CHAPTER 3

An Introduction to Acutumine

3.1. Introduction

A second collection of alkaloids that exhibit the azapropellane structural framework is exemplified by acutumine (**133**, Figure 1). 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 neopentylic chloride. Since the original structural elucidation of **133** in the late 1960s, a total of 12 related alkaloids have been identified to date, which possess slight variations in their oxidation state and peripheral structure (see Figure 1).

In addition to its unique structural architecture, acutumine has been found to exhibit distinctive medicinal properties, including selective T-cell cytotoxicity[1] and antiamnesic properties.[2] More recently, dauricumidine (**136**) was found to display modest cytoxicity

against a hepatitis B virus-transfected cell line.[3] Not surprisingly, these structural and biological properties have attracted considerable attention from the synthetic community. This chapter 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.

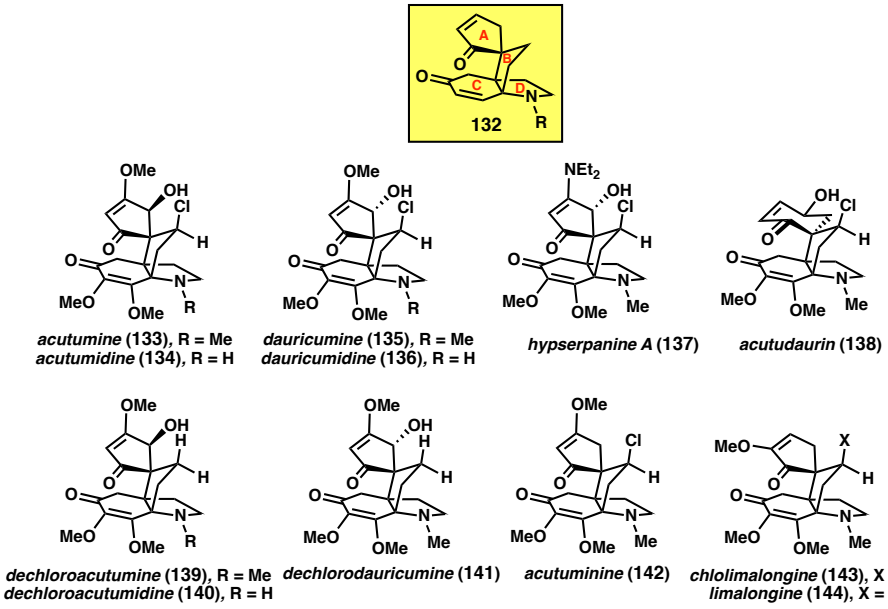

Figure 1. The acutumine alkaloids.

3.2. Isolation

In 1929, Goto and Sudzuki reported the isolation of acutumine from *Sinomenium acutum*, a climbing plant of the Menispermaceae family.[4] 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.[5] In this series of studies, the authors also obtained an X-ray crystal structure of **133**, thereby confirming their structural assignment. The absolute

configuration of acutumine was determined via comparison of its CD spectral patterns with those of hasubanonine.[6] Using this data, the authors also elucidated the structure of acutumidine (**134**), a natural product they isolated alongside **133**.

Over two decades elapsed before other natural products bearing the acutumine framework began to emerge. The new alkaloids were characterized by comparison of their spectral data to that of acutumine.[1,3,7-10] These acutumine analogs mainly differ in (1) the presence of a stereogenic C-Cl bond, and (2) the composition of the spirocyclic enone. These structural differences can be subtle—such as the epimeric relationship between **133** and dauricumine—or more pronounced, as is the case with the cylcohexenone-bearing acutudaurin (**138**). 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.

3.3. Biosynthesis

As part of their studies regarding the biosynthesis of several morphinan alkaloids, Barton and coworkers put forth a biosynthetic pathway for acutumine.[11] The authors speculated that isoquinoline derivative **145** undergoes intramolecular phenol coupling to deliver spirocycle **146**. Sequential epoxidation of this intermediate provides diepoxide **147**, an intermediate proposed to undergo a Favorskii-type rearrangement to install the A ring of the natural product. Acid **148** can be elaborated to cyclopentenone **150** via a decarboxylative epoxide opening followed by oxidation of the resulting diol. To establish the propellane core, the quinone functionality of **150** is hypothesized to undergo

nucleophilic attack by the pendant isoquinoline nitrogen, thereby furnishing aziridinium ion **151**. A 1,2-hydride shift can then afford carbocation **152**, which upon nucleophilic attack by a chloride anion and D-ring isomerization can yield the natural product.

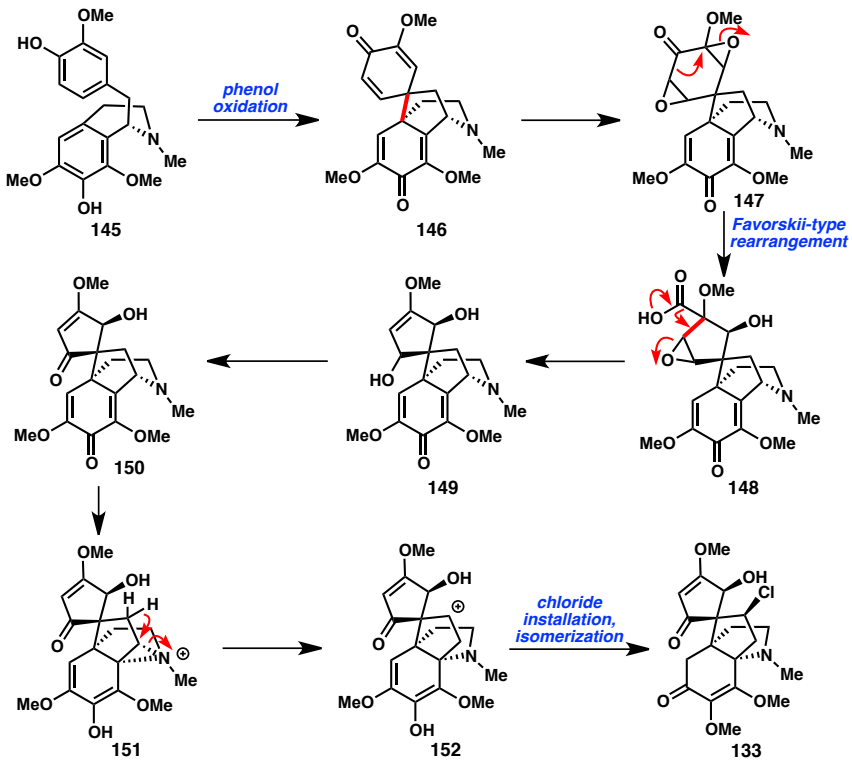

Figure 2. Barton's proposed biosynthesis of the spirocyclic cyclopentenone.

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 **153**.[12] Exposure of epoxyenone **153** to *m*-CPBA in refluxing 1,1,1-trichloroethane delivered lactone **154** in 52% yield. Unfortunately, other attempts to prepare bisepoxide **155** from the corresponding dienone proved unfruitful. More recently, Wipf and coworkers were met

with a similar reactivity patterns. In their case, addition of **153** to a buffered solution of *m*-CPBA in CH_2Cl_2 only provided epoxylactone **159**.[13] The formation of **159** is speculated to arise from an initial epoxide opening of **156**, which generates the corresponding oxocarbenium ion. Peracid addition to this oxocarbenium ion delivers **157**, an intermediate hypothesized to undergo a Baeyer-Villiger ring expansion and translactonization reaction to form **159**.

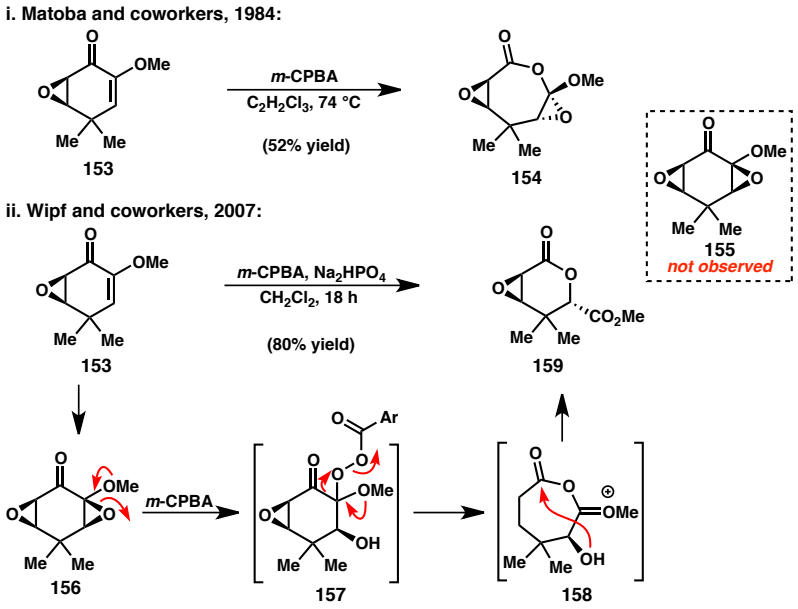

Figure 3. Bisepoxidation studies by Matoba and Wipf.

Based on this unexpected reactivity, Wipf and coworkers put forth an alternative mechanism for cyclopentenone biosynthesis. In this scenario, epoxidation of dienol **160** initially yields ketone hydrate **162**, which is converted to **163** via a semipinacol-type rearrangement. Decarboxylation of **163** is then thought to establish the cyclopentenone moiety of acutumine. Interestingly, the authors posit that the isolation of acutudaurin

(**138**, see Figure 1), a potential acutumine alkaloid precursor, provides further evidence for their biosynthetic proposal.

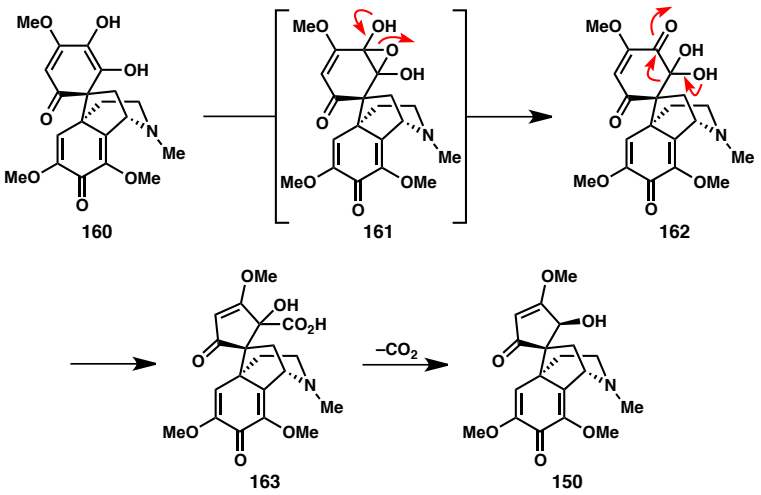

Figure 4. Wipf's biosynthetic proposal.

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, which demonstrated that two molecules of tyrosine are incorporated into acutumine.[14] Additionally, the authors found that ^{3}H-labeled dechloroacutumine (**134**, see Figure 5) can be converted to **133** in vitro, suggesting that dechloroacutumine is a precursor of **133**. To further investigate the potential interrelationship between the acutumine alkaloids, Sugimoto more recently disclosed feeding experiments using ^{36}Cl-labeled **133**-**136** in *Menispermum dauricum* root cultures (Figure 5).[9] These studies revealed a mutual interconversion between each pair of *N*-alkyl and *N*-H compounds (e.g., **133** and **134**, **135** and **136**). Moreover, the authors determined that dauricumine

could be epimerized to acutumine; however, the converse relationship was not observed. This collective data suggests that dauricumine (**135**) is a biogenetic precursor to **133**, **134**, and **136**.

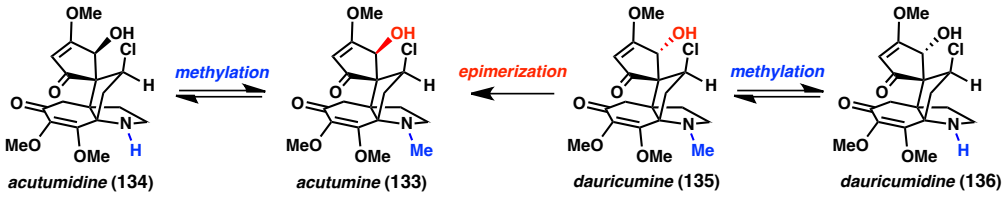

Figure 5. Potential interconversion between the acutumine alkaloids.

In spite of these biosynthetic investigations, there remain a number of aspects of the proposed pathway that need to be addressed. Although a number of parallels can be drawn between propellane formation of acutumine and the hasubanan alkaloids,[15] 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 chlorination reactions.[16] Further studies that carefully examine these potential biogenetic pathways will ultimately deepen our understanding of propellane alkaloid synthesis.

3.4. Previous Synthetic Studies

Despite the fact that its structure was elucidated over 40 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.

3.4.1. Sorensen's Strategy

In 2007, Sorensen and Moreau reported their synthetic approach toward acutumine. Specifically, the authors sought to harness the reactivity of enolates to construct the propellane framework.[17] To this end, readily available pyrrolidinone **164** was advanced to alkyne **166** following an enolate alkylation/Grignard addition reaction sequence. Exposure of **166** to $VO(acac)_2$ and *t*-BuOOH facilitated a directed epoxidation of the pendant olefin, thereby delivering **167** in good yield. Palladium-catalyzed carbonylative cyclization of **167** afforded the corresponding vinylogous ester, which was subjected to periodate-mediated oxidation to yield ketone **168**.

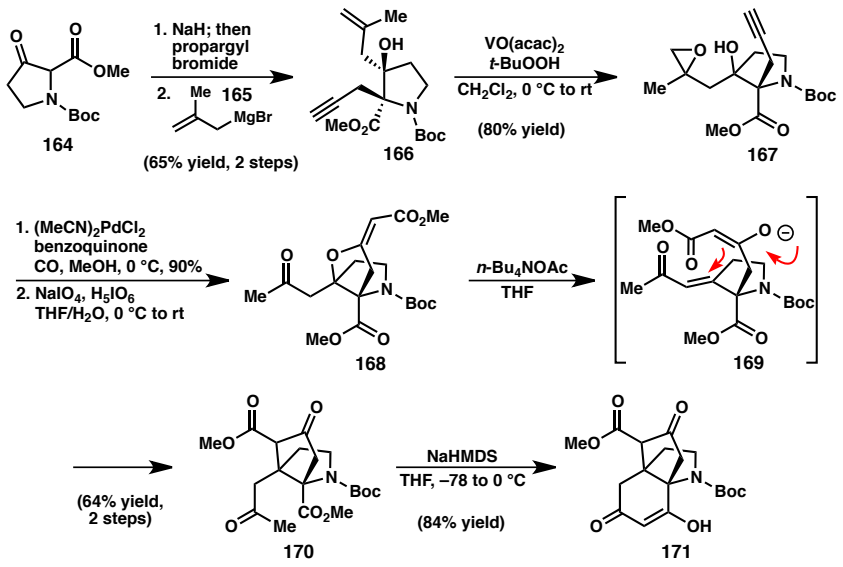

Figure 6. Sorensen's approach to acutumine.

In a key step in their synthesis, the authors found that treatment of **168** with a mild base unveils enolate **169**, which immediately attacks the α,β-unsaturated ketone moiety to afford β-ketoester **170**. The D ring of acutumine was then constructed by a Dieckmann cyclization, which yielded propellane **171** in 84% yield. Using this sequence, **171** could be accessed in 10 steps from commercially available starting materials. Unfortunately, attempts to advance this and similar intermediates to the natural product have proven unfruitful.[18,19]

3.4.2. Castle's Total Synthesis

The first total synthesis of acutumine was accomplished by Castle and coworkers in 2009.[20] Their synthetic efforts commenced with Weinreb amide **173**, an intermediate that suffers nucleophilic attack by the Grignard reagent of vinyl iodide **172** to give enone **174**. 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 **175** in 59% yield over two steps. Enone **176** could be prepared from **175** via cleavage of the TES group and subsequent oxidation of the free alcohol.

With access to **176**, 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,[21] the desired transformation was effected by irradiation of **176** in the presence of $(Bu_3Sn)_2/Et_3Al$ followed by addition of oxaziridine **177**, ultimately providing **178** in 69% yield. After an additional five steps, **178** could be elaborated to *o*-quinone monoketal **179**. Allylation of this intermediate with chiral allylzinc reagent **180** afforded alcohol **181** in good yield and excellent diastereoselectivity. At this point, 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 **133** was constructed by treatment of amine **182** with BCl_3, which provided propellane **183** in 45% yield. Additional functional group manipulations led to the synthesis of acutumine (**133**) in a total of 29 steps from commercially available starting materials.

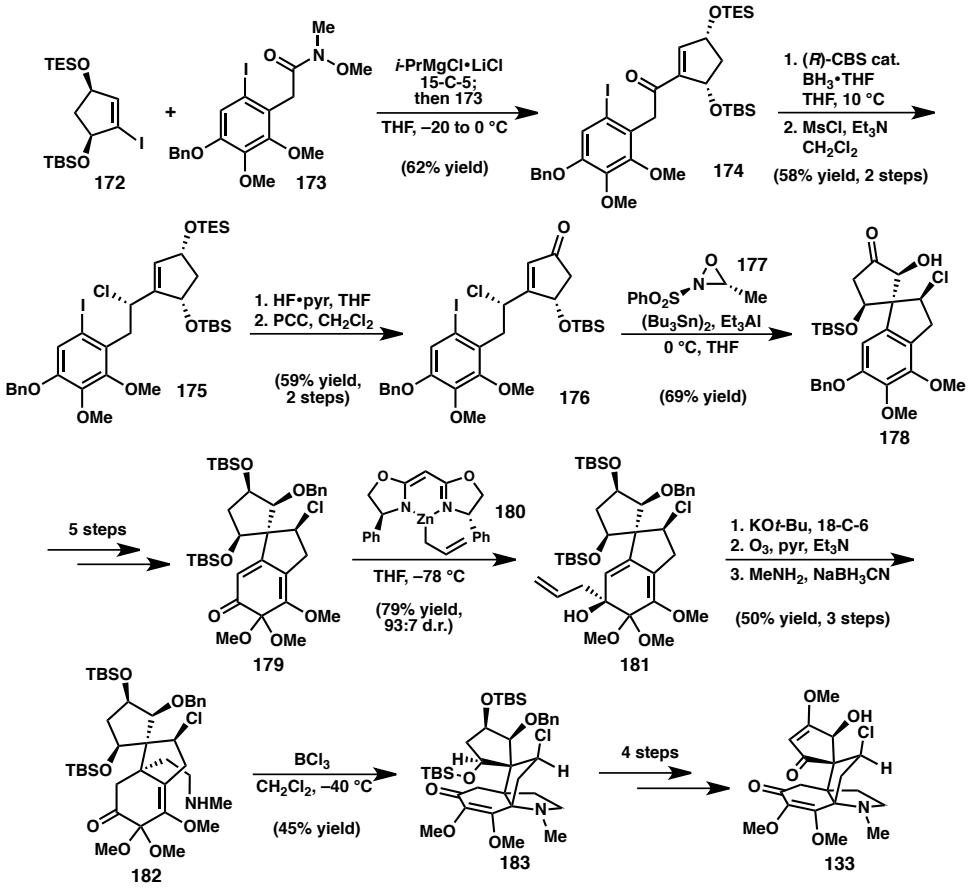

Figure 7. Castle's total synthesis of acutumine.

3.4.3. Herzon's Total Synthesis

The Herzon group recently disclosed their efforts toward a number of propellane alkaloids, which has culminated in the preparation of acutumine.[22] In accord with their

synthetic strategy toward the hasubanan alkaloids,[23] treatment of **184** with MeOTf followed by addition of organolithium **185** at –90 °C afforded 1,2-addition product **186** in 85% yield (Figure 8). Thermal extrusion of 5-trimethylsilylcyclopentadiene and hydrostannylation of **186** delivered dienone **187**. Moving forward, the authors were able to install both all-carbon quaternary stereocenters in a single step by treatment of **187** with TBAF in DMF; however, this key reaction furnishes **188** in only 37% yield.

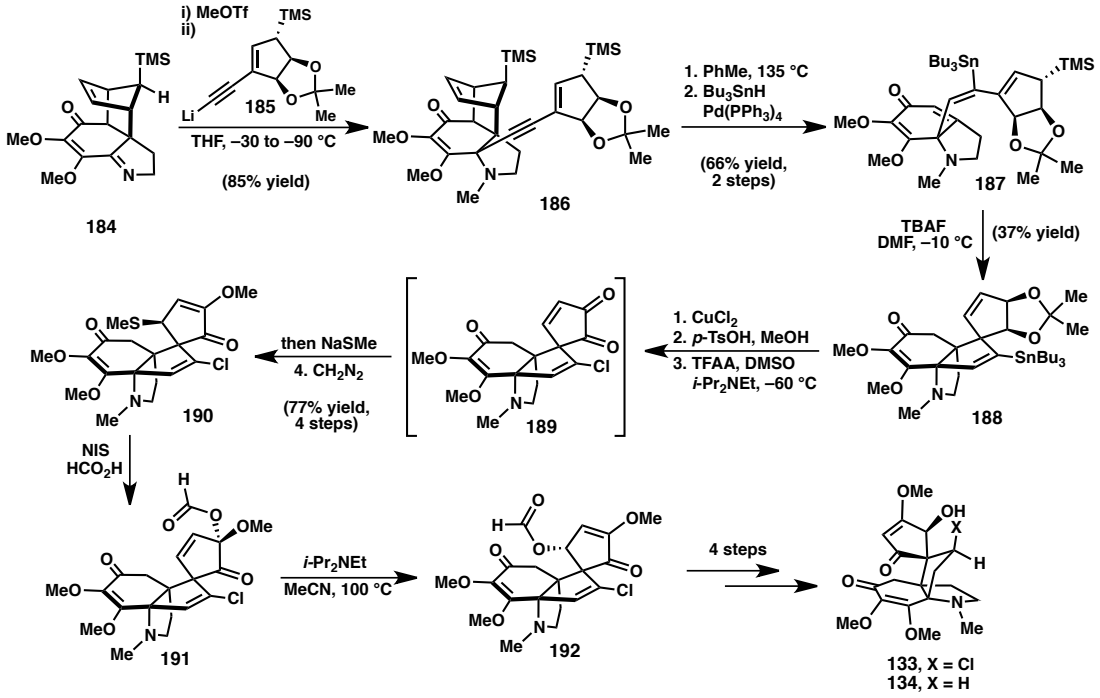

Figure 8. Herzon's synthesis of **133** and **134**.

At this point, completion of the synthesis required installation of the chloride and elaboration of the A-ring (see Figure 1, **132**) to the requisite cyclopentenone. Toward this goal, chlorodestannylation and acid-mediated acetonide cleavage afforded the corresponding diol, which was oxidized to diketone **189**. In situ trapping of **189** with

sodium methanethiolate and treatment with diazomethane yielded methoxyenone **190**. Activation of the sulfide with *N*-iodosuccinimide in formic acid promoted the formation of mixed ketal **191**, an intermediate subjected to thermal [3,3] sigmatropic rearrangement conditions to deliver formate ester **192**. In four additional steps, the authors could advance **192** to acutumine (**133**) and dechloroacutumine (**134**).

3.5. Concluding Remarks

Almost 50 years have elapsed since the first investigations regarding the biosynthesis and structure of acutumine were reported. Despite its decades of history, this alkaloid remains an elusive target for total chemical synthesis. Nevertheless, the studies discussed in this chapter highlight our ability as synthetic chemists to implement novel synthetic technologies toward densely functionalized, polycyclic alkaloid natural products. As new members of this family continue to emerge, it will become increasingly important to develop novel and efficient approaches to access these complex alkaloids.

3.6. Notes and References

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