the presence of $CeCl_3$•$7H_2O$ and TFA. Finally, lactonization of the hydroxy ester was promoted under basic conditions, and deallylation of the resulting lactone delivered **127** in 67% yield over 2 steps.

2. The Acutumine Alkaloids

2.1 Introduction

A second collection of alkaloids that exhibit an azapropellane structural framework is exemplified by acutumine (**178**, Figure 2). In contrast to its hasubanan counterparts, acutumine bears a [4.3.3] propellane backbone adorned with a spirocyclic cyclopentenone moiety. Embedded within this densely functionalized molecule are five contiguous stereocenters, two of which are all-carbon quaternary centers. Additionally, one of the stereogenic carbons bears a neopentyl chloride. Since the original structural elucidation of **178** in the late 1960s, a total of 15 related

alkaloids have been identified to date, which possess slight variations in their oxidation states and peripheral structure (see Figure 2).

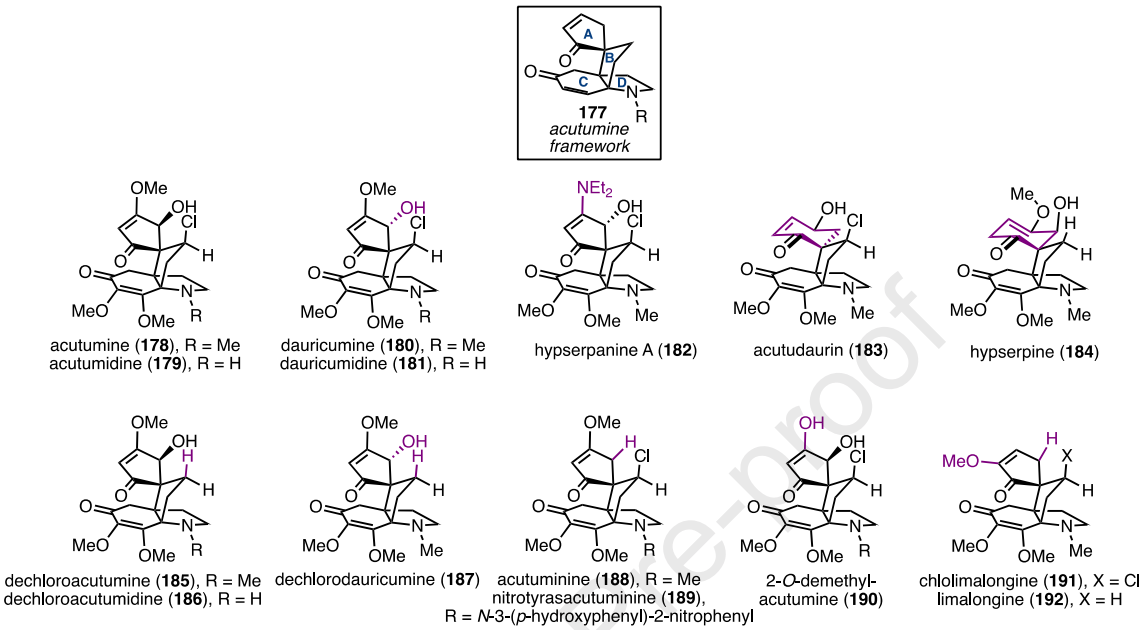


Figure 2. The acutumine alkaloids.

In addition to its unique structural architecture, acutumine has been found to exhibit distinctive medicinal properties, including selective T-cell cytotoxicity[56] and antiamnesic properties.[57] More recently, dauricumidine (**181**) was found to display modest cytoxicity against a hepatitis B virus-transfected cell line.[58] Not surprisingly, these structural and biological properties have attracted considerable attention from the synthetic community. This section is intended to present a brief introduction to acutumine, beginning with its isolation, characterization, and potential biosynthetic origins. This background will lead into a discussion of the synthetic approaches toward this challenging target.

2.2 Isolation

In 1929, Goto and Sudzuki reported the isolation of acutumine from *Sinomenium acutum*, a climbing plant of the *Menispermaceae* family.[59] However, its molecular formula was misassigned

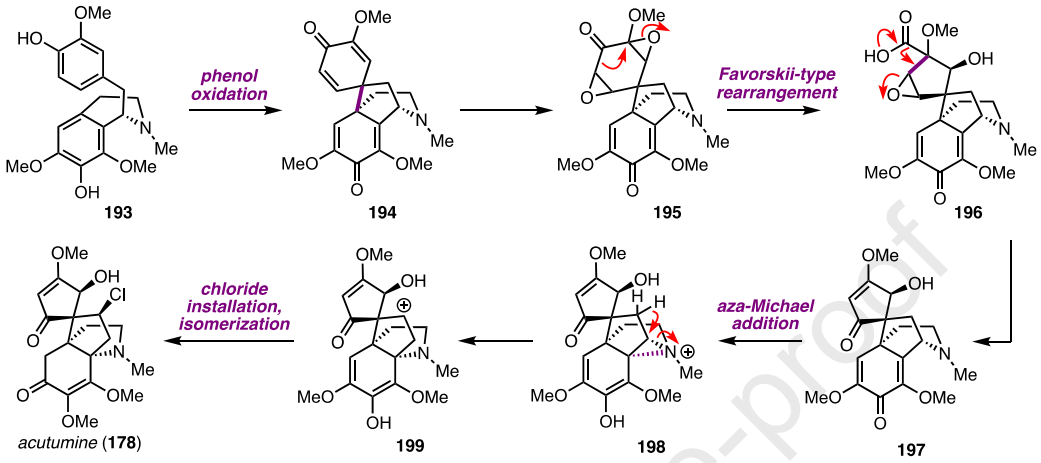
as $C_{20}H_{27}NO_8$. Tomita and coworkers corrected it to $C_{19}H_{24}NO_6Cl$ in 1967, when they conducted an extensive spectroscopic and chemical analysis of the natural product.[60–62] In this series of studies, the authors also reported an X-ray crystal structure of acutumine (**178**) that confirmed the original structural assignment. The authors also elucidated the structure of acutumidine (**179**), a natural product that was isolated alongside **178**. In this case, *N*-methylation of **179** afforded acutumine, thereby validating the proposed structure of acutumidine.

Over two decades elapsed before other natural products bearing the acutumine framework began to emerge.[56,58,63–69] The new alkaloids were characterized by comparison of their spectral data to that of acutumine. These acutumine analogs mainly differ in the presence of a stereogenic C-Cl bond and the composition of the spirocyclic enone. These structural differences can be subtle—such as the epimeric relationship between acutumine (**178**) and dauricumine (**180**)—or more pronounced, as is the case with the cylcohexenone-bearing acutudaurin (**183**). These slight deviations from the common spirocycle-containing [4.4.3] propellane framework have led to queries regarding the biosynthetic origins of the acutumine alkaloids. These studies are discussed in detail below.

2.3 Biosynthesis

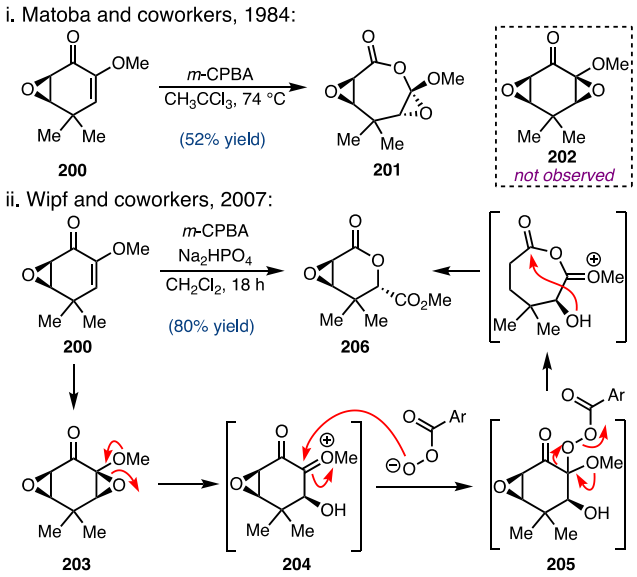
As part of their studies regarding the biosynthesis of several morphinan alkaloids, Barton and coworkers put forth a biosynthetic pathway for acutumine (Scheme 24).[70] The authors speculated that isoquinoline derivative **193** undergoes oxidative intramolecular phenol coupling to deliver spirocycle **194**. Sequential epoxidation of this intermediate provides bis-epoxide **195**, an intermediate proposed to undergo a Favorskii-type rearrangement to install the A ring of the natural product. Acid **196** can be elaborated to cyclopentenone **197** via a decarboxylative epoxide opening, followed by oxidation of the resulting diol. The propellane core is hypothesized to arise

from quinone **197** by nucleophilic attack of the pendant isoquinoline nitrogen, thereby furnishing aziridinium ion **198**. A 1,2-hydride shift could afford carbocation **199**, which upon nucleophilic attack by a chloride anion and D-ring isomerization can yield the natural product.



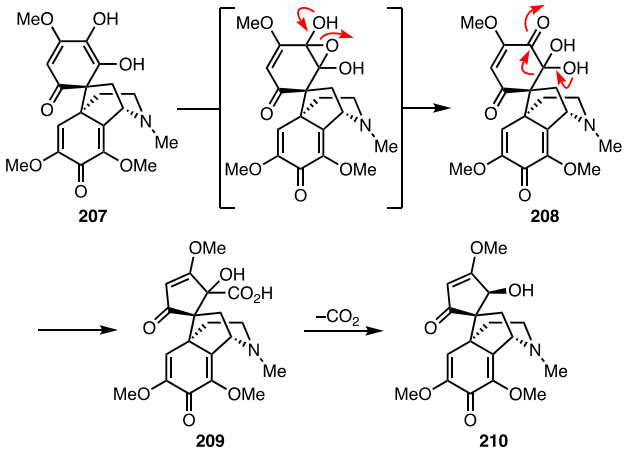
Scheme 24. Barton's proposed biosynthesis of the spirocyclic cyclopentenone.

While Barton's proposal offers intriguing biosynthetic transformations, the authors present limited experimental data to verify this potential route. To examine the feasibility of a Favorskii-type cyclopentenone formation, Matoba and coworkers set out to prepare and examine the reactivity of a simple model substrate, epoxide **200** (Scheme 25).[71] Exposure of epoxyenone **200** to *m*-CPBA in refluxing 1,1,1-trichloroethane delivered lactone **201** in 52% yield. Unfortunately, other attempts to prepare bisepoxide **202** from the corresponding dienone proved unfruitful. More recently, Wipf and coworkers were met with similar reactivity patterns. In their case, addition of **200** to a buffered solution of *m*-CPBA in CH_2Cl_2 only provided epoxylactone **206**.[72] The formation of **206** is speculated to arise from an initial epoxide opening of **203**, which generates oxocarbenium ion **204**. Peracid addition to this oxocarbenium ion delivers **205**, an intermediate hypothesized to undergo a Baeyer-Villiger ring expansion and translactonization reaction to form **206**.



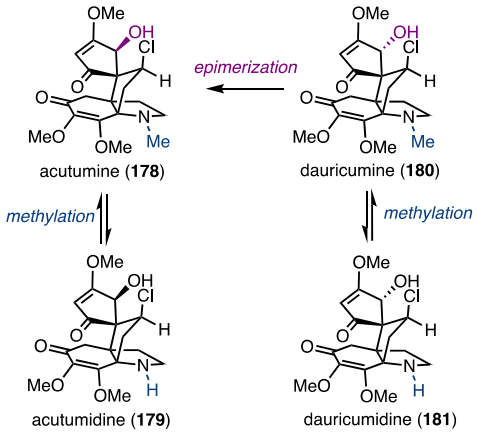
Scheme 25. Bisepoxidation studies by Matoba and Wipf.

Based on this unexpected reactivity, Wipf and coworkers put forth an alternative mechanism for the cyclopentenone biosynthesis. In this proposed route, epoxidation of dienol **207** initially yields ketone hydrate **208**, which is converted to **209** via a semipinacol-type rearrangement (Scheme 26). Decarboxylation of **209** is then thought to establish the cyclopentenone moiety of acutumine (i.e., **210**). Interestingly, the authors posit that the isolation of acutudaurin (**183**, see Figure 2), a potential acutumine alkaloid precursor, provides further evidence for their biosynthetic proposal.



Scheme 26. Wipf's biosynthetic proposal.

While the studies discussed above present plausible reaction pathways for acutumine biosynthesis, thorough biological investigations to probe these mechanistic possibilities are limited. In 1999, Sugimoto and coworkers conducted feeding experiments with ^{13}C-labeled tyrosine in *Menispermum dauricum* root culture, which demonstrated that two molecules of tyrosine are incorporated into acutumine.[73] The authors found that ^{3}H-labeled dechloroacutumine (**185**, see Figure 2) can be converted to acutumine (**178**) in vitro; however, only small quantities of ^{3}H-labeled **178** were isolated relative to the amount of of ^{3}H-labeled **185** taken up by the plant, suggesting that the conversion of **185** to **178** is a possible but not definitive biosynthetic pathway. Further evidence for this potential biosynthetic relationship was disclosed by Weng and coworkers, who discovered an Fe(II)-dependent and 2-oxoglutarate-depedent halogenase that efficiently catalyzes the conversion of (–)-dechloroacutumine (**185**) to (–)-acutumine (**178**).[74] To further investigate the potential interrelationship between the acutumine alkaloids, Sugimoto disclosed feeding experiments using ^{36}Cl-labeled **178–181** in *Menispermum dauricum* root cultures (Scheme 27).[67] These studies revealed a mutual interconversion between each pair of *N*-alkyl and *N*-H compounds (e.g., **178** and **179**, **180** and **181**). Moreover, the authors determined that dauricumine (**180**) could be epimerized to acutumine (**178**); however, the converse relationship was not observed. This collective data suggests that dauricumine (**180**) is a biogenetic precursor to **178**, **179**, and **181**.



Scheme 27. Potential interconversion between the acutumine alkaloids.

In spite of these biosynthetic investigations, there remain a number of aspects of the proposed pathway that need to be addressed. Although several parallels can be drawn between propellane formation of acutumine and the hasubanan alkaloids (see Section 1.3), mechanistic studies that probe this key transformation in the context of acutumine have not been reported. Moreover, chloride installation remains an elusive mechanistic query. Barton suggests nucleophilic attack by a chloride anion to be an operative mechanism; on the other hand, a wealth of literature data suggests that organochlorides are commonly bioengineered via electrophilic and radical chlorination reactions.[75] Further studies that carefully examine these potential biogenetic pathways will ultimately deepen our understanding of propellane alkaloid synthesis.

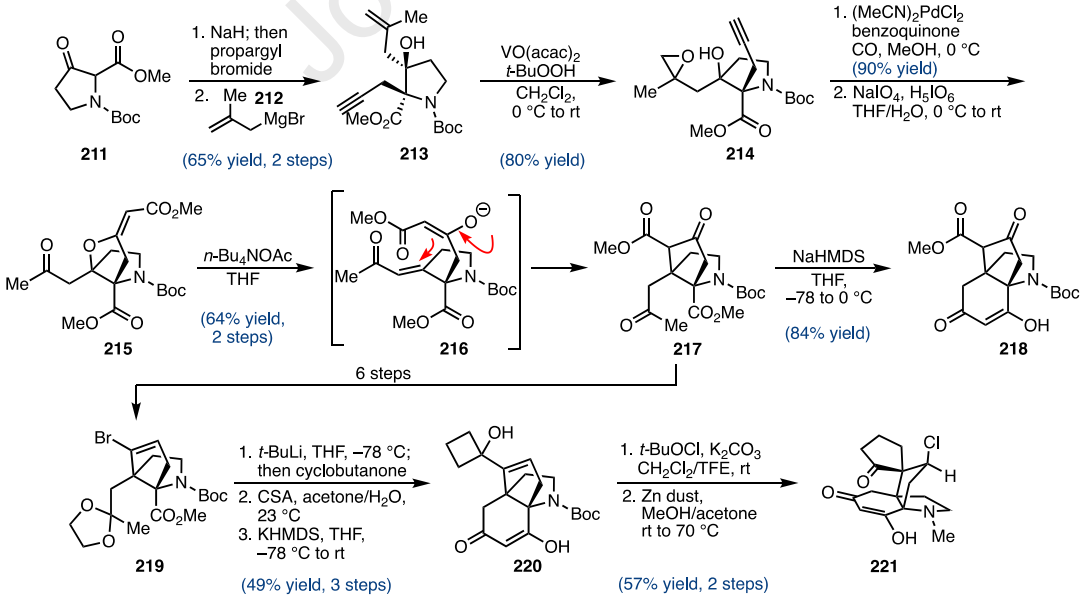
2.4 Previous Synthetic Studies

Despite the fact that its structure was elucidated over 50 years ago, acutumine remains a challenging target for total synthesis endeavors. Indeed, only two completed syntheses of acutumine have been reported to date. The discussion below showcases existing strategies toward the acutumine alkaloids, and focuses on the key transformations of each. Given the limited number of synthetic studies relative to the hasubanan alkaloids, the following section is structured to

highlight the innovative approaches that each research laboratory has devised to access this complex family of alkaloids.

2.4.1. Sorensen's Strategy

In 2007, Sorensen and Moreau reported their synthetic approach toward the acutumine framework. Specifically, the authors sought to harness the reactivity of enolates to construct the propellane framework (Scheme 28).[76] Readily available pyrrolidinone **211** was advanced to alkyne **213** following an enolate alkylation/Grignard addition reaction sequence. Exposure of **213** to $VO(acac)_2$ and *t*-BuOOH resulted in hydroxyl-directed epoxidation of the pendant olefin to deliver **214** in good yield. Palladium-catalyzed carbonylative cyclization of **214** afforded the corresponding vinylogous ester, which was subjected to periodate-mediated oxidation to generate ketone **215**. In a key step in their synthesis, the authors found that treatment of **215** with a mild base unveils enolate **216**, which rapidly engaged the α,β-unsaturated ketone moiety to afford β-ketoester **217**. The D ring of acutumine was then constructed by a Dieckmann cyclization, which yielded propellane **218** in 84% yield.



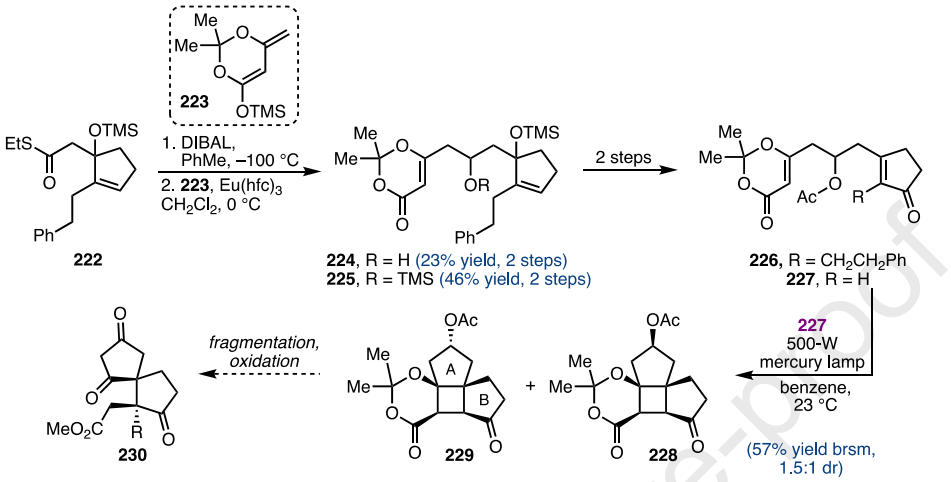
Scheme 28. Sorensen's approach to the acutumine framework.

As part of their efforts to efficiently install the spirocyclic cyclopentenone and neopentyl chloride, the authors investigated a chloronium-ion induced semi-pinacol rearrangement of cyclobutanol **220**.[77,78] To this end, diketone **217** was elaborated to vinyl bromide **219**, which was found to undergo lithium-halogen exchange and subsequent trapping of the organolithium with cyclobutanone. Deprotection of the ketal under acidic conditions followed by KHMDS-mediated Dieckmann condensation delivered tricycle **220** in 49% over 3 steps. In the event, treatment of **220** with excess *t*BuOCl in a 1:5 mixture of 2,2,2-trifluoroethanol/CH_2Cl_2 facilitated the desired semi-pinacol rearrangement, albeit with concomitant dichlorination of the A ring to afford a 1,3-diketone intermediate. Reduction of the geminal dichloride moiety with Zn dust furnished spirocycle **221** in 57% yield over 2 steps. Efforts to advance this and similar intermediates to the natural product have yet to be reported.

2.4.2. Kobayashi's Strategy

Shortly after Sorensen's preliminary reports, Kobayashi and Nguyen reported a synthetic approach to the acutumine framework that relies on a photochemical [2+2] cycloaddition to access its A/B-ring spirocycle (e.g., **230**, Scheme 29).[79] Evaluation of their strategy begins with thioester **222**, which was prepared in 7 steps from 3-phenylpropanal. Monoreduction of **222** with DIBAL followed by a $Eu(hfc)_3$-mediated addition of **223** to the intermediate aldehyde furnished a mixture of free- and silylated alcohols **224** and **225** in a combined 69% yield over 2 steps. Subsequent acetylation of this mixture and allylic transposition delivered [2+2] photocycloaddition precursor **226**. Unfortunately, irradiation of a solution of **226** in benzene with UV light (500-W mercury lamp) failed to promote cyclobutene formation. The authors speculated that the sterically congested nature of the anticipated cyclobutane product was precluding reactivity; therefore, enone **227** was prepared and evaluated. Photo [2+2] cycloaddition of **227** furnished cycloadducts

228 and **229** in 57% yield brsm as a 1.5:1 mixture of diastereomers. To the best of our knowledge, the fragmentation and oxidation of these cyclobutane intermediates to reveal the spirocyclic core of acutumine (e.g., **230**) has not been reported.



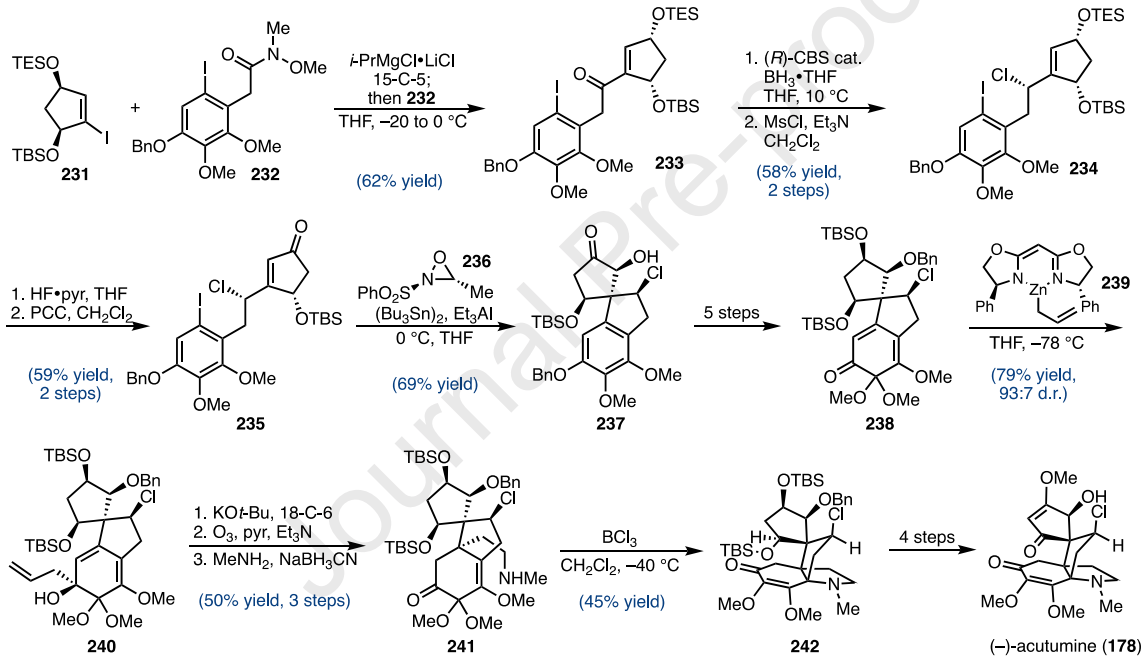
Scheme 29. Kobayashi's approach to the acutumine framework.

2.4.3 Castle's Strategy

The first total synthesis of (–)-acutumine (**178**) was accomplished by Castle and coworkers in 2009 (Scheme 30).[80] Their synthetic efforts commenced with Weinreb amide **232**, an intermediate that underwent nucleophilic addition by the Grignard reagent derived from vinyl iodide **231** to afford enone **233**. Selective 1,2-reduction of the ketone was effected using the Corey-Bakshi-Shibata (CBS) catalyst, and the resulting alcohol was treated with MsCl/Et_3N to furnish chloride **234** in 58% yield over two steps. Enone **235** was prepared from **234** via chemoselective cleavage of the TES group and subsequent oxidation of the free alcohol.

With access to **235**, the authors were poised to examine a radical-polar crossover reaction to install the 5,5-spirocycle of the natural product. After a screen of reaction parameters,[81] the desired transformation was effected by irradiation of $(Bu_3Sn)_2$/Et_3Al followed by addition of oxaziridine **236**, ultimately providing **237** in 69% yield. In an additional five steps, **237**

was elaborated to *o*-quinone monoketal **238**. Allylation of this intermediate with chiral allylzinc reagent **239** afforded alcohol **240** in good yield and excellent diastereoselectivity. At this stage, the ethylamine bridge was installed following a three-step sequence involving oxy-Cope rearrangement, ozonolysis of the resulting olefin, and reductive amination. Finally, the pyrrolidine ring of **178** was constructed by treatment of amine **241** with BCl_3, which provided propellane **242** in 45% yield. Additional functional group manipulations led to the synthesis of (–)-acutumine (**178**) in a total of 29 steps from commercially available starting materials.

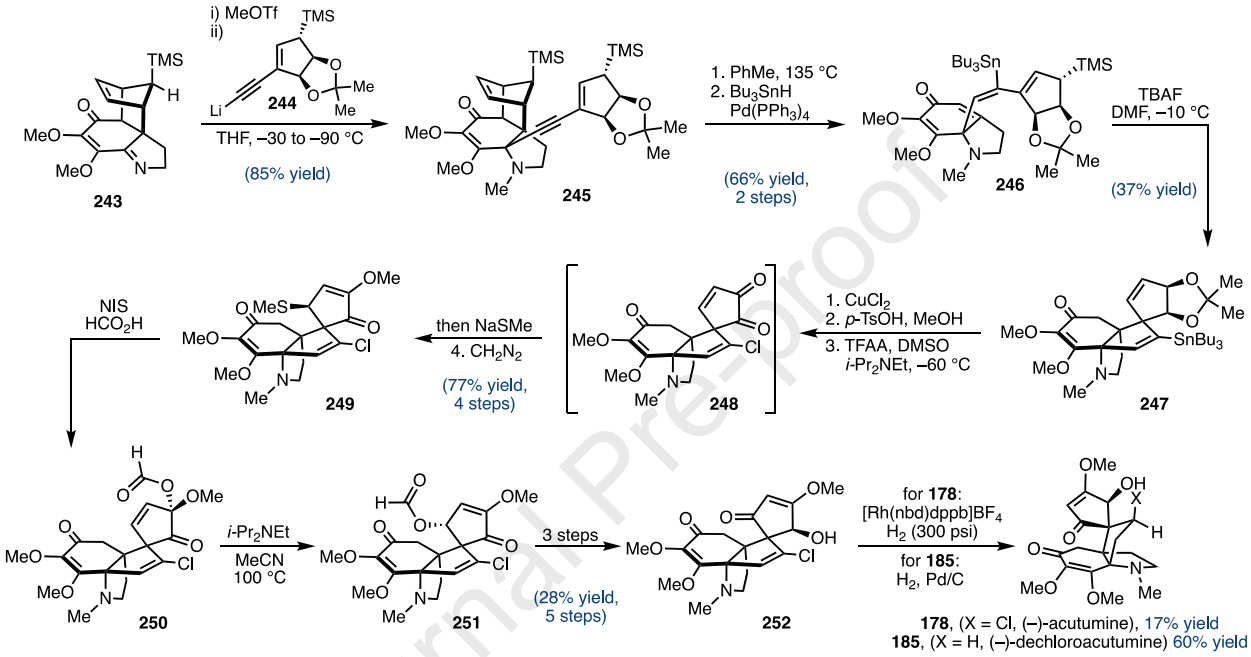


Scheme 30. Castle's total synthesis of (–)-acutumine.

2.4.4 Herzon's Strategy

The second enantioselective synthesis of (–)-acutumine (**178**) was disclosed by Herzon and coworkers in 2013.[45,82] In accord with their synthetic strategy toward the hasubanan alkaloids,[44] treatment of **243** with MeOTf followed by addition of organolithium **244** at –90 °C afforded 1,2-addition product **245** in 85% yield (Scheme 31). Thermal extrusion of 5-trimethylsilylcyclopentadiene and hydrostannylation of **245** delivered dienone **246**. Subsequently,

synthesis of the carbocyclic core of the natural product was achieved by treatment of **246** with TBAF in DMF at –10 °C. Although this key reaction furnished **247** in modest yield, the allylic silane nucleophile proved uniquely effective in this transformation, enabling the installation of both all-carbon quaternary stereocenters in a single step.



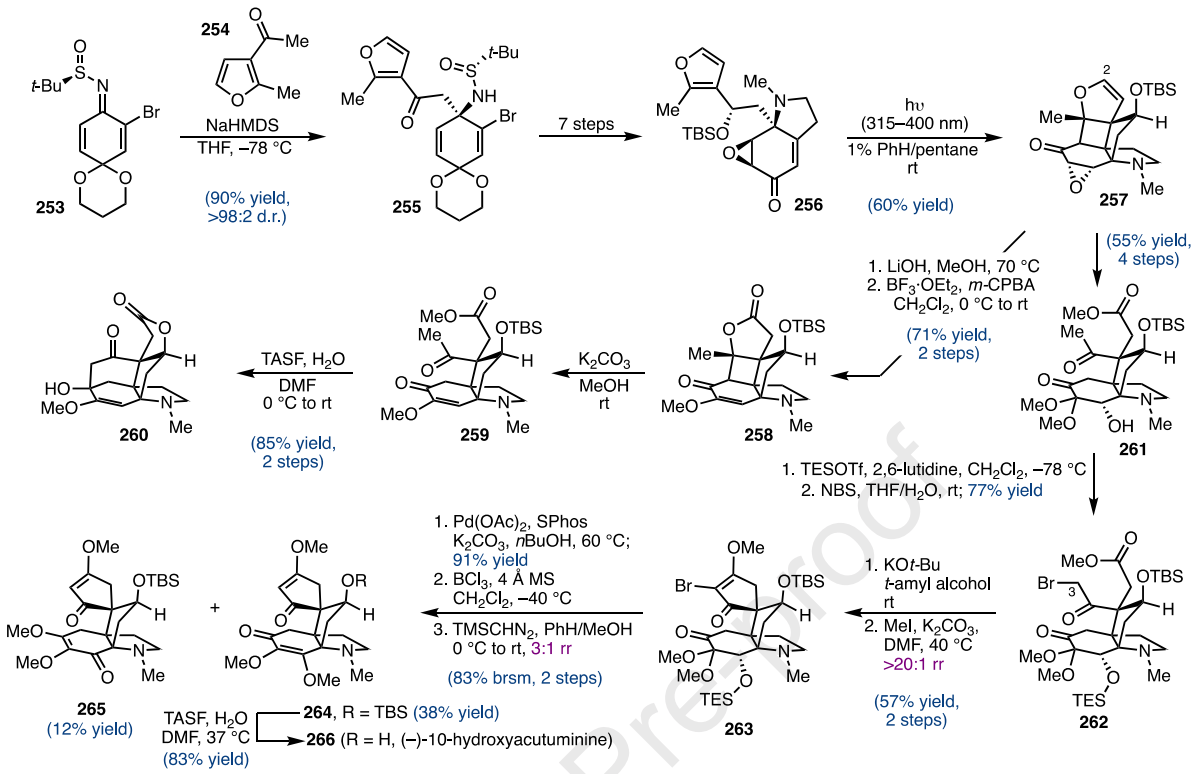
Scheme 31. Herzon's total synthesis of (–)-acutumine (**178**) and (–)-dechloroacutumine (**185**).

Completion of the synthesis required installation of the chloride and elaboration of the A-ring to the requisite cyclopentenone. Toward this goal, chlorodestannylation and acid-mediated acetonide cleavage afforded the corresponding diol, which was oxidized to diketone **248**. In situ trapping of **248** with sodium methanethiolate and treatment with diazomethane yielded methoxyenone **249**. Activation of the sulfide with *N*-iodosuccinimide in formic acid promoted the formation of mixed ketal **250**, an intermediate subjected to thermal [3,3] sigmatropic rearrangement conditions to deliver formate ester **251**. In three additional steps, the authors advanced this intermediate to spirocycle **252**, thereby setting the stage to evaluate a challenging metal-mediated reduction of the vinyl chloride. The authors found that subjection of **252** to

homogeneous hydrogenation conditions and stopping the reaction at low conversion proved critical to deliver (–)-acutumine (**178**) in 17% yield. Alternatively, **252** could be converted to (–)-dechloroacutumine (**185**) in 60% yield by exposure to heterogenous hydrogenation conditions (i.e., H_2 and Pd/C). Both **178** and **185** were accessible in 23 steps from commercially available reagents.

2.4.5 Reisman's Strategy

In 2022, Reisman and coworkers disclosed the application of their sulfinimine-based approach to the enantioselective synthesis of (–)-10-hydroxyacutuminine (**266**, Scheme 32), a synthetic alkaloid that was envisioned to serve as a precursor to (–)-acutuminine (**188**, see Figure 2).[83] Starting with sulfinimine **253**, 1,2-addition of the enolate derived from ketofuran **254** furnished sulfinamide **255** in 90% yield and excellent diastereoselectivity. In 7 additional steps, **255** was converted to epoxy enone **256** via a series of reactions including the diastereoselective reduction of the C7 ketone and pyrrolidine ring and epoxide formation using conditions adapted from the authors' work on the hasubanan alkaloids.[45] In a key step in the synthesis, exposure of **256** to UVA light facilitated intramolecular [2+2] cycloaddition to afford **257** in 60% yield, thereby installing the vicinal all-carbon quaternary stereocenters in a single step. Treatment of **257** with LiOH in MeOH at 70 °C facilitated epoxide-opening to generate the corresponding enol ether, and also resulted in addition of methanol to the dihydrofuran to afford a C2 methyl acetal. This reactivity was leveraged to promote C2 oxidation using $BF_3{\cdot}OEt_2$ and *m*-CPBA, delivering lactone **258** in 73% yield over 2 steps.



Scheme 32. Reisman's asymmetric synthesis of (–)-10-hydroxyacutuminine (**266**).

At this stage, a base-mediated retro-aldol fragmentation and subsequent Dieckmann condensation was anticipated to provide access to the requisite spirocyclic cyclopentenone. In the event, subjection of lactone **258** to K_2CO_3 in MeOH resulted in the desired retro-aldol fragmentation to furnish **259**. Interestingly, attempts to promote desilylation of **259** under basic conditions (e.g., TASF and H_2O in DMF) were accompanied by lactonization of the resulting alkoxide with the methyl ester and an intramolecular aldol reaction to deliver **260** in 85% yield. Efforts to promote a retro-aldol fragmentation of bridging ketone **260** and subsequent Dieckmann cyclization to forge the spirocycle were unsuccessful. The authors hypothesized that introduction of an electron-withdrawing substituent at C3 could help establish an equilibrium between **260** and its retro-aldol enolate, thereby giving the enolate an opportunity to engage the tethered lactone in the desired Dieckmann condensation. To test this hypothesis, propellane **257** was elaborated to

dimethyl ketal **261**, which underwent a 2-step α-bromination of the methyl ketone. Treatment of **262** to KO*t*-Bu in *t*-amyl alcohol promoted the desired spirocycle formation, delivering a vinylogous acid that was methylated with K_2CO_3 and MeI to furnish **263**. In 3 additional steps, **263** was converted to a 3:1 mixture of regiosiomeric enones **264** and **265**, respectively. The major regioisomer (**264**) was readily deprotected to afford (–)-10-hydroxyacutuminine (**266**); however, attempts to promote a late-stage chlorination of this intermediate to access (–)-acutuminine (**188**, see Figure 2) proved unsuccessful.

3. Conclusion

Nearly 60 years have elapsed since the first investigations of the biosynthesis and structure of the hasubanan and acutumine alkaloids were reported. These studies serve as a strong foundation that guides the range of innovative strategies that chemists have developed to access their densely functionalized aza-propellane core. The synthetic undertakings—from Ibuka's pioneering total syntheses in the 1960s to the more recent disclosure of asymmetric endeavors—highlight the tremendous progress that organic chemistry has made as a field, which has enabled new synthetic disconnections, modes of catalysis, and enantioselective transformations. Despite the significant progress discussed in this review, the hasubanan and acutumine alkaloids remain challenging and attractive targets for total chemical synthesis. Indeed, the enantioselective synthesis of the aza-propellanes have only begun to gain traction in the last 25 years, a timeframe during which many new members of this family of natural products have continued to emerge. As the number new bioactive hasubanan and acutumine alkaloids continues to grow, so too does chemists' interests in their biological properties and structural complexity. Consequently, there remains significant need for the continued development of novel and efficient approaches to access these complex alkaloids.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: