CHAPTER 1

An Introduction to the Hasubanan Alkaloids

1.1. Introduction

The hasubanan alkaloids comprise a large class 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.[1,2] Each of these compounds can be structurally characterized by the presence of a densely functionalized [4.4.3] propellane framework (**3**, Figure 1); and can be further organized based on the oxidation pattern that adorns their propellane core. For example, 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 stephabenine (**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.[1] 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.[3]

As a result of their unique molecular architecture and potential biological applications, the hasubanans have been the subject of numerous synthetic endeavors over the last 50 years. Herein, the diverse array of strategies employed to target their propellane framework are discussed. Preceding the discussion of these reports, a brief history of the hasubanan family of natural products is presented, including their isolation and biosynthetic origins.

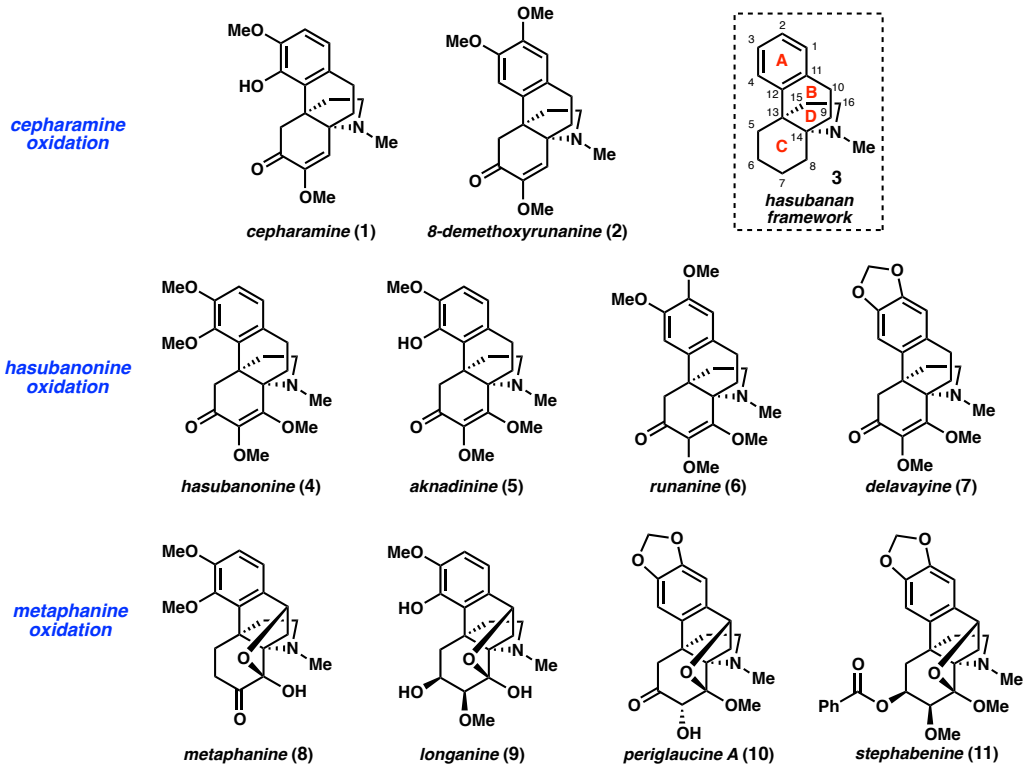

Figure 1. Representative members of the hasubanan alkaloids.

1.2. Isolation

In 1924, Kondo and coworkers described the isolation of metaphanine (**8**), an oxo-bridged hasubanan alkaloid.[4] Its structure was not elucidated until 1964, when Takeda and coworkers characterized the new compound by IR and 1D NMR spectroscopy, as well as a number of derivitazation studies.[5] Specifically, degradation of **8** under reducing conditions delivered anthracene derivative **12**, a structural motif observed to arise from the degradation of morphine alkaloids (Figure 2). In addition, sequential reduction of **8** afforded hasubanan **13**, a known compound whose enantiomer has been prepared from a codeinone intermediate. Using these structural techniques, Tomita and coworkers disclosed the structures of cepharamine (**1**)[6] and hasubanonine (**4**).[7] These structural

assignments were validated in 1968, when Kupchan and coworkers obtained an X-ray crystal structure of the brosylate derivative of aknadinine (**5**).[8] 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.[9] This type of fragmentation is characteristic of propellane alkaloids bearing the hasubanonine framework.[10] Taken together, these pioneering studies laid the foundation for the characterization of subsequently discovered hasubanan alkaloids.

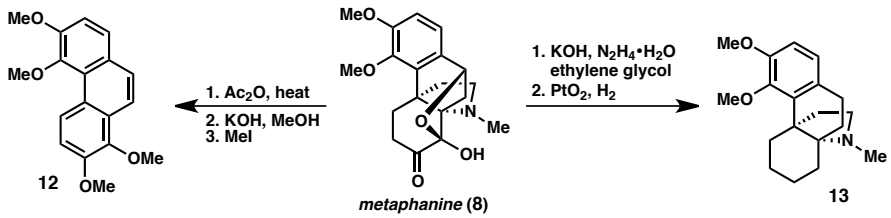

Figure 2. Structural elucidation of metaphanine (**8**).

In more recent years, a significant number of natural products comprising the metaphanine oxidation pattern have been discovered: over 20 oxo-bridged hasubanans have been reported in the last 10 years.[11] Interestingly, members of this subfamily of alkaloids are the only hasubanans found 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. While studies that probe the biological relationship of these alkaloids are

limited, elegant studies that shed light on their biosynthesis have been conducted and are presented below.

1.3. Biosynthesis

The structural similarities between the morphinan and hasubanan alkaloids have been exploited to examine the biosynthesis of hasubanonine. Specifically, it is known that morphine is derived from the coupling of two tyrosine building blocks, which initially generates an isoquinoline intermediate.[12] 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.[13] These investigations revealed that the hasubanan framework is indeed derived from two different tyrosine-based building blocks. Moreover, the authors concluded that the C ring of **5** originates from trioxygenated intermediate **14** (Figure 3). Importantly, the oxidation of tyrosine occurs prior to isoquinoline formation: a number of analogous mono- and dioxygenated isoquinolines were not incorporated into the natural product.

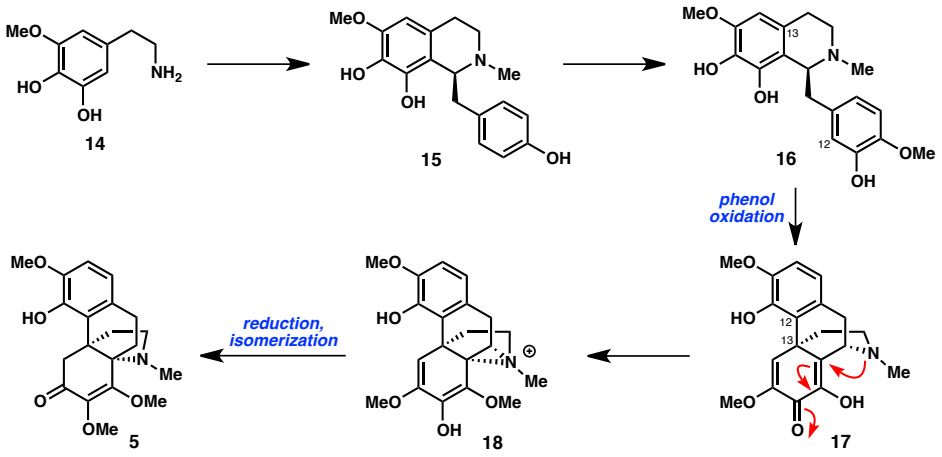

Figure 3. Proposed biosynthesis of the hasubanan alkaloids.

Based on these findings, **14** is believed to undergo a condensation reaction with a tyrosine derivative to deliver **15**, which upon oxidation affords **16**.[10] In analogy to morphinan biosynthesis, an intramolecular oxidative coupling between the C12-C13 carbons is believed to deliver piperidine **17**. At this point, the propellane backbone is hypothesized to 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**.

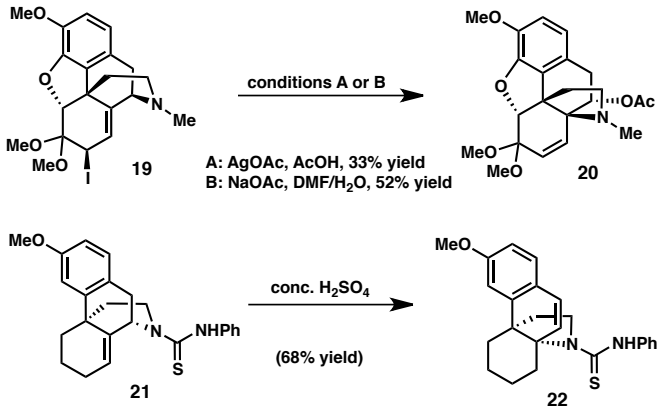

Figure 4. Conversion of morphinans to propellane intermediates.

Although the proposed skeletal rearrangement of **17** to **5** has not been validated with experimental data, 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 (Figure 4);[14] this reaction presumably proceeds 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.[15] 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 five decades, the hasubanan alkaloids have been the subject of numerous synthetic studies. While a number of racemic syntheses of the hasubanan core have been described, there exist few reports that details their enantioselective total synthesis. Nevertheless, these collective studies highlight the diverse array of strategies that can be implemented 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 synthetic studies toward the hasubanan framework, the most common relies on a late-stage intramolecular aminocyclization reaction 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.[16] Benzylic oxidation of sinomenine-derived alkaloid **23** gave ketone **24** after protecting group manipulations (Figure 5). Reductive cleavage of the C9-N bond of **24** with zinc dust, followed by exposure to 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 undergoes cyclization by the pendant amine to yield propellane **26**, albeit in poor yield.

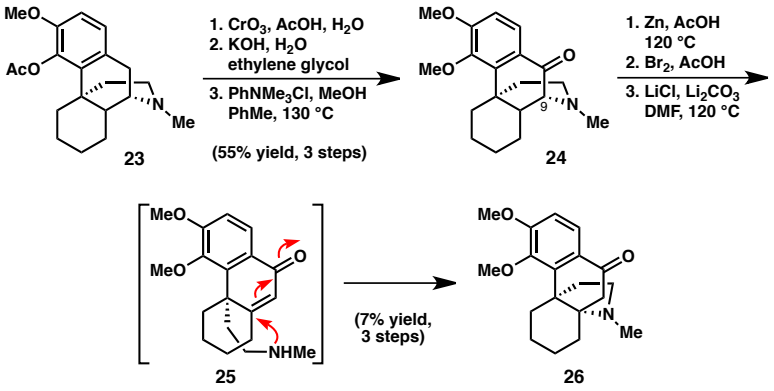

Figure 5. Synthesis of **26** from a sinomenine derivative.

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** (Figure 6).[17] 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 effected 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 the hydrobromide salt of propellane **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. Concomitant to the studies by Bristol-Myers, Shiotani and Kometani reported the direct aminocyclization reaction of amine **28**.[18] In the event, propellane **31** was obtained in 90% yield by exposure of **28** to paraformaldehyde and formic acid. Presumably, cyclization of the pendant amine occurs via the intermediacy of a C14 carbocation, and the resulting pyrrolidine can then undergo an Eschweiler-Clark methylation.[19]

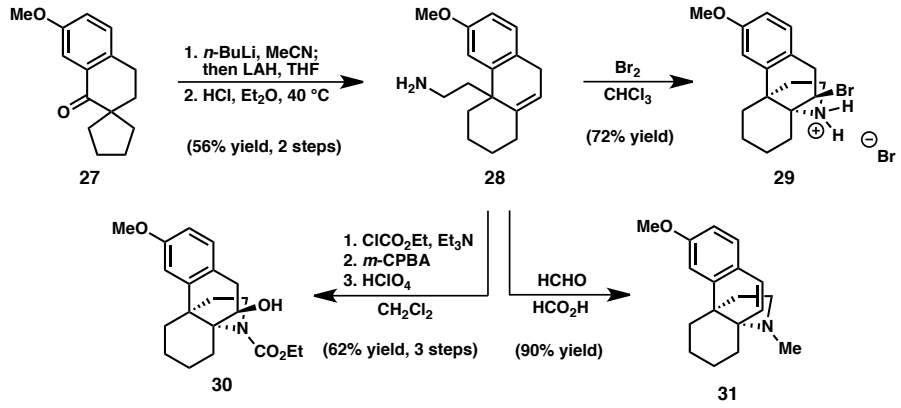

Figure 6. Bristol–Myers' and Kometani's aminocyclization approaches.

The most recent core synthesis involving an aminocyclization reaction stems from work by the Mulzer group. Their synthetic endeavors commenced with tricyclic enone **32**, which is available in 3 steps from commercially available 4-(3,4-dimethoxyphenyl)butyric acid (Figure 7).[20] Vinylcuprate addition to the enone yields olefin **33**, which in eight steps can be elaborated to azide **34**. To facilitate formation of the requisite pyrrolidine ring, a thermal (3+2) dipolar cycloaddition reaction of **34** was conducted to access triazene **35** in good yield. Decomposition of the triazene can then be achieved by heating **35** in refluxing pyridine to give propellane **36**.

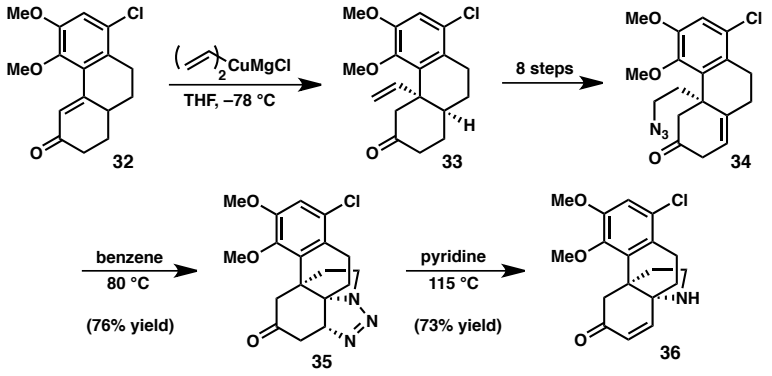

Figure 7. Mulzer's (3+2) cycloaddition approach to the propellane alkaloids.

Another 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 (Figure 8).[21,22] However, this reaction promotes the formation of **37** in only modest yield.[23] Evans observed in improvement in the yield of this reaction when methyl pentadienoate (**39**) was used as the electrophile, thereby furnishing **40** in 50% yield.[24]

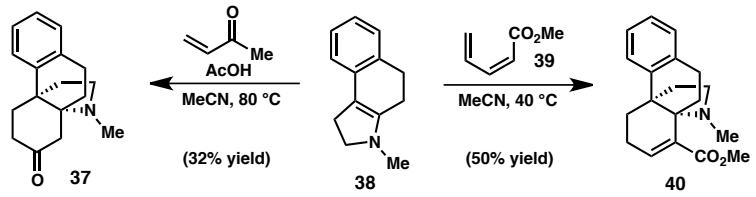

Figure 8. Preparation of the hasubanan core via enamine **38**.

The Hoffman-La Roche group devised an approach to the hasubanan framework starting from cyclohexanone derivative **41** (Figure 9).[25] 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 adds into the conjugated enone to produce *cis*-fused pyrrolidine **44**. Installation of the B ring is accomplished by an acid-mediated Friedel-Crafts reaction of the arene with the ester moiety of **44**, providing tetracycle **45** in 83% yield.

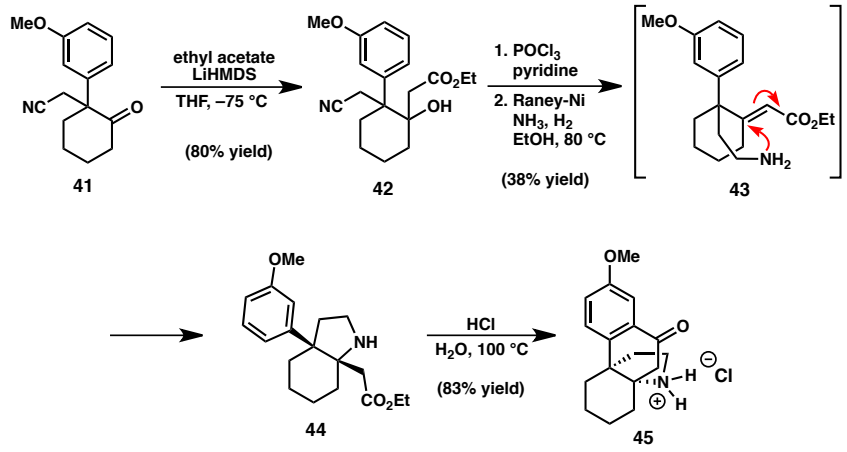

Figure 9. Synthesis of **45** from cyclohexanone **41**.

In contrast to the previously discussed core syntheses, the Kobayashi group pursued an approach that focused on a late-stage C-ring formation.[26] To this end, β–tetralone was readily converted to alcohol **46**, which upon Swern oxidation and cleavage of the Boc group generates unstable imine intermediate **47** (Figure 10). 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 acetic anhydride to afford tricycle **48**. Reduction of the nitrile functionality 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.

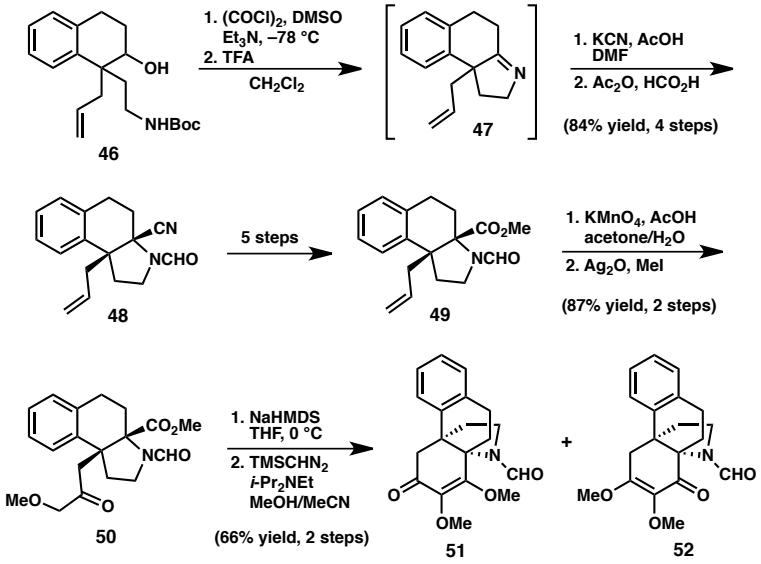

Figure 10. Kobayashi's synthesis of hasubanan congener **51**.

1.4.2. Total Syntheses

Shortly after the structure of hasubanonine was confirmed, Ibuka and coworkers embarked on a research campaign aimed at preparing a number of hasubanan alkaloids. Specifically, their synthetic strategy was highly dependent on the preparation and differential oxidation of propellane **56** (Figure 11). Beginning with tetralone derivative **53**, an interrupted Robinson annulation with methyl vinyl ketone furnished bridged ketone **54**.[27,28] 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 phenol **56**.

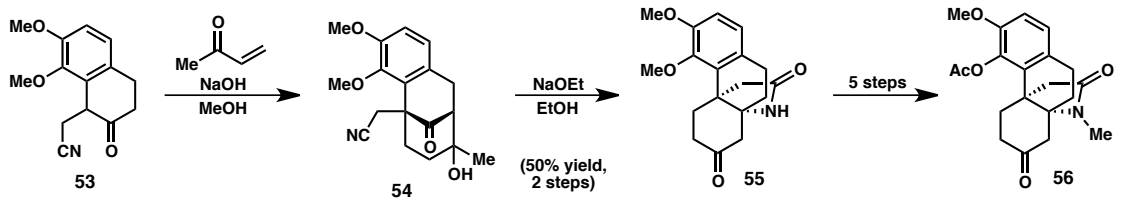

Figure 11. Ibuka's synthesis of tetracycle **56**.

With **56** in hand, the authors initially pursued a synthesis of cepharamine (**1**, Figure 12). Methoxy enone **57** was prepared from **56** via oxidation to the diketone followed by methylation with BF_3•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**) in low yield.[28] Alternatively, **56** could be elaborated to the hasubanonine oxidation pattern by an initial α-acetoxylation to give **58**.[29,30] A series of oxidative manipulations provided diketone **59**, an intermediate that was treated with diazomethane to give aknadilactam (**60**)[31] 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.[32,33] After an exhaustive screen of reducing conditions, the authors found reduction of the ketone with Al(O*i*-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 undergoes intramolecular ketalization after deprotection of the THP group to furnish oxo-bridged compound **63**. To complete the synthesis, the amide functionality of **63** was reduced utilizing Meerwein's salt and $NaBH_4$, and the ketal was hydrolyzed under acidic conditions.

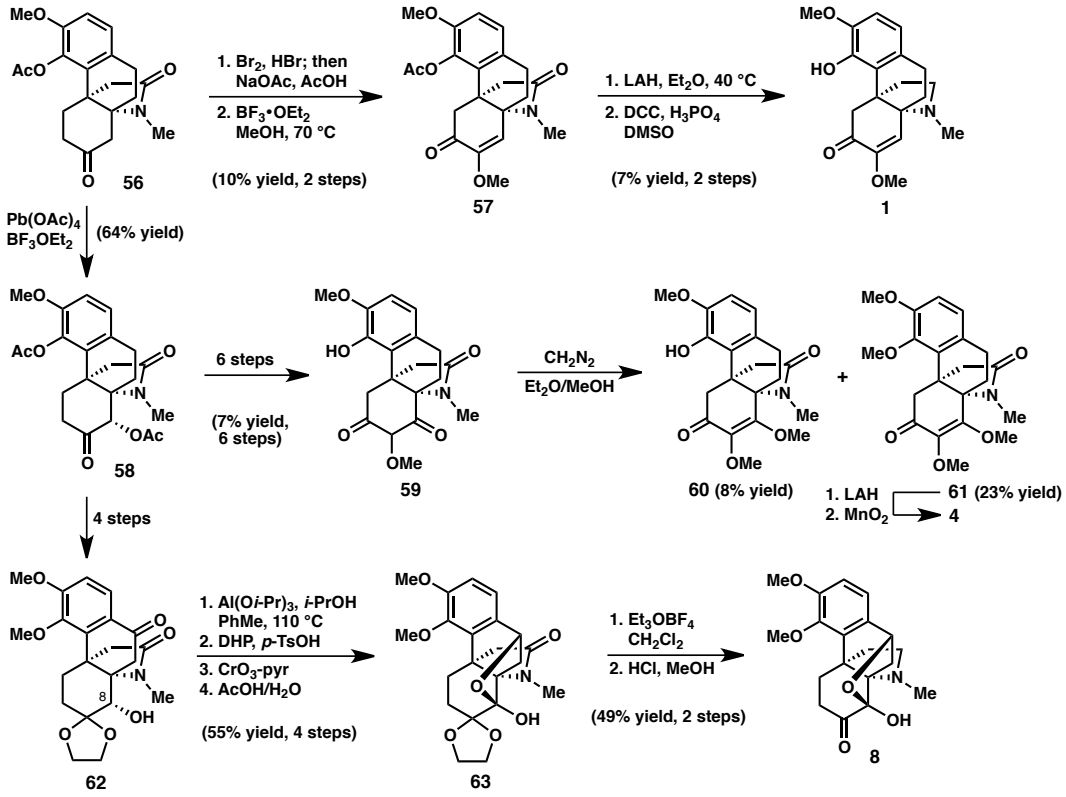

Figure 12. Ibuka's syntheses of hasubanan alkaloids.

Soon after the publication of Ibuka's studies, Kametani and coworkers reported their efforts toward capharamine (**1**, Figure 13).[34] In this biomimetic approach, the authors sought to construct the hasubanan backbone from simple isoquinoline precursors. To this end, reticuline-derived isoquinoline **64** was sequentially subjected to TFAA and Adam's

catalyst to access intermediate **65**. In the key step in their synthesis, 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 cyclization of the amine into 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.[35]

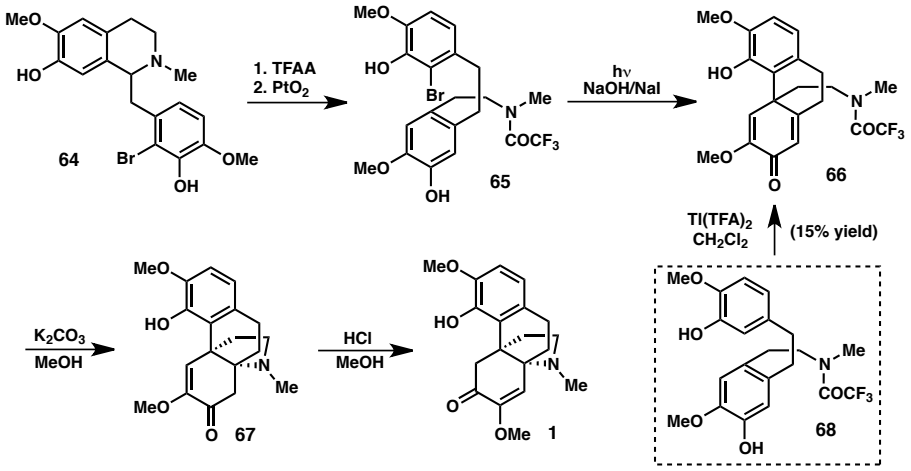

Figure 13. Kametani's preparation of cepharamine (**1**).

The synthetic endeavors of Ibuka and Kametani represented the sole completed syntheses of the hasubanans for over 20 years. Indeed, the subsequent total synthesis of a propellane alkaloid was not reported until 1998, when Schultz and Wang disclosed their preparation of (+)-cepharamine.[36] 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 (Figure 14). In an additional 6 steps, the authors could access lactone **72**. Exposure of **72** to AIBN and Bu_3SnH in refluxing benzene facilitated an intramolecular radical cyclization, thereby delivering hydrophenanthrene **73** after a few protecting group manipulations in 55% yield over 3 steps. Introduction of the amine was effected under a Hoffman rearrangement to give carbamate **74**, which upon LAH reduction unveils amide **75** and undergoes cyclization to furnish 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 represents the first enantioselective preparation of any member of the hasubanan alkaloids.

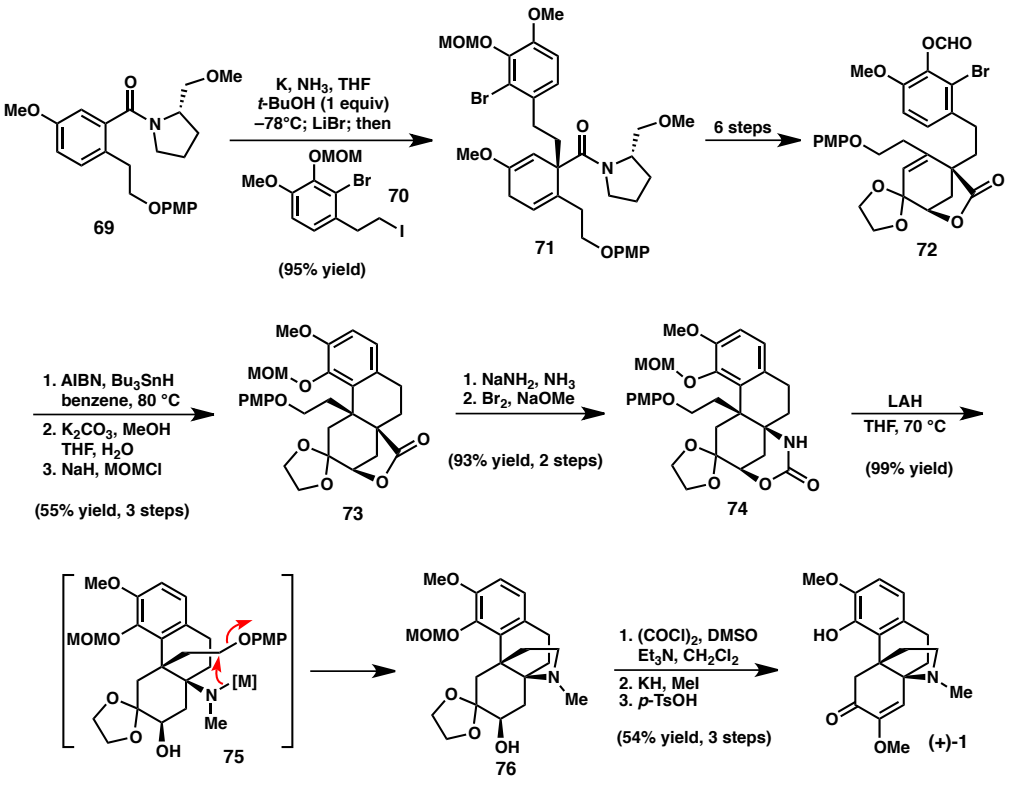

Figure 14. Schultz's enantioselective synthesis of (+)-cepharamine (**1**).

In 2011, Herzon and coworkers reported the development of a unified strategy for the enantioselective synthesis of several hasubanan alkaloids.[37] In contrast to Schultz's report, this synthetic approach relied on the enantioselective installation of the C14 stereocenter. To achieve this, an oxazaborolidine-catalyzed Diels-Alder reaction between quinone **77** and cyclopentadiene **78** afforded enedione **80** in 78% yield and 93% ee (Figure 15). Staudinger reduction of **80** then generated the corresponding quinone imine, which was activated toward nucleophilic attack by treatment with methyl triflate to give iminium salt **81**. Addition of an alkynyl lithium reagent (e.g., **82**) then gives pyrrolidine **83** in good yield. Using this 1,2-addition strategy, the authors can access an array of hasubanan frameworks by modifying the nature of the alkynyllithium nucleophile employed.

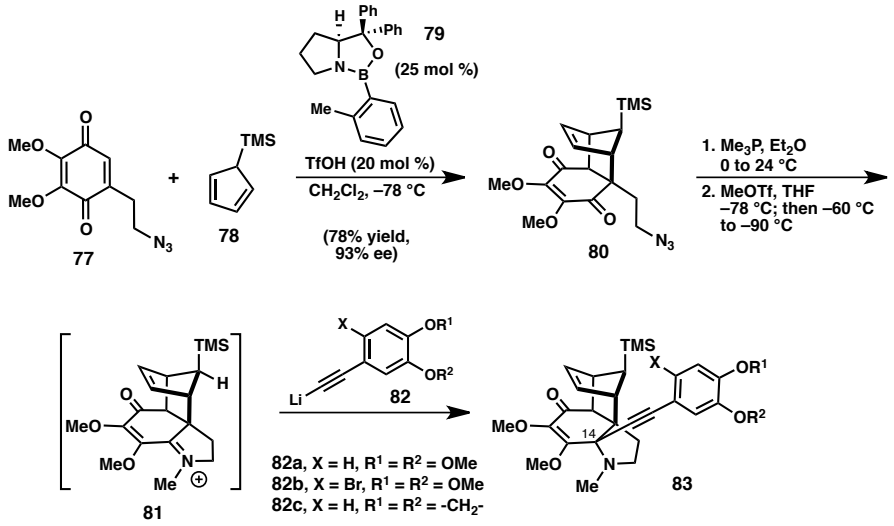

Figure 15. Herzon's general approach to the hasubanans.

To prepare (–)-runanine (**6**), addition of **82a** to iminium **81** afforded **83a** in 93% yield (Figure 16). Thermolysis of the cyclopentenyl group and monoreduction of the alkyne

with Crabtree's catalyst provides dienone **85**, an intermediate found to undergo a triflic acid-mediated intramolecular conjugate addition to give the propellane core. Finally, hydrogenation of the resulting olefin with Wilkinson's catalyst generates **6**. Using a similar reaction sequence, the authors could also access (–)-hasubanonine (**4**) and (–)-delavayine (**7**). Alternatively, hydration of alkene **89** with $Co(acac)_2$ under an atmosphere of oxygen followed by addition of formic acid gave periglaucine B (**90**) in 55% yield.

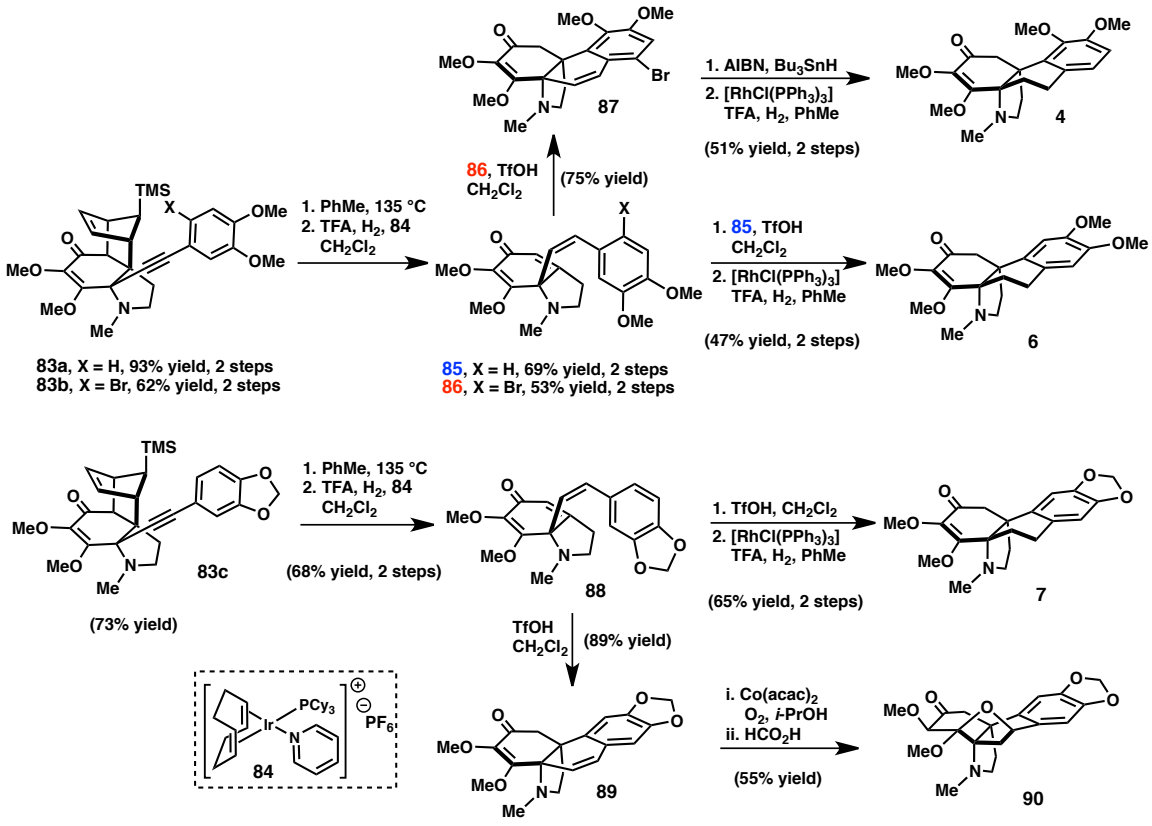

Figure 16. Herzon's synthesis of hasubanan alkaloids.

1.5. Concluding Remarks

Today, the hasubanan alkaloids remain an important family of biologically relevant natural products. Indeed, as the number of new hasubanans continue to grow, so too does

chemists' interest in their biological properties and structural complexity. The studies discussed above serve as a testament to this growing interest: a number of elegant approaches that target the hasubanan core have been developed, and enantioselective syntheses of their unique molecular architecture have begun to emerge. The further development of new, enantioselective approaches to the hasubanans will ultimately allow researchers to further characterize their biological properties, as well as contribute novel reactions for complex molecule synthesis.

1.6. References Cited

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