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Substrate-Modified Functional Group Reactivity: Hasubanan and Acutumine Alkaloid Syntheses

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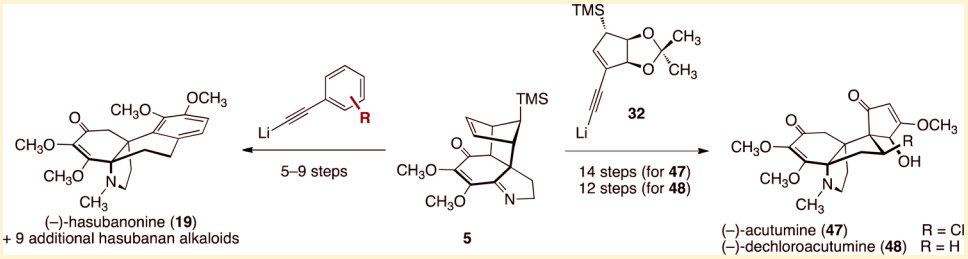

ABSTRACT: Functional group taxonomy provides a powerful conceptual framework to classify and predict the chemical reactivity of molecular structures. These principals are most effective in monofunctional settings, wherein individual functional groups can be analyzed without complications. In more complex settings, the predictive value of these analyses decreases as alternative reaction pathways, promoted by neighboring substituents and aggregate molecular properties, emerge. We refer to this phenomenon as substrate-modified functional group reactivity. In this Perspective, we explain how substrate-modified functional group reactivity molded our synthetic routes to the hasubanan and acutumine alkaloids. These investigations underscore the potential for discovery and insight that can only be gained by studying the reactivity of complex multifunctional structures.

I. INTRODUCTION

Our recent syntheses of the hasubanan and acutumine alkaloids[1−3] inspired the topic of this perspective: substrate-modified functional group reactivity. As with all synthetic endeavors, we developed sequences to the targets by an a priori analysis of starting materials, potential intermediates, and the established chemical reactivity principles of their functional groups.[4] However, when attempting to implement the proposed transformations on many of our substrates, we often encountered a breakdown in this functional group taxonomy. We refer to this disconnect, which will be apparent to many, as substrate-modified functional group reactivity. We argue that an accurate assessment of the reactivity of functional groups embedded in complex structures necessarily includes an understanding of (1) the molecules' chemical reactivity in aggregate and (2) its bulk physical properties. These modified assessments often depart considerably from simpler, first-order analyses. In our work, a deeper understanding of our advanced intermediates was essential to completing the routes. Importantly, synthetically useful intermediates, which were not anticipated at the outset, emerged from these studies, and these intermediates drove our synthetic planning in new directions. In this Perspective, we will use our unified synthetic route to the hasubanan and acutumine alkaloids to illustrate the concept of substrate-modified functional group reactivity.

II. BACKGROUND

The hasubanan alkaloids are a family of over 70 botanical metabolites.[5−8] The namesake member, (−)-hasubanonine (**19**), was first isolated from *Stephania japonica* in 1951;[9−11] these alkaloids possess a variety of biological properties, including antimicrobial,[12] antiviral (hepatitis B),[13] and opioid receptor binding activities.[14] The acutumine alkaloids are a smaller family, with 15 members currently known.[8] The foremost member, (−)-acutumine (**47**), was first isolated from *Menispermum dauricum* in 1929.[15−19] The acutumine alkaloids have been reported to possess antiviral (hepatitis B)[20] and memory-enhancing properties[21] and to selectively inhibit human T-cell proliferation.[22] The hasubanan alkaloids have received much attention from the synthetic community, with synthetic studies dating back to 1966.[23−43] Prior to our work, racemic syntheses of (±)-hasubanonine (**19**),[44,45] (±)-cepharamine (not shown),[46−48] and (±)-metaphanine (not shown),[49,50] and the enantioselective synthesis of (+)-cepharamine,[51] had been reported. Recently, syntheses of (−)-8-demethoxyrunanine (not shown), the related metabolites (−)-cepharatines A, C, and D (not shown),[52] and (±)-cepharatine A (not shown) were also completed.[53] In the acutumine family, several groups had reported approaches toward (−)-acutumine (**47**),[54−58] and a single completed route, by Castle and co-workers,[59−62] had been disclosed.

Our synthetic efforts culminated in syntheses of 10 hasubanan and two acutumine alkaloids, including the namesake alkaloids (−)-hasubanonine (**19**) and (−)-acutumine (**47**). We first reported syntheses of four hasubanan alkaloids (**19**, **22**, **30**, and **31**)[1] and later adapted our synthetic strategy to syntheses of the acutumine alkaloids **47** and **48**.[2] Recently,

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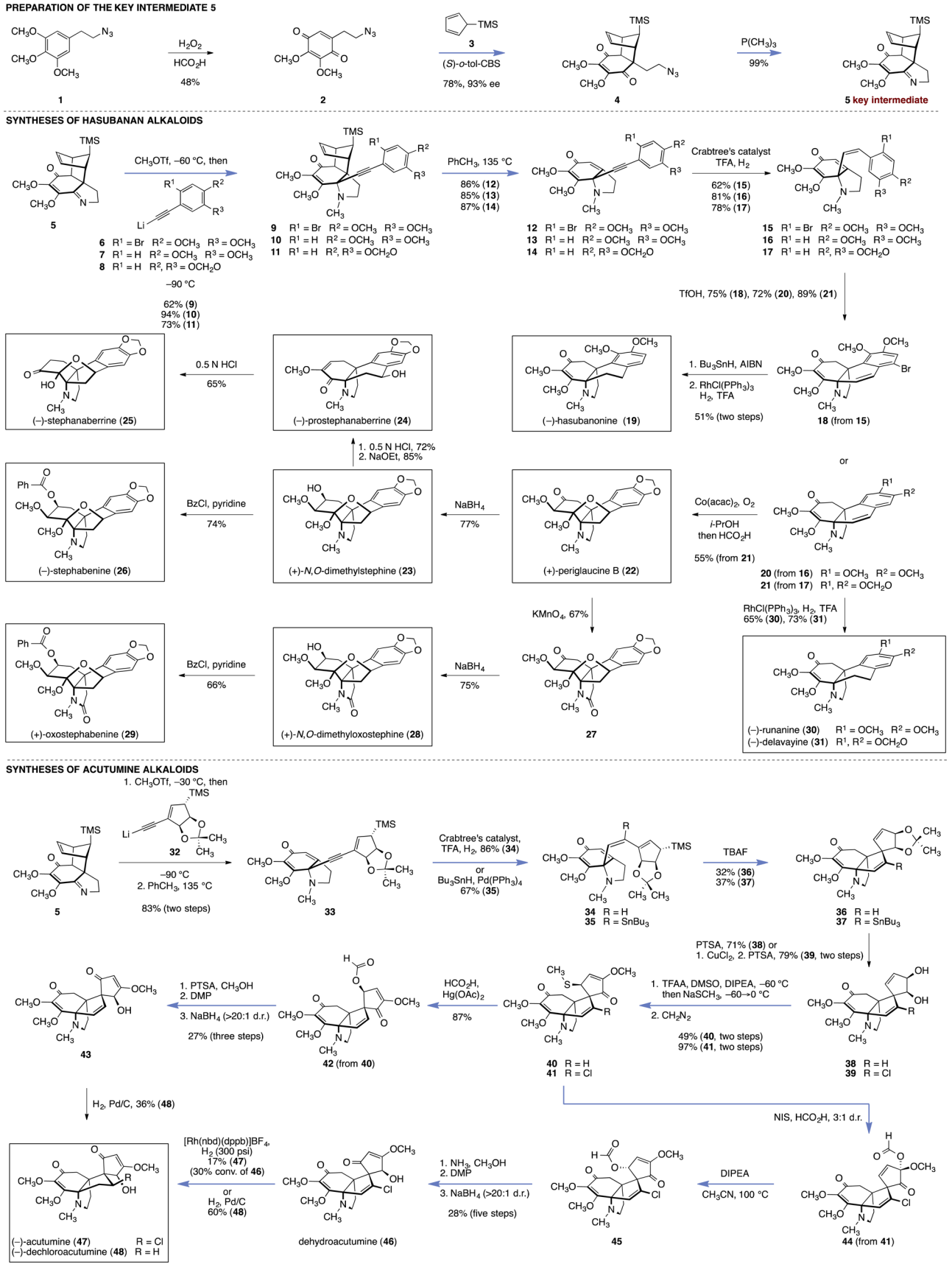

Figure 1. Summary of our unified synthetic route to the hasubanan and acutumine alkaloids. Blue arrows indicate examples of substrate-modified functional group reactivity.

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we described the syntheses of six additional hasubanan alkaloids (**23**–**26**, **28**, and **29**).[3] This latter manuscript also includes a full account of our work,[3] and so a detailed presentation is not duplicated here. We begin this Perspective by summarizing our approach and then highlight nine examples of substrate-modified functional group reactivity encountered in our studies. The insights gained from each structure, and the ways in which these insights modified our synthetic planning, will be presented.

III. OVERVIEW OF THE FINAL SYNTHETIC ROUTES

Our unified synthetic route to the hasubanan and acutumine alkaloids is shown in Figure 1. The blue arrows signify steps where substrate-modified functional group reactivity was encountered. Our route began with a three-step synthesis of the tetracyclic imine **5**, which is the universal precursor to all of the alkaloids. First, the aryl azide **1**[63] was oxidized (hydrogen peroxide, formic acid)[64] to form the quinone **2** (48%). Then, regio- and stereoselective Diels–Alder cycloaddition of the quinone **2** with 5-(trimethylsilyl)cyclopentadiene (**3**),[65] using the protonated form of the Corey–Bakshi–Shibata oxazaborolodine,[66−69] provided the *endo*-adduct **4** as a single diastereomer and regioisomer (78% yield, 93% ee). A Staudinger reduction–aza-Wittig (trimethylphosphine) reaction provided the tetracyclic imine **5** in quantitative yield.

In total, 10 hasubanan alkaloids were accessed from the tetracyclic imine **5** in five to nine steps and 7–32% overall yield. Since the two primary structural variations among the hasubanan alkaloids are the oxidation pattern and aryl substituents, each synthesis commenced with the addition of an aryl acetylide (**6**–**8**), containing the substitution pattern of the target, to the *N*-methyliminium ion derived from **5**. The acetylide addition products (**9**–**11**) were obtained as single diastereomers (surprisingly, addition occurred *syn* to the silylcyclopentene substituent; see ref 3 and below for a discussion). Retrocycloaddition of **9**–**11** was affected by mild thermolysis (toluene, 135 °C) to provide the dienones **12**–**14**. Semihydrogenation of **12**–**14** (Crabtree's catalyst)[70,71] provided the key *cis*-alkenes **15**–**17**, which underwent acid-mediated cyclization to form the tetracycles **18**, **20**, and **21**, respectively. A two-step sequence comprising debromination and hydrogenation transformed **18** to (−)-hasubanonine (**19**).[38,72] Hydrogenation of **20** and **21** (Wilkinson's catalyst) provided (−)-runanine (**30**)[73] and (−)-delavayine (**31**),[74−76] respectively. Hasubanan alkaloids of varying oxidation states were then accessed from the tetracycle **21**. Mukaiyama hydration[77] of **21**, followed by in situ acid-mediated cyclization, afforded (+)-periglaucine B (**22**),[13] which served as a precursor to six additional alkaloids (**23**–**26**, **28**, and **29**).[78−81]

At the initiation of our acutumine studies, we identified two major challenges in attempting to adapt our hasubanan route to these targets. The first involved construction of the two contiguous quaternary centers of the acutumine alkaloid skeleton. The second involved introduction of the secondary alkyl chloride of **47**. The initial steps of our acutumine alkaloid route mirror our hasubanan alkaloid pathway.

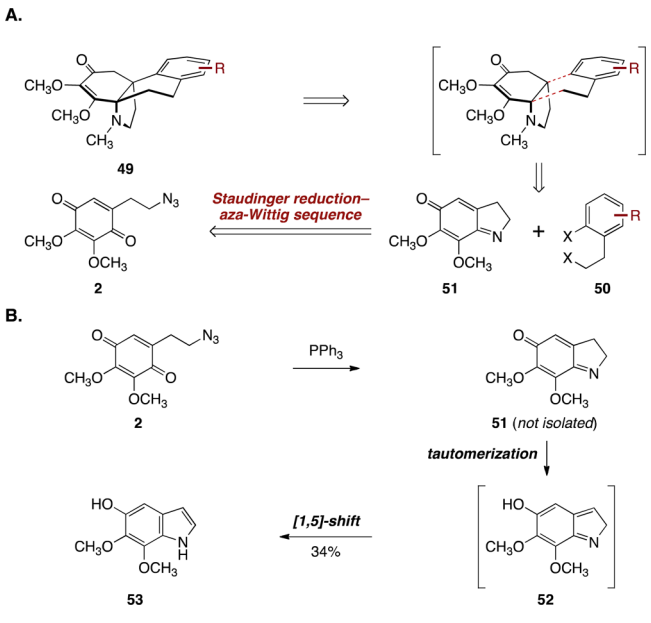
Addition of the acetylide **32** to the *N*-methyliminium ion derived from **5** provided an addition product (not shown) as a single diastereomer. Retrocycloaddition of the addition product afforded the dienone **33** (83%, two steps). At this juncture, two different alkyne addition reactions were investigated. Semihydrogenation of **33** with Crabtree's catalyst provided the *cis*-alkene **34** (86%), which is a potential precursor to (−)-dechloroacutumine (**48**). Alternatively, hydrostannylation of **33** formed the vinylstannane **35** (67%).[82] We envisioned that the stannyl group of **35** could serve as a precursor to the alkyl chloride of **47** by copper-mediated chlorodestannylation.[83] In a key step, the spirocyclic centers of the targets were constructed by a fluoride-promoted Hosomi–Sakurai cyclization of **34** and **35**,[84,85] which afforded the tetracycles **36** (32%) and **37** (37%), respectively. Acetonide deprotection of **36** revealed the diol **38** (71%). Chlorodestannylation of **37**, followed by acetonide cleavage, provided the diol **39** (79%, two steps). In advancing the diols **38** and **39**, many instances of substrate-modified functional group reactivity were encountered, including the reactions that transformed **38** and **39** to the corresponding formates **42** and **45** (vide infra). Parallel three-step sequences comprising formate cleavage, oxidation of the newly formed alcohol, and site- and stereoselective reduction converted the formates **42** and **45** to the final precursors **43** and **46**, respectively. Hetereogeneous hydrogenation of **43** and **46** (palladium on carbon) provided (−)-dechloroacutumine (**48**) in 36% and 60% yield, respectively.[86,87] Homogeneous hydrogenation of dehydroacutumine (**46**) ([Rh(nbd)(dppb)]-BF_4, 300 psi H_2) furnished (−)-acutumine (**47**, 17% yield of **47** at 30% conversion of **46**).[88−91]

In the sections that follow, we describe in detail each example of substrate-modified functional group reactivity we encountered en route to the targets.

IV. FORMATION OF THE TETRACYCLIC IMINE 56 AS A MEANS TO CIRCUMVENT A PROBLEMATIC AROMATIZATION PATHWAY

Our initial strategy targeted the iminoquinone **51** (Scheme 1A). We postulated that the iminoquinone **51** could be derived from the quinone **2** by azide reduction and condensation of the resulting amine (or iminophorphorane) with the vicinal ketone (Staudinger reduction–aza-Witting sequence). However, attempts to access the iminoquinone **51** by this approach were unsuccessful. For example, treatment of the quinone **2** with

Scheme 1. (A) Initial Synthetic Strategy Employing the Iminoquinone 51. (B) Attempted Synthesis of the Iminoquinone 51



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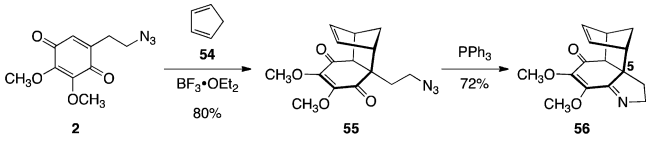
triphenylphosphine produced the hydroxyindole **53** (34%), in addition to unidentified decomposition products (Scheme 1B). We postulated that the hydroxyindole **53** was formed by an internal redox process involving tautomerization of **53** and 1,5-hydrogen atom shift.

Simple *p*-iminoquinones that are not linked through a fused five-membered ring are isolable.[92−94] The instability of **51** appeared to derive from the presence of a low energy pathway for aromatization. Indeed, this pathway has been exploited as a means to access highly substituted hydroxyindole derivatives.[95−98] We postulated that the first step in this pathway (tautomerization) could be blocked by the installation of a quaternary center within the six-membered ring of **51**. Accordingly, we targeted the tetracyclic imine **56**, in which a C-5 quaternary center is installed by a Diels−Alder cycloaddition between cyclopentadiene (**54**) and **2** (Scheme 2).[99−101] In the racemic series, the cycloaddition was efficiently

Scheme 2. Synthesis of the Tetracyclic Imine 56

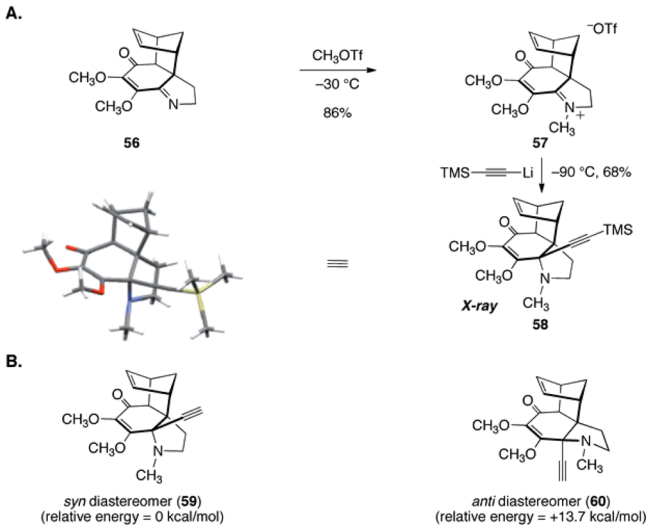


promoted by boron trifluoride etherate complex to provide the *endo*-adduct **55** as a single diastereomer and regioisomer (80%, ^{1}H NMR analysis). Treatment of **55** with triphenylphosphine initiated the Staudinger reduction−aza-Wittig sequence to provide the tetracyclic imine **56** (72%). The tetracyclic imine **56** was stable to acid−base extraction (to remove triphenylphosphine oxide) and purification by flash-column chromatography. Ultimately, further study of substrate-modified functional group reactivity of advanced intermediates would lead to replacement of the tetracyclic imine **56** with the silylcyclopentene tetracyclic imine **5** in the synthetic sequence (vide infra).

V. NUCLEOPHILIC ADDITION TO THE TETRACYCLIC IMINE 56: IMINE ACTIVATION AND UNANTICIPATED STEREOSELECTIVITY

Our synthetic strategy called for the addition of a nucleophile to the imine function of the tetracycle **56**. This is a challenging bond construction, as the imine is less electrophilic and more hindered than the carbonyl, and there is a possibility for 1,4-addition−elimination to the *β*-positions of the imine or carbonyl. Since the hasubanan and acutumine alkaloids contain an *N*-methyl substituent, we speculated that we could productively activate the imine toward 1,2-addition by *N*-methylation in situ. The iminium ion **57** was accessed by treatment of the tetracyclic imine **56** with methyl triflate (86%, Scheme 3A). This iminium ion was stable toward isolation and storage, which likely reflects the steric encumbrance about the imine carbon atom. After extensive investigation, we found that acetylide-based nucleophiles were uniquely suited in the 1,2-addition step. For example, addition of 2-lithio-1-(trimethylsilyl)acetylene at −90 °C afforded the addition product **58** as a single detectable diastereomer (68%, ^{1}H NMR analysis). Attempted addition of more reactive or bulky nucleophiles (enolates, alkyl Grignard reagents, or organocopper or zinc reagents) resulted in competitive addition to both the ketone and iminium functions, *N*-dealkylation, and

Scheme 3. (A) Synthesis and X-ray Analysis of the Acetylide Addition Product 58. (B) *Syn* and *Anti* Addition Products 59 and 60



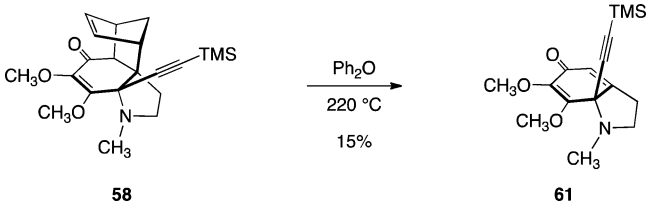
presumably, deprotonation of **57** to form an extended azomethine ylide.

X-ray analysis of the reaction product provided insights into the basis for these observations. Based on molecular models, we anticipated that the cyclopentene substituent of the iminium salt **57** would block nucleophilic addition to the top face to render the *anti* addition product (see structure **60**). To our surprise, the X-ray analysis of **58** revealed that the nucleophile had added *syn* to the cyclopentene substituent of the iminium ion **57**. We postulate that a developing eclipsing interaction between the *N*-methyl substituent and the adjacent methoxy group, as well as the strain associated with the *anti* addition to form the *anti*-6,5 ring fusion in **60**, may impede this pathway.[102,103] DFT calculations indicated that the *syn* diastereomer **59** is 13.7 kcal/mol more stable than the *anti* diastereomer **60** (Scheme 3B). Thus, while the cyclopentene substituent served to stabilize our intermediates, it also altered the reactivity in an unanticipated way by the introduction of conformational biasing elements not appreciated at the outset.

VI. RETROCYCLOADDITION OF THE ACETYLIDE ADDITION PRODUCTS 58 AND 62: A USEFUL RATE ACCELERATION FROM THE SILYLCYCLOPENTENE ADDUCTS

Late-stage removal of the cyclopentene fragment by retrocycloaddition was a necessary step when we adopted the cyclopentadiene blocking strategy. To probe the feasibility of this transformation, we studied the retrocycloaddition of the acetylide addition product **58** (Scheme 4). Thermolytic cleavage of the cyclopentene substituent required heating in

Scheme 4. Retrocycloaddition of the Addition Product 58



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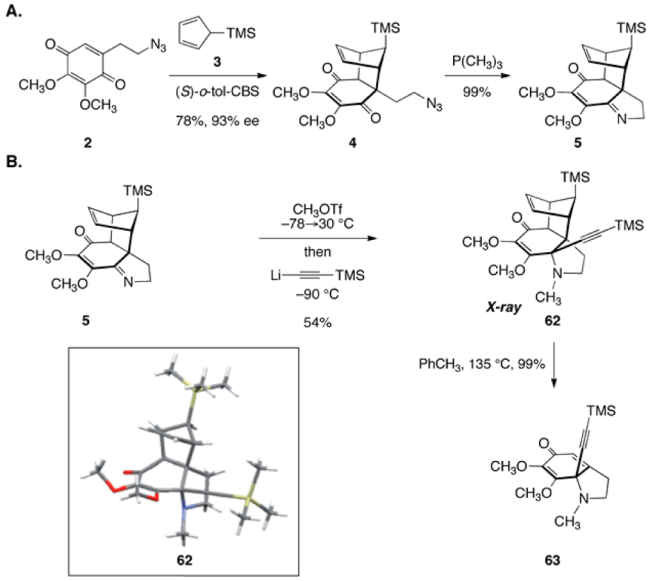
diphenyl ether at 220 °C. Under these conditions, extensive decomposition of both the starting material and product also occurred, and the retrocycloaddition product **61** was obtained in only 15% isolated yield. The high barrier for the retrocycloaddition was not surprising: in the installation of the cyclopentadiene substituent (**2** → **55**, Scheme 2), the dienophile **2** is activated by two electron-withdrawing groups, but after the 1,2-addition, only one electron-withdrawing group remains. All attempts to improve the yield of this transformation, including application of Lewis acid mediated procedures,[104] were unsuccessful. In fundamental work, Magnus and co-workers had studied the retrocycloaddition of Diels–Alder adducts of 5-(trimethylsilyl)cyclopentadiene (**3**). These researchers showed that the Diels–Alder adduct of 1,4-benzoquinone and 5-(trimethylsilyl)cyclopentadiene (**3**) undergoes retrocycloaddition 95 times faster at 60 °C than the analogous Diels–Alder adduct of 1,4-benzoquinone and cyclopentadiene (**54**).[105] This rate enhancement is attributed to the donation of electron density from the carbon–silicon bonding orbital to the antibonding orbitals of the carbon–carbon σ bonds that are cleaving in the retrocycloaddition, allowing for progression through a lower energy asynchronous transition state.

This strategy was appealing to us, as it could potentially circumvent the high-temperature extrusion of cyclopentadiene (**54**) itself. Accordingly, we investigated the feasibility of replacing cyclopentadiene (**54**) with 5-(trimethylsilyl)-cyclopentadiene (**3**) in our synthetic sequence (Scheme 5A).

Scheme 5. (A) Synthesis of the Tetracyclic Imine 5. (B) Synthesis, X-ray Analysis, and Retrocycloaddition of the Acetylide Addition Product 62



To render the route enantioselective, we utilized the protonated form of the Corey–Bakshi–Shibata oxazaborolidine (22 mol %)[66−69] in the Diels–Alder reaction. Under optimized conditions, the cycloaddition afforded the *endo*-adduct **4** in 78% yield, as a single diastereomer and regioisomer (^{1}H NMR analysis), and in 93% ee (chiral stationary phase HPLC analysis). To our knowledge, this constitutes the first example of an enantioselective Diels–Alder reaction employing 5-(trimethylsilyl)cyclopentadiene (**3**).

Treatment of the *endo*-adduct **4** with triphenylphosphine initiated the Staudinger reduction–aza-Wittig sequence. However, whereas the parent tetracyclic imine **56** derived from cyclopentadiene (**54**) was stable toward acid–base extraction, the silylcyclopentene derivative **5** did not withstand acidic conditions. Fortunately, we found that the Staudinger reduction–aza-Wittig sequence could be affected with trimethylphosphine. The trimethylphosphine oxide could be easily removed by neutral aqueous workup. Additionally, the *endo*-adduct **4** and the tetracyclic imine **5** undergo retrocycloaddition rapidly in the presence of acid and slowly under neutral conditions at ambient temperature, presumably due to the electron-donating ability of the trimethylsilyl group.

Differences in the reactivity of the 5-(trimethylsilyl)cyclopentadiene-derived imine **5** and the cyclopentadiene-derived imine **56** continued to emerge as we advanced **5** through the synthetic sequence (Scheme 5B). Notably, unlike the stable iminium salt **57**, attempted isolation of the *N*-methyliminium salt derived from **5** resulted in retrocycloaddition and decomposition. We attributed this to the activating effect of the trimethylsilyl substituent, which promotes retrocycloaddition. Upon further study of the stability limitations of **5**, we found that the iminium ion could be generated cleanly and in high yield at low temperatures (−60 to −30 °C); direct addition of 2-lithio-1-(trimethylsilyl)acetylene furnished the addition product **62** in 54% yield. X-ray analysis of the addition product **62** revealed that, as in the parent system **58**, the nucleophile had added *syn* to the (trimethylsilyl)cyclopentene substituent. Since the (trimethylsilyl)cyclopentene fragment of **62** was installed by an enantioselective Diels–Alder cycloaddition (**2** → **3**), we had therefore developed a handle for control of absolute stereochemistry in the sequence. In assessing the requirements for the key retrocycloaddition of the addition product **62**, we found that the trimethylsilyl group facilitated retrocycloaddition at lower temperatures, as anticipated. Optimal results were obtained by heating **62** in toluene at 135 °C, which quantitatively afforded the retrocycloaddition product **63**.

Thus, in our final synthetic route, 5-(trimethylsilyl)-cyclopentadiene (**3**) had three primary reactivity-altering roles: (1) stabilizing the iminoquinone intermediates toward aromatization, (2) directing the addition of acetylide nucleophiles to the *N*-methyliminium ion, and (3) facilitating the thermal retrocycloaddition to unmask the cyclohexanedienone. These reactivity-altering roles were observed when employing the aryl acetylides **6**–**8** in our hasubanan alkaloid syntheses and the cyclopentenyl acetylide **32** in our acutumine alkaloid syntheses. The retrocycloaddition of the hasubanan (**9**–**11**) and acutumine (not shown) acetylide addition products also proceeded smoothly in toluene at 135 °C, thereby affording products containing all of the carbon atoms of the target alkaloids (**12**–**14**, **33**).

VII. HYDROSTANNYLATION OF THE ALKYNE 33

The syntheses of the hasubanan alkaloids from the retrocycloaddition products (**12**–**14**) employed two key steps: semihydrogenation (Crabtree's catalyst) to access the *cis*-alkenes **15**–**17**, followed by acid-mediated cyclization to provide **18**, **20**, and **21**, which contain the carbon skeleton of the targets. In applying this strategy to (−)-acutumine (**47**), we planned to access the *cis*-alkene **64** by a parallel route but anticipated two major challenges: (1) cyclization to form the C-8–C-9 bond and (2) installation of the alkyl chloride group

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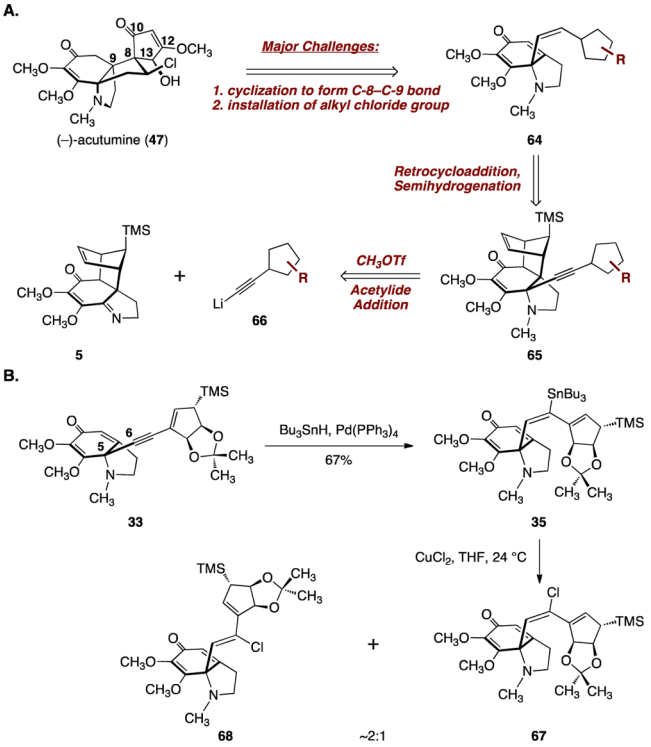
(Scheme 6A). To address the second challenge, we pursued installation of the alkyl chloride group earlier in the synthetic

Scheme 6. (A) Initial Synthetic Strategy for (−)-Acutumine (47). (B) Hydrostannylation of the Dienone 33



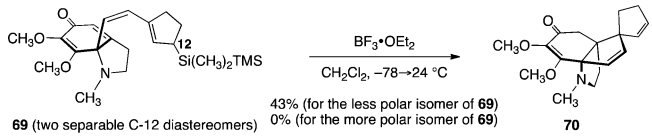
route. Specifically, we aimed to replace the semihydrogenation step with a hydrofunctionalization reaction. We pursued hydrostannylation of the dienone **33**,[82] since it was known that a vinylstannane could serve as a handle for the chlorine atom.[83]

The regioselectivity of the hydrostannylation step was important, and thus the inherent reactivity of the dienone **33** was evaluated. Hydrostannylation of the dienone **33** [tributyltin hydride, tetrakis(triphenylphosphine)] afforded the vinylstannane **35** as a single regioisomer (67%, Scheme 6B). The connectivity of **35** was determined by HMBC and HMQC analysis. We attribute the selectivity of this transformation to the more favorable insertion of the alkyne **33** into a palladium hydride to form an intermediate with η^3-allyl character. The regioselectivity could also result from the steric congestion of the fully substituted C-5 carbon, which would disfavor palladium−carbon bond formation at C-6. To install the chloride group of (−)-acutumine (**47**), chlorodestannylation of the vinylstannane **35** was attempted, but this led to erosion of the exocyclic olefin stereochemistry. Thus, our efforts turned to construction of the C-8−C-9 bond of (−)-acutumine (**47**) prior to installation of the chloride. We anticipated that chlorodestannylation of the cyclized product would proceed cleanly.

VIII. CYCLIZATION OF THE ALLYLIC SILANES 34 AND 35

We prepared the model substrate **69** to investigate formation of the C-8−C-9 bond by Lewis acid mediated pathways (Scheme 7). We had established that this bond could be made in our hasubanan route (**15**−**17** → **18**, **20**, **21**) under protic

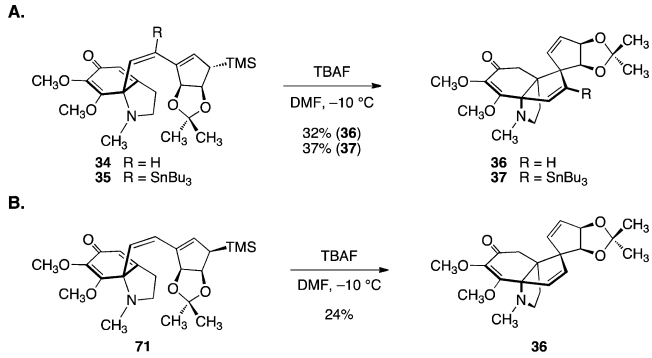
Scheme 7. Synthesis of the Model Cyclization Product 70



conditions, and exploratory experiments indicated that various cyclization precursors were unstable under basic conditions. The model substrate **69** was prepared as a mixture of two C-12 diastereomers, which could be separated by preparative thin-layer chromatography, although the C-12 stereochemistry of each diastereomer could not be assigned. We found that treatment of the less polar diastereomer of **69** with boron trifluoride etherate complex at 0 °C provided the cyclization product **70** as a single diastereomer (43%, ^{1}H NMR analysis). Under all conditions examined, the more polar diastereomer did not undergo cyclization.

To apply this reaction in the synthesis of (−)-dechloroacutumine (**48**), the functionalized allylic silane **34** was prepared by semihydrogenation of the dienone **33** (Crabtree's catalyst, 86%, Scheme 8A). However, the cyclization conditions

Scheme 8. (A) Cyclization of the *exo*-Allylic Silanes 34 and 35. (B) Cyclization of the *endo*-Allylic Silane 71



developed for the model system **69** were ineffective; treatment of **34** with Lewis or protic acids resulted in decomposition, acetonide cleavage, or elimination of one of the cyclopentenyl oxygen atoms. The latter pathways were not entirely remarkable given the acidic nature of the reaction conditions. Further study of the reactivity of the functionalized allylic silane **34** revealed that the cyclization of **34** could be affected by a basic/nucleophilic pathway. Treatment of **34** with tetrabutylammonium fluoride at −10 °C provided the cyclization product **36** in 32% yield. The low yield of this transformation was initially attributed to unfavorable steric interactions between the trimethylsilyl group and the dienone of **34**. To alleviate this, we prepared the *endo*-allylic silane **71**, in which the stereochemistry of the silyl group is inverted. However, the cyclization of **71** proceeded in similar yield (24%, Scheme 8B). To access (−)-acutumine (**47**), the analogous fluoride-mediated cyclization of the vinylstannane **35** was attempted, and the reaction proceeded in 37% yield (Scheme 8A).

IX. TRANSFORMATION OF THE DIOL 38 TO THE METHYL ETHER 40

Acid-mediated deprotection of the cyclization product **36** afforded the diol **38** (71%). Our efforts turned toward elaboration of the cyclopentene of the diol **38** to the

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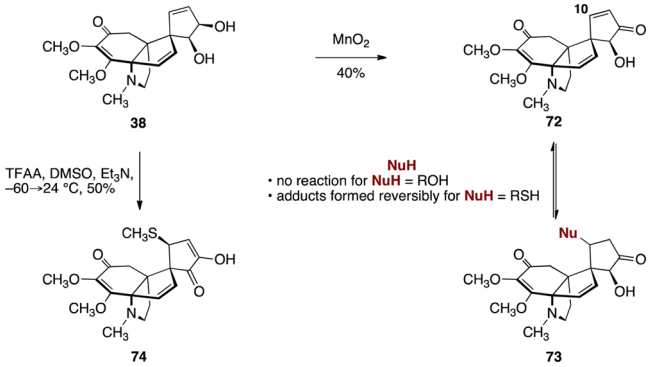
cyclopentenone of (−)-dechloroacutumine (**48**). This synthetic transformation required installation of the C-10 oxygen functionality of (−)-dechloroacutumine (**48**). Our initial approach to install the C-10 ketone involved selective oxidation of the diol **38** (manganese oxide) to the enone **72** (40%, Scheme 9). We anticipated that Michael addition of an oxygen

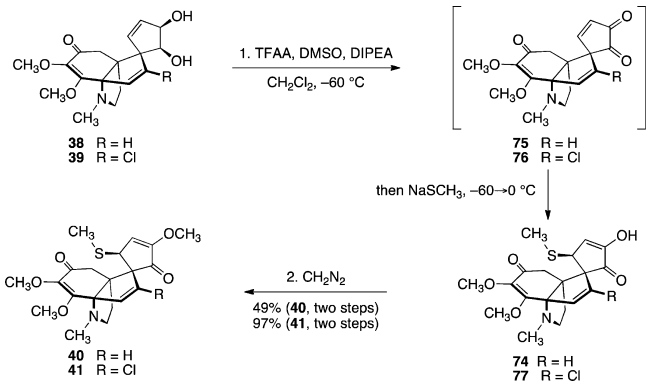
Scheme 9. Synthesis of the Enone 72 and the Sulfide 74



nucleophile to **72** would provide the intermediate **73**, which contains all the cyclopentenone heteroatoms present in (−)-dechloroacutumine (**48**). In studying the reactivity of the enone **72**, we found oxygen-based nucleophiles (including sodium hydrogen peroxide, carboxylate salts, oximes, primary alcohols, and water) were unreactive in the nucleophilic addition. We attribute this lack of reactivity to the neopentyl nature of C-10. Sulfur-based nucleophiles did add to the enone **72**, but these addition products formed reversibly and often reverted to the enone **72** during chromatographic purification or attempted *S*-functionalization.

In order to render the 1,4-addition reaction successful, it was deemed necessary to decrease the kinetic barrier to addition and to increase the thermodynamic stability of the resulting adducts. We recognized that exhaustive oxidation of **38** would form the α-dicarbonyl (or enedione) **75**, which cannot adopt the preferred enol tautomer[106] due to the absence of any exchangeable protons in the cyclopentyl ring (Scheme 10). We

Scheme 10. Synthesis of the Methyl Ethers 40 and 41



reasoned that this activated dicarbonyl should be much more electrophilic and that the resulting 1,4-addition products, which can now adopt the enol tautomer, would be more stable. To access the enedione **75**, Swern oxidation of the diol **38** using methyl sulfoxide, trifluoroacetic anhydride, and triethylamine was investigated.[107,108] Owing to the small scales of these early exploratory experiments, an excess of reagents was employed, and the major product was the sulfide **74** (50%). The sulfide **74** is believed to derive from the expected enedione **75** by 1,4-addition of methanethiol, formed by degradation of the activated methyl sulfoxide. While unexpected, the formation of the sulfide **74** directly from the diol **38** was a useful transformation because it accomplished the oxidation and 1,4-addition in a single step.

Ultimately, a more reproducible and scalable oxidation−1,4-addition procedure was developed. This procedure includes two key modifications: (1) replacement of triethylamine with Hünig's base, which was less prone to decomposition under the reaction conditions, and (2) addition of a standard solution of sodium thiomethoxide (3.30 equiv) directly to the enedione **75** following oxidation. Under these conditions, the enedione **75** could be formed reproducibly and quantitatively using a slight excess of reagents (3 equiv of trifluoroacetic anhydride, 6 equiv of methyl sulfoxide, 10 equiv of Hünig's base); addition of sodium thiomethoxide completed the transformation. Although the 1,4-addition product **74** could be isolated, it was prone to elimination (to regenerate the enedione **75**) and other decomposition pathways. To circumvent this, the unpurified sulfide **74** was treated directly with diazomethane to provide the methyl ether **40** as a single detectable diastereomer (^{1}H NMR analysis, 49%, two steps). In this way, the methyl group serves as a cap that prevents reversion of the 1,4-addition product **74**. The inherent reactivity of the diol **39**, which contains the chloride group of (−)-acutumine (**47**), mirrored that of the parent diol **38**. Subjection of **39** to the same two-step sequence afforded the corresponding methyl ether **41** in 97% yield.

X. SUBSTITUTION OF THE PARENT AND CHLORINATED METHYL ETHERS 40 AND 41

With the parent and chlorinated methyl ethers **40** and **41** in hand, we envisioned installation of the C-10 ketone of the acutumine alkaloids by elimination of the sulfide group to form an oxocarbenium ion, followed by 1,4-addition of an oxygen nucleophile (Scheme 11). Our initial studies focused on using this strategy to transform the parent methyl ether **40** to the formate **42**. Extensive studies of the reactivity of **40** revealed that the desired transformation could be achieved with mercuric acetate in formic acid,[109] which furnished the stereoretentive substitution product **42** in 87% yield (Scheme 11A). However, these conditions did not provide the expected substitution product **77** when applied to the chlorinated methyl ether **41**, and the only isolable product was the enedione **76**. We attributed the difference in the reactivity of the parent **40** and chlorinated **41** methyl ethers to the steric encumbrance introduced by the vinyl chloride of **41**, which blocks addition of formate to the β-position.

Further study of the reactivity of the chlorinated methyl ether **41** revealed the formation of an unexpected product, the 1,2-addition product **44**, upon treatment of **41** with *N*-iodosuccinimide in formic acid.[110] The production of **44** is proposed to occur by activation of the sulfide of **41** to provide a putative oxocarbenium ion (not shown), followed by 1,2-addition. The 1,2-addition product was obtained as a 3:1 mixture of diastereomers, in favor of the isomer shown. The diastereoselectivity of this 1,2-addition is distinct from the 1,4-addition to form **42**. We attribute this change to the steric encumbrance of the chloride group in the methyl ether **41**, which forces addition from the opposite face. We hypothesize

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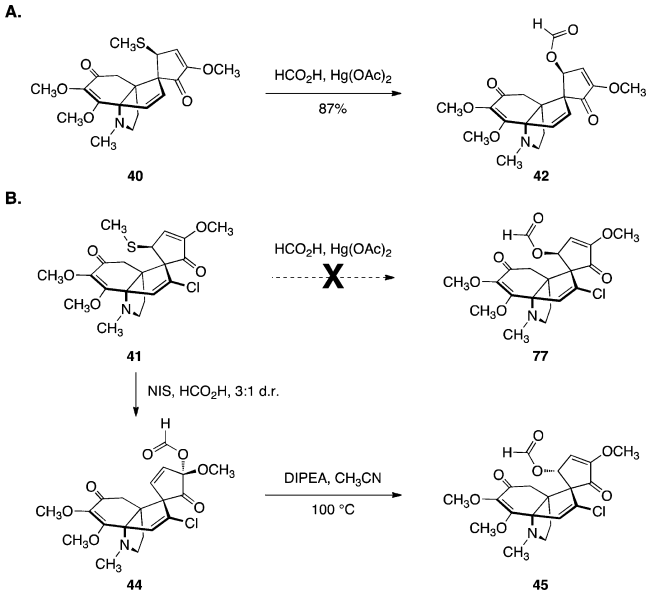
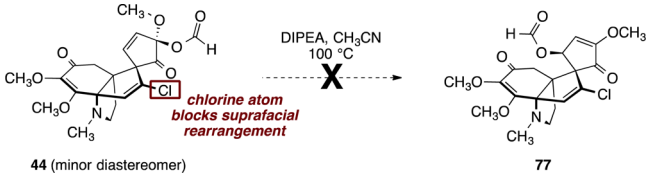
Scheme 11. (A) Synthesis of the Parent formate 42. (B) Synthesis of the Chlorinated Formate 45



that under these conditions (formic acid as solvent) trapping by formate is faster than cleavage of the methyl ether. Ultimately, we accessed the target chlorinated formate **45** by a [3,3]-rearrangement of the 1,2-addition product **44** (100 °C, acetonitrile).[111] Here too, interesting reactivity trends were observed. Specifically, the minor diastereomer of **44** did not undergo efficient rearrangement, presumably due to unfavorable steric interactions with the chloride group (Scheme 12).

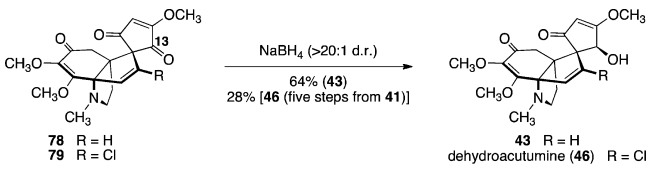
Scheme 12. Possible Explanation for the Failure of the Minor Diastereomer of 44 To Rearrange



XI. SITE- AND STEREOSELECTIVE REDUCTION OF THE VINYLOGOUS α-DIKETONES 78 AND 79

The syntheses of (−)-dechloroacutumine (**48**) and (−)-acutumine (**47**) required the site- and stereoselective reduction of the C-13 carbonyl group of the vinylogous α-diketones **78** and **79**, respectively (Scheme 13). We anticipated that the site-selectivity of this transformation would not be an issue, because the remaining carbonyls in **78** and **79** are vinylogous esters. The stereoselectivity for this transformation was less predictable, but based on our studies in the sulfide displacement and [3,3]-shifts above, it seemed that the chloride substituent effectively shields the β-face of the cyclopentyl ring. Thus, it was anticipated that the vinyl chloride of **79** could impart selectivity in the reduction of **79**, but the selectivity in the deschloro series **78** was not unambiguous. In the event, we found that treatment of the parent vinylogous α-diketone **78** with sodium borohydride afforded the desired alcohol **43** as a single stereoisomer (64%, ^{1}H NMR analysis). Similar site- and stereoselectivity was obtained in the analogous reduction of the chlorinated vinylogous α-diketone **79**. Thus, the stereoselectivity may be due to gross topological biases introduced by the tetracyclic skeleton, rather than any specific steric effects introduced by the vinyl chloride.

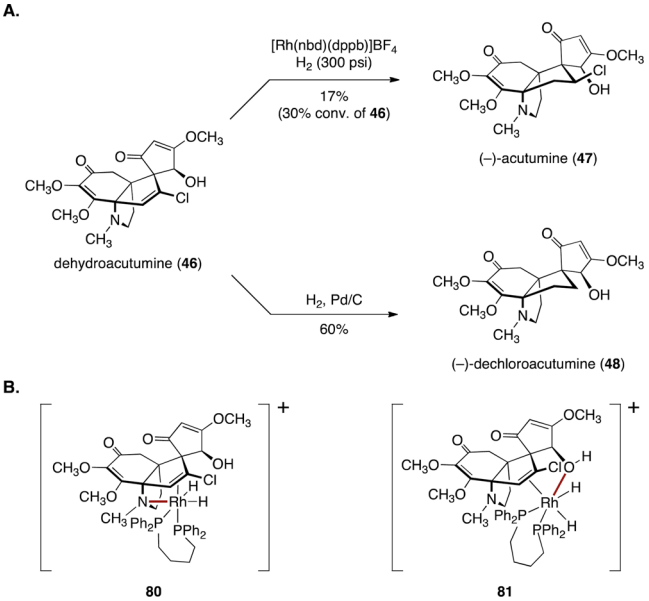
Scheme 13. Site- and Stereoselective Reduction of the Vinylogous α-Diketones 78 and 79



XII. DIRECTED HYDROGENATION OF DEHYDROACUTUMINE (46) TO FORM (−)-ACUTUMINE (47)

The final step in the synthesis of (−)-acutumine (**47**) called for the directed hydrogenation of the vinyl chloride group of dehydroacutumine (**46**). The selective hydrogenation of vinyl halides to alkyl halides is a difficult transformation because hydrodehalogenation byproducts are often formed. For example, heterogeneous hydrogenation of dehydroacutumine (**46**) with palladium on carbon cleanly produced (−)-dechloroacutumine (**48**) in 60% yield (Scheme 14A). However, we anticipated that nearby functional groups in **46** could modify the inherent reactivity of the vinyl chloride group. It was expected that a catalyst could bind to the amine or alcohol group of **46** to direct the hydrogenation reaction (Scheme 14B).[112] After extensive study, we found that homogeneous hydrogenation of dehydroacutumine (**46**) with [Rh(nbd)(dppb)]BF$_4$ under 300 psi of hydrogen affected the desired transformation,[88−91] affording (−)-acutumine (**47**) as a single detectable diastereomer (^{1}H NMR analysis, 17% yield of **47** at

Scheme 14. (A) Hydrogenation of Dehydroacutumine (46) To Form (−)-Acutumine (47) and (−)-Dechloroacutumine (48). (B) Proposed Substrate−Catalyst Complexes for the Directed Hydrogenation of Dehydroacutumine (46)



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30% conversion of **46**). Attempts to increase the yield of this transformation by increasing the conversion of **46** using $[Rh(nbd)(dppb)]BF_4$ led to the formation of (−)-dechloroacutumine (**48**) exclusively. We attribute the exclusive formation of (−)-acutumine (**47**) at low conversion of **46** to the coordination of the amine or alcohol functional group to the catalyst. Subsequently, we have developed a more general process for the reduction of alkenyl halides by a hydrogen atom transfer pathway.[113]

XIII. SUMMARY AND CONCLUSION

In this Perspective, we have tried to articulate the concept of substrate-modified functional group reactivity and demonstrate how it influenced the development of our syntheses of the hasubanan and acutumine alkaloids. In the course of our synthetic work, progress through many steps was only achieved after developing an understanding of the innate reactivity of our intermediates. For many of these steps, the reactivity differed significantly from what was anticipated based on a first-order functional group analysis.

These syntheses illustrate the challenges of predicting molecular reactivity a priori and argue for the inherent value in the study of complex molecular architectures. In many instances, unexpected functional group reactivity led us to incorporate molecules into our final synthetic route that were not included in our initial synthetic analysis. In this way, the reactivity and stability profiles of the synthetic intermediates were the primary driver in the development of the synthetic route. While most synthetic chemists possess an innate understanding of the concept of substrate-modified functional group reactivity, it is our hope that this perspective will promote appreciation of this concept by younger students and further motivate the study of complex molecular architectures en route to natural product targets.

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Notes

The authors declare no competing financial interest.

Biographies

Sandra M. King was born in Waterloo, IA, in 1985. She received her BA in Chemistry and Mathematics from Grinnell College (2008) and her MPhil in Chemistry from the University of Cambridge (2009), under the guidance of Professor Steven V. Ley. In 2009, she began graduate studies at Yale University in the laboratory of Professor Seth B. Herzon. Her research focuses on the syntheses of the hasubanan and acutumine alkaloids and the development of a general method for the selective reduction of alkenyl halides.

Seth B. Herzon obtained his undergraduate degree from Temple University in 2002. He was a graduate student at Harvard University in the laboratory of Andrew G. Myers and conducted postdoctoral studies with John F. Hartwig at the University of Illinois, Urbana−Champaign. He joined the Yale faculty in 2008 as an Assistant Professor of Chemistry. In 2012 he was appointed to Associate Professor of Chemistry and in 2013 was appointed to Professor of Chemistry. His research focuses on organic synthesis, organometallic chemistry, and chemical biology.

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■ REFERENCES

(1) Herzon, S. B.; Calandra, N. A.; King, S. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 8863.

(2) King, S. M.; Calandra, N. A.; Herzon, S. B. *Angew. Chem., Int. Ed.* **2013**, *52*, 3642.

(3) Calandra, N. A.; King, S. M.; Herzon, S. B. *J. Org. Chem.* **2013**, *78*, 10031.

(4) Hason, J. R. *Functional Group Chemistry*; Royal Society of Chemistry: Cambridge, 2001.

(5) Bentley, K. W. Morphine Alkaloids. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1971; Vol. *13*, pp 1−163.

(6) Inubushi, Y.; Ibuka, T. The Hasubanan Alkaloids. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1977; Vol. *16*, pp 393−430.

(7) Matsui, M. Hasubanan Alkaloids. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1988; Vol. *33*, pp 307−347.

(8) King, S. M.; Herzon, S. B. The Hasubanan and Acutumine Alkaloids. In *The Alkaloids*; Knölker, H.-J., Ed.; Academic Press: Burlington, 2014; Vol. *73*, pp 161−222.

(9) Kondo, H.; Satomi, M.; Odera, T. *Ann. Rep. ITSUU Lab.* **1951**, *2*, 1.

(10) Tomita, M.; Ibuka, T.; Inubushi, Y.; Watanabe, Y.; Matsui, M. *Tetrahedron Lett.* **1964**, *5*, 2937.

(11) Tomita, M.; Ibuka, T.; Inubushi, Y.; Watanabe, Y.; Matsui, M. *Chem. Pharm. Bull.* **1965**, *13*, 538.

(12) Semwal, D. K.; Rawat, U. *Planta Med.* **2009**, *75*, 378.

(13) Yan, M.-H.; Cheng, P.; Jiang, Z.-Y.; Ma, Y.-B.; Zhang, X.-M.; Zhang, F.-X.; Yang, L.-M.; Zheng, Y.-T.; Chen, J.-J. *J. Nat. Prod.* **2008**, *71*, 760.
(14) Carroll, A. R.; Arumugan, T.; Redburn, J.; Ngo, A.; Guymer, G. P.; Forster, P. I.; Quinn, R. J. *J. Nat. Prod.* **2010**, *73*, 988.
(15) Goto, K.; Sudzuki, H. *Bull. Chem. Soc. Jpn.* **1929**, *4*, 220.
(16) Goto, K.; Tomita, M.; Okamoto, Y.; Sasaki, Y.; Matoba, K. *Proc. Jpn. Acad.* **1966**, *42*, 1181.
(17) Tomita, M.; Okamoto, Y.; Kikuchi, T.; Osaki, K.; Nishikawa, M.; Kamiya, K.; Sasaki, Y.; Matoba, K.; Goto, K. *Tetrahedron Lett.* **1967**, *8*, 2421.
(18) Tomita, M.; Okamoto, Y.; Kikuchi, T.; Osaki, K.; Nishikawa, M.; Kamiya, K.; Sasaki, Y.; Matoba, K.; Goto, K. *Tetrahedron Lett.* **1967**, *8*, 2425.
(19) Goto, K.; Tomita, M.; Okamoto, Y.; Kikuchi, T.; Osaki, K.; Nishikawa, M.; Kamiya, K.; Sasaki, Y.; Matoba, K. *Proc. Jpn. Acad.* **1967**, *43*, 499.
(20) Cheng, P.; Ma, Y.-b.; Yao, S.-y.; Zhang, Q.; Wang, E.-j.; Yan, M.-h.; Zhang, X.-m.; Zhang, F.-x.; Chen, J.-j. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5316.
(21) Qin, G.-W.; Tang, X.-C.; Lestage, P.; Caignard, D.-H.; Renard, P. Acutumine and Acutumine Compounds, Synthesis and Use. Patent WO2004000815A1, 2003.
(22) Yu, B.-W.; Chen, J.-Y.; Wang, Y.-P.; Cheng, K.-F.; Li, X.-Y.; Qin, G.-W. *Phytochemistry* **2002**, *61*, 439.
(23) Tomita, M.; Ibuka, T.; Kitano, M. *Tetrahedron Lett.* **1966**, *7*, 6233.
(24) Ibuka, T.; Kitano, M. *Chem. Pharm. Bull.* **1967**, *15*, 1944.
(25) Tomita, M.; Kitano, M.; Ibuka, T. *Tetrahedron Lett.* **1968**, *9*, 3391.
(26) Evans, D. A. *Tetrahedron Lett.* **1969**, *10*, 1573.
(27) Evans, D.; Bryan, C.; Wahl, G. *J. Org. Chem.* **1970**, *35*, 4122.
(28) Keely, S. L., Jr.; Martinez, A. J.; Tahk, F. C. *Tetrahedron* **1970**, *26*, 4729.
(29) Evans, D. A.; Bryan, C. A.; Sims, C. L. *J. Am. Chem. Soc.* **1972**, *94*, 2891.
(30) Kametani, T.; Kobari, T.; Fukumoto, K. *J. Chem. Soc., Chem. Commun.* **1972**, 288.
(31) Belleau, B.; Wong, H.; Monkovic, I.; Perron, Y. G. *J. Chem. Soc., Chem. Commun.* **1974**, 603.
(32) Kametani, T.; Kobari, T.; Shishido, K.; Fukumoto, K. *Tetrahedron* **1974**, *30*, 1059.
(33) Monkovic, I.; Wong, H.; Belleau, B.; Pachter, I. J.; Perron, Y. G. *Can. J. Chem.* **1975**, *53*, 2515.
(34) Monkovic, I.; Wong, H. *Can. J. Chem.* **1976**, *54*, 883.
(35) Shiotani, S.; Kometani, T. *Tetrahedron Lett.* **1976**, *17*, 767.
(36) Bruderer, H.; Knopp, D.; Daly, J. J. *Helv. Chim. Acta* **1977**, *60*, 1935.
(37) Schwartz, M. A.; Wallace, R. A. *Tetrahedron Lett.* **1979**, *20*, 3257.
(38) Trauner, D.; Porth, S.; Opatz, T.; Bats, J. W.; Giester, G.; Mulzer, J. *Synthesis* **1998**, 653.
(39) Jones, S. B.; He, L.; Castle, S. L. *Org. Lett.* **2006**, *8*, 3757.
(40) Nguyen, T. X.; Kobayashi, Y. *J. Org. Chem.* **2008**, *73*, 5536.
(41) Nielsen, D. K.; Nielsen, L. L.; Jones, S. B.; Toll, L.; Asplund, M. C.; Castle, S. L. *J. Org. Chem.* **2009**, *74*, 1187.
(42) Jones, S. B.; He, L.; Castle, S. L. *Org. Lett.* **2009**, *11*, 785.
(43) Pihko, A. J.; Koskinen, A. M. P. *Tetrahedron* **2005**, *61*, 8769.
(44) Ibuka, T.; Tanaka, K.; Inubushi, Y. *Tetrahedron Lett.* **1970**, *11*, 4811.
(45) Ibuka, T.; Tanaka, K.; Inubushi, Y. *Chem. Pharm. Bull.* **1974**, *22*, 782.
(46) Inubushi, Y.; Ibuka, T.; Kitano, M. *Tetrahedron Lett.* **1969**, *10*, 1611.
(47) Inubushi, Y.; Kitano, M.; Ibuka, T. *Chem. Pharm. Bull.* **1971**, *19*, 1820.
(48) Kametani, T.; Nemoto, H.; Kobari, T.; Shishido, K.; Fukumoto, K. *Chem. Ind. (London, U.K.)* **1972**, 538.
(49) Ibuka, T.; Tanaka, K.; Inubushi, Y. *Tetrahedron Lett.* **1972**, *13*, 1393.
(50) Ibuka, T.; Tanaka, K.; Inubushi, Y. *Chem. Pharm. Bull.* **1974**, *22*, 907.
(51) Schultz, A. G.; Wang, A. *J. Am. Chem. Soc.* **1998**, *120*, 8259.
(52) Chuang, K. V.; Navarro, R.; Reisman, S. E. *Angew. Chem., Int. Ed.* **2011**, *50*, 9447.
(53) Magnus, P.; Seipp, C. *Org. Lett.* **2013**, *15*, 4870.
(54) Matoba, K.; Karibe, N.; Yamazaki, T. *Chem. Pharm. Bull.* **1982**, *30*, 3906.
(55) Matoba, K.; Karibe, N.; Yamazaki, T. *Chem. Pharm. Bull.* **1984**, *32*, 2639.
(56) Waller, D. L.; Stephenson, C. R. J.; Wipf, P. *Org. Biomol. Chem.* **2007**, *5*, 58.
(57) Moreau, R. J.; Sorensen, E. J. *Tetrahedron* **2007**, *63*, 6446.
(58) Navarro, R.; Reisman, S. E. *Org. Lett.* **2012**, *14*, 4354.
(59) Reeder, M. D.; Srikanth, G. S. C.; Jones, S. B.; Castle, S. L. *Org. Lett.* **2005**, *7*, 1089.
(60) Li, F.; Castle, S. L. *Org. Lett.* **2007**, *9*, 4033.
(61) Li, F.; Tartakoff, S. S.; Castle, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 6674.
(62) Li, F.; Tartakoff, S. S.; Castle, S. L. *J. Org. Chem.* **2009**, *74*, 9082.
(63) Soderquist, J. A.; Kock, I.; Estrella, M. E. *Org. Process Res. Dev.* **2006**, *10*, 1076.
(64) Orita, H.; Shimizu, M.; Hayakawa, T.; Takehira, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1652.
(65) Ashe, A. J. *J. Am. Chem. Soc.* **1970**, *92*, 1233.
(66) Corey, E. J.; Shibata, T.; Lee, T. W. *J. Am. Chem. Soc.* **2002**, *124*, 3808.
(67) Ryu, D. H.; Lee, T. W.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 9992.
(68) Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650.
(69) Ryu, D. H.; Zhou, G.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 4800.
(70) Crabtree, R. H.; Felkin, H.; Morris, G. E. *J. Organomet. Chem.* **1977**, *141*, 205.
(71) Suggs, J. W.; Cox, S. D.; Crabtree, R. H.; Quirk, J. M. *Tetrahedron Lett.* **1981**, *22*, 303.
(72) Ramanathan, A.; Jimenez, L. S. *Synthesis* **2010**, 217.
(73) Zhi-Da, M.; Ge, L.; Guang-Xi, X.; Iinuma, M.; Tanaka, T.; Mizuno, M. *Phytochemistry* **1985**, *24*, 3084.
(74) Fadeeva, I. I.; Il'inskaya, T. N.; Perel'son, M. E.; Kuzovkov, A. D. *Chem. Nat. Compd.* **1970**, *6*, 139.
(75) Fadeeva, I. I.; Il'inskaya, T. N.; Perel'son, M. E.; Kuzovkov, A. D. *Chem. Nat. Compd.* **1971**, *7*, 756.
(76) Patra, A. *Phytochemistry* **1987**, *26*, 2391.
(77) Mukaiyama, T.; Isayama, S.; Inoki, S.; Kato, K.; Yamada, T.; Takai, T. *Chem. Lett.* **1989**, 449.
(78) Van Wyk, A. J.; Wiechers, A. *J. S. Afr. Chem. Inst.* **1974**, *27*, 95.
(79) Kondo, S.; Matsui, M.; Watanabe, Y. *Chem. Pharm. Bull.* **1983**, *31*, 2574.
(80) Yamamura, Y.; Matsui, M. *J. Nat. Prod.* **1985**, *48*, 746.
(81) Matsui, M.; Yamamura, Y. *J. Nat. Prod.* **1986**, *49*, 588.
(82) Alami, M. d.; Ferri, F. *Synlett* **1996**, 755.
(83) Takeda, T.; Kanamori, F.; Matsusita, H.; Fujiwara, T. *Tetrahedron Lett.* **1991**, *32*, 6563.
(84) Hosomi, A.; Endo, M.; Sakurai, H. *Chem. Lett.* **1976**, *5*, 941.
(85) Hosomi, A.; Sakurai, H. *J. Am. Chem. Soc.* **1977**, *99*, 1673.
(86) Sugimoto, Y.; Inanaga, S.; Kato, M.; Shimizu, T.; Hakoshima, T.; Isogai, A. *Phytochemistry* **1998**, *49*, 1293.
(87) Sugimoto, Y.; Matsui, M.; Takikawa, H.; Sasaki, M.; Kato, M. *Phytochemistry* **2005**, *66*, 2627.
(88) Brown, J. M.; Naik, R. G. *J. Chem. Soc., Chem. Commun.* **1982**, 348.
(89) Crabtree, R. H.; Davis, M. W. *Organometallics* **1983**, *2*, 681.
(90) Stork, G.; Kahne, D. E. *J. Am. Chem. Soc.* **1983**, *105*, 1072.
(91) Evans, D. A.; Morrissey, M. M. *J. Am. Chem. Soc.* **1984**, *106*, 3866.
(92) Ma, H. C.; Jiang, X. Z. *Synthesis* **2007**, 412.
(93) Ma, H. C.; Jiang, X. Z. *Synlett* **2007**, 1679.

(94) Ma, H.; Wu, S.; Sun, Q.; Li, H.; Chen, Y.; Zhao, W.; Ma, B.; Guo, Q.; Lei, Z.; Yan, J. *Synthesis* **2010**, 3295.
(95) Cromartie, R. I. T.; Harley-Mason, J. *J. Chem. Soc.* **1952**, 2525.
(96) Harley-Mason, J.; Jackson, A. H. *J. Chem. Soc.* **1954**, 1165.
(97) Ozaki, Y.; Quan, Z.-S.; Watabe, K.; Kim, S.-W. *Heterocycles* **1999**, *51*, 727.
(98) Stoffman, E. J. L.; Clive, D. L. J. *Org. Biomol. Chem.* **2009**, *7*, 4862.
(99) Stork, G.; Nelson, G. L.; Rouessac, F.; Gringore, O. *J. Am. Chem. Soc.* **1971**, *93*, 3091.
(100) Ichihara, A. *Synthesis* **1987**, 207.
(101) Klunder, A. J. H.; Zhu, J.; Zwanenburg, B. *Chem. Rev.* **1999**, *99*, 1163.
(102) Bachmann, W. E.; Ross, A.; Dreiding, A. S.; Smith, P. A. S. *J. Org. Chem.* **1954**, *19*, 222.
(103) Eliel, E. L.; Pillar, C. *J. Am. Chem. Soc.* **1955**, *77*, 3600.
(104) Grieco, P. A.; Abood, N. *J. Org. Chem.* **1989**, *54*, 6008.
(105) Magnus, P.; Cairns, P. M.; Moursounidis, J. *J. Am. Chem. Soc.* **1987**, *109*, 2469.
(106) Raimondi, W.; Bonne, D.; Rodriguez, J. *Chem. Commun.* **2012**, *48*, 6763.
(107) Huang, S. L.; Omura, K.; Swern, D. *Synthesis* **1978**, 297.
(108) Amon, C. M.; Banwell, M. G.; Gravatt, G. L. *J. Org. Chem.* **1987**, *52*, 4851.
(109) Liu, G.; Wang, Z. *Synthesis* **2001**, 119.
(110) Veeneman, G. H.; van Leeuwen, S. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 1331.
(111) Overman, L. E. *Angew. Chem., Int. Ed.* **1984**, *23*, 579.
(112) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.
(113) King, S. M.; Ma, X.; Herzon, S. B. *J. Am. Chem. Soc.* **2014**, *136*, 6884.