

# The aporhoadane alkaloids

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## Abstract

The aporhoadane alkaloids, exemplified by the natural products chilenine and lennoxamine, have received significant attention from the synthetic community over the course of nearly 50 years. This review details the approaches to these heterocycles, as well as their major reactions.

**Keywords:** Isoindolobenzazepines, chilenine, lennoxamine, Schöpf's base VI, chilenamine

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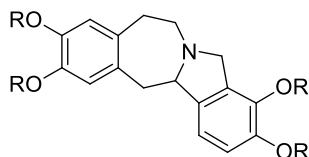
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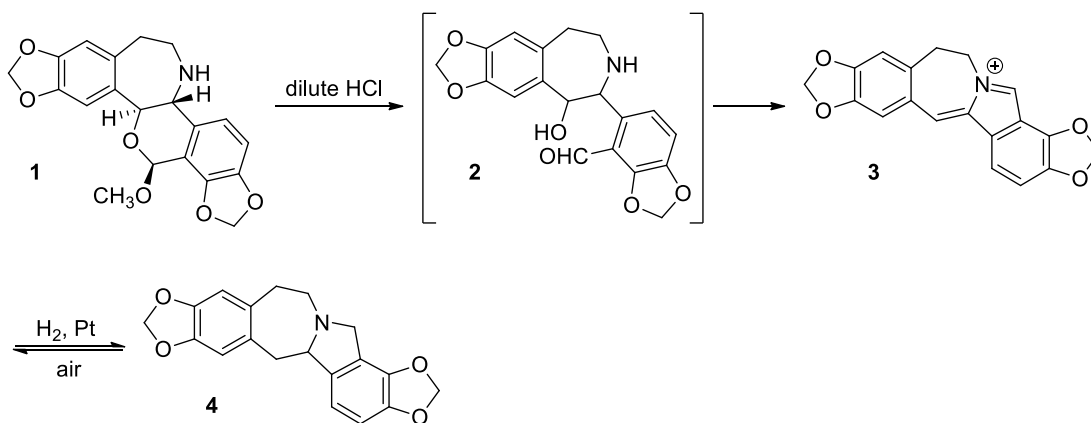
## 1. Introduction

The substituted isoindolo[2,3-*c*][3]benzazepine shown in Figure 1 has been termed aporhoeadane, suggesting structural similarity to the rhoeadane and papaverrubine alkaloids.<sup>1</sup>



**Figure 1.** The aporhoeadane core.

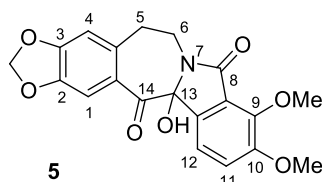
This structural similarity is highlighted by the fact that norisorhoeadine, also known as papaverrubine A (**1**, Scheme 1), is converted into the isoindolobenzazepine **4** upon treatment with dilute hydrochloric acid. Fragmentation of the acetal leads to aldehyde **2**, which cyclizes and dehydrates to form iminium ion **3**. This iminium ion can be reduced to provide aporhoeadane **4**, which oxidizes freely back to **3** upon exposure to air.<sup>2</sup>



**Scheme 1.** Conversion of papaverrubine A to an aporhoeadane.

Since the intermediate iminium ion is intensely red, this reaction had been used to identify opium samples, which commonly contain papaverrubines.<sup>1</sup>

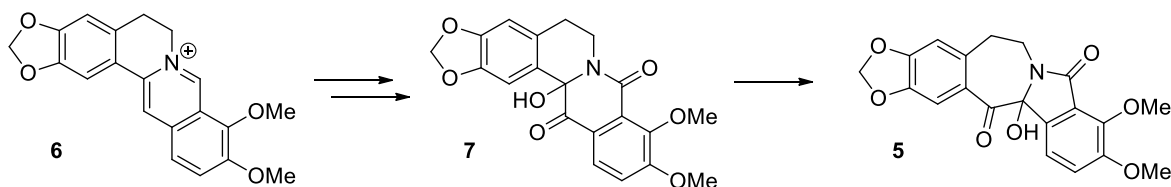
(±)-Chilenine (**5**, Figure 2), isolated from Chilean barberries (*Berberis empetrifolia* Lam), was the first example of the aporhoadane skeleton appearing in a natural product.<sup>3</sup> Various numbering schemes have been used for structures of this type. The numbering system designated by Shamma and co-workers, who isolated this natural product, will be used in this review.



**Figure 2.** Chilenine.

Chilenine exhibits weak cytotoxic activity against breast, lung, colon, and prostate cancer cells, as well as epidermoid carcinoma of the nasopharynx, with  $IC_{50}$  values in the  $\mu M$  range. Chilenine also demonstrated weak antimalarial activity.<sup>4</sup>

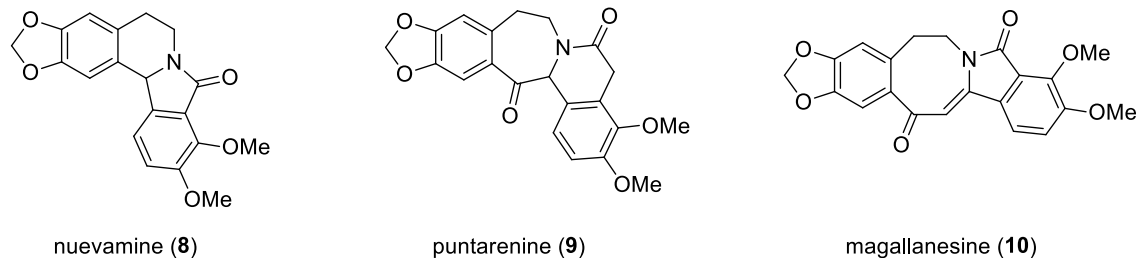
Biosynthetically, chilenine is believed to originate from berberine (**6**) via oxidation to a compound that has been termed prechilenine (**7**) and subsequent base-catalyzed rearrangement of the six/six ring system to a seven/five system (Scheme 2).<sup>3</sup>



**Scheme 2.** Proposed biosynthesis of chilenine from berberine via prechilenine.

Prechilenine was isolated as its *O*-methyl ether from *Berberis darwinii* Hook.<sup>5</sup> The *O*-methyl ether is believed to originate from prechilenine, particularly since this transformation happens readily *in vitro* (*vide infra*).<sup>6</sup>

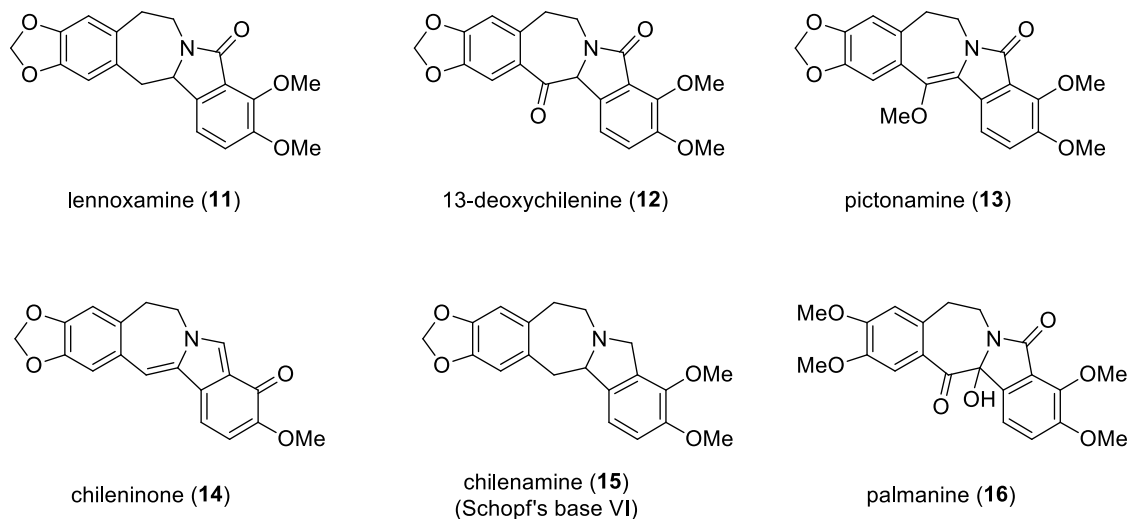
Several analogues have been isolated from plants of the family *Berberidaceae*. These include analogues having different ring sizes, such as: the nor analogue (±)-nuevamine (**8**, from *Berberis darwinii*), the first known isoindoloisoquinoline natural product,<sup>7</sup> the homologue (±)-puntarenine (**9**, from *Berberis empetrifolia*, as well as from *Xanthorhiza simplicissima* Marsha.),<sup>8,9</sup> and the isoindolobenzazocine (±)-magallanesine (**10**, from *Berberis darwinii*)<sup>10</sup> (Figure 3).



**Figure 3.** Analogues of chilenine having different ring sizes.

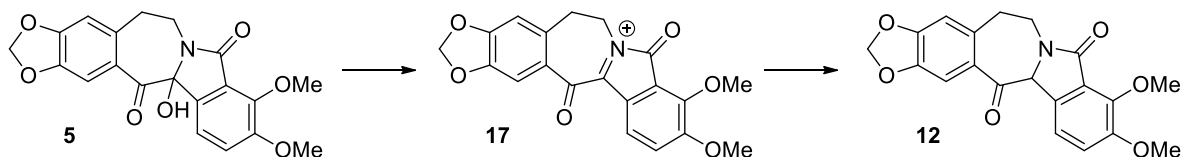
The diversity of ring systems illustrates that “the family *Berberidaceae* possesses a unique propensity for expansion as well as contraction of nitrogenous rings.”<sup>10</sup> Interestingly, saulatine, a congener of puntarenine in which the methylenedioxy bridge is replaced by two methoxy groups, was isolated from *Abuta bullata* Moldenke (family *Menispermaceae*).<sup>11</sup> A similar analogue of chilenine is described shortly.

Additionally, a number of analogues bearing the aporphoadane core have been isolated, including: the partially reduced analogue ( $\pm$ )-lennoxamine (**11**, from *Berberis darwinii*).<sup>7</sup> ( $\pm$ )-13-deoxychilenine (**12**, from *Berberis actinacantha* Mart. Ex Schult.),<sup>5</sup> pictonamine, the methyl enol ether of deoxychilenine (**13**, from *Berberis darwinii*),<sup>5</sup> chileninone (**14**, from *Berberis actinacantha*, *Berberis darwinii*, and *Berberis valdiviana* Phil.),<sup>5</sup> ( $\pm$ )-chilenamine (**15**), also widely known as Schöpf’s base VI or Schöpf-Schweickert base VI (from *Berberis darwinii*),<sup>5</sup> and ( $\pm$ )-palmanine (**16**), the tetramethoxy analogue of chilenine (from *Berberis actinacantha*)<sup>5</sup> (Figure 4).



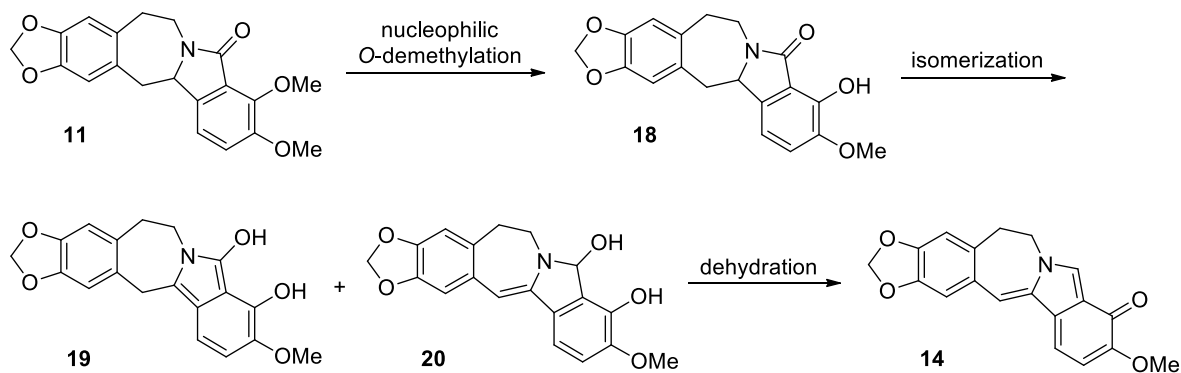
**Figure 4.** Uniquely functionalized analogues of chilenine.

It is suspected that the biogenesis of lennoxamine results from a series of dehydrations and reductions of chilenine.<sup>7</sup> Similarly, 13-deoxychilenine (**12**) is believed to result from chilenine (**5**) via loss of the hydroxyl group to form iminium ion **17** and subsequent reduction (Scheme 3).<sup>5</sup>



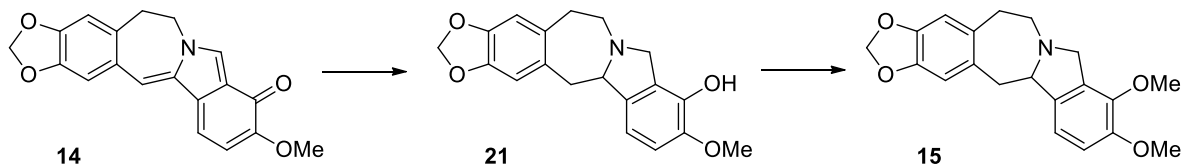
**Scheme 3.** Proposed biogenesis of 13-deoxychilenine.

A possible biosynthesis of chileninone (**14**) has been proposed to involve nucleophilic *O*-demethylation of lennoxamine, yielding a phenol (**18**) whose isomerization and dehydration would result in chileninone (Scheme 4).



**Scheme 4.** Possible biosynthesis of chileninone.

While the biogenesis of chilenamine (**15**) is less clear, one hypothesis involves the *in vivo* reduction of chileninone (**14**) to phenol **21** followed by enzymatic *O*-methylation (Scheme 5).<sup>5</sup>



**Scheme 5.** Proposed biogenesis of chilenamine.

Structural similarities between the aporphoeadanes and several other classes of alkaloids (e.g. the berberines, papaverrubines, protopines, and rhoeadines) explain why the aporphoeadanes are common degradation products of other heterocycles isolated from natural sources, why they can

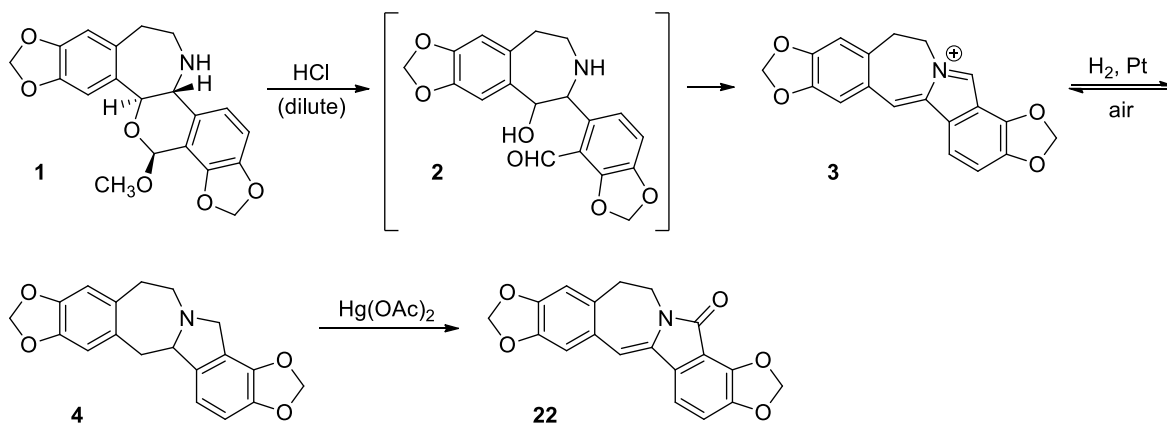
be prepared from these natural products, and why the aporphoeadanes might serve as synthetic precursors to diverse heterocyclic structures.

Sections 2-4 here describe the syntheses of aporphoeadanes. The syntheses within each section are ordered chronologically, and each synthetic strategy is categorized by the bond or bonds formed during the end game of the synthesis. Section 5 details the principal reactions of aporphoeadanes.

## 2. Late-stage Synthesis of the Isoindole

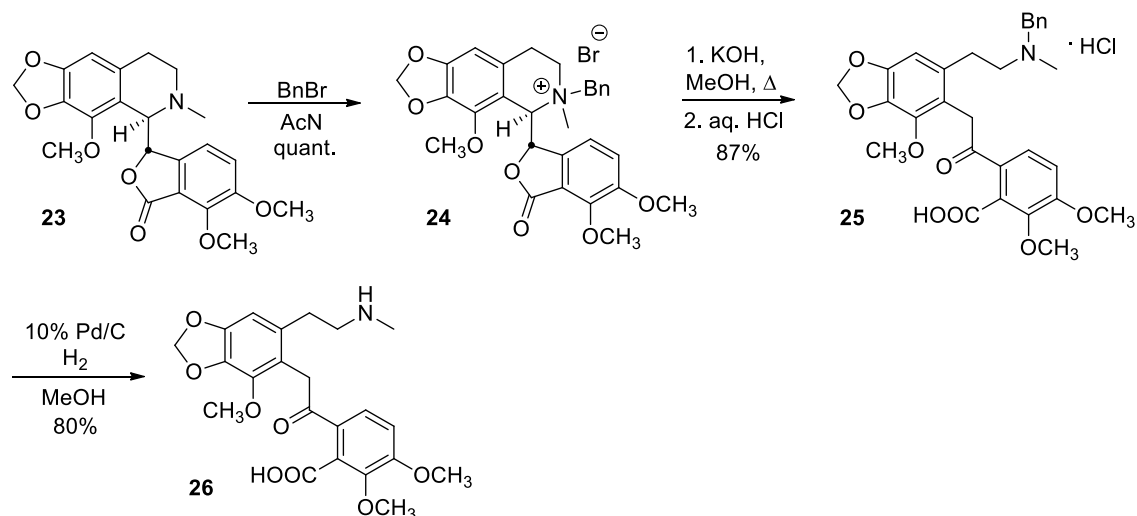
### 2.1. Formation of the N7-C8 bond

Papaverrubine A (**1**, the *N*-desmethyl analogue of isorhoeadine) has been modified to provide the aporphoeadane skeleton (Scheme 6).<sup>2,12-15</sup> Treatment of papaverrubine A with dilute hydrochloric acid produces the intensely red iminium salt **3**. Reduction to the tertiary amine (**4**) is readily reversed through exposure to air. However, oxidation with mercuric acetate yields the enelactam **22**.



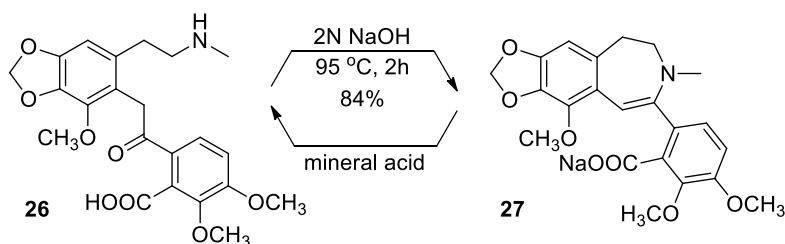
**Scheme 6.** Synthesis of an aporphoeadane enelactam from papaverrubine A.

The phthalide alkaloids (–)- $\alpha$ -narcotine and (–)- $\beta$ -hydrastine have also served as starting materials for aporphoeadane synthesis. For instance, (–)- $\alpha$ -narcotine (**23**) undergoes benzylation (**24**), Hofmann degradation/hydrolysis (**25**), and hydrogenolysis to yield the opium alkaloid nornarceine (**26**, Scheme 7).<sup>16</sup>



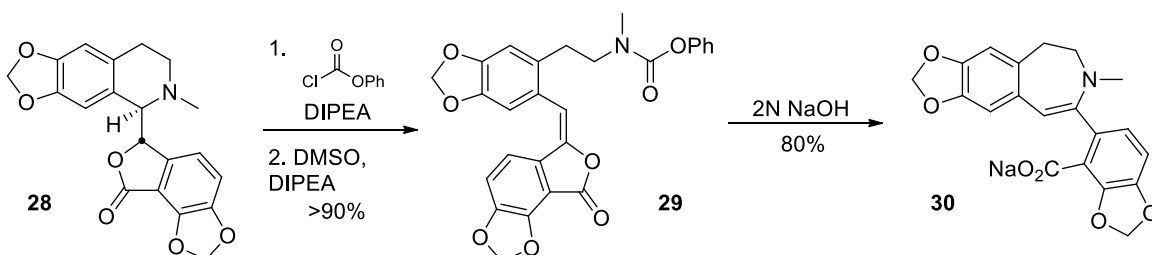
**Scheme 7.** The conversion of (-)- $\alpha$ -narcotine to normarceine.

Normarceine (**26**) can be subjected to reversible cyclization to produce dihydrobenzazepine **27**.<sup>17</sup>



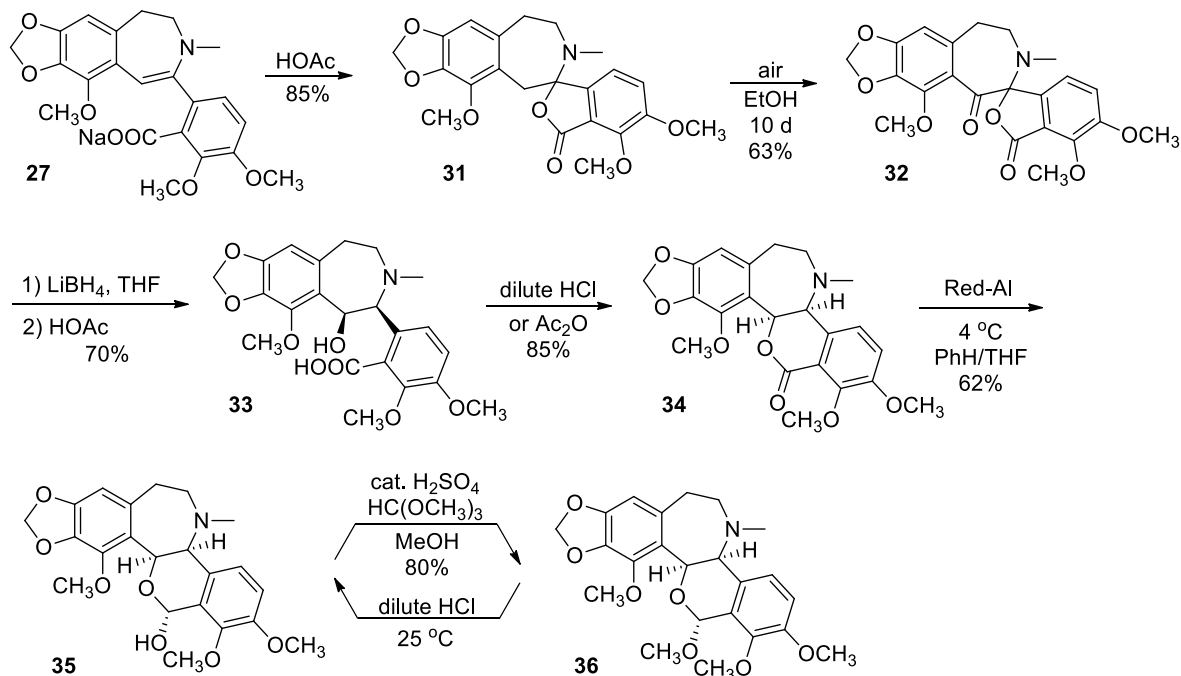
**Scheme 8.** Reversible cyclization of normarceine.

A closely related analog of dihydrobenzazepine **27** has also been produced from (-)- $\beta$ -hydrastine via (-)-bicuculline (**28**, Scheme 9).<sup>18</sup> Bicuculline yields urethane **29** upon treatment with phenyl chloroformate and elimination, and this urethane cyclizes in base to dihydrobenzazepine **30**.



**Scheme 9.** Conversion of (-)- $\beta$ -hydrastine to a dihydrobenzazepine.

Dihydrobenzazepines **27** and **30** have proven to be useful intermediates in the preparation of both rheadans and aporphoadanes. For instance, dihydrobenzazepine **27** been converted into 11-methyl-2,3-methylenedioxy-4,6,7,8-tetramethoxyrheadan (**36**, Scheme 10).<sup>17</sup> Conversion into the spiro lactone **31** was followed by oxidation to ketolactone **32**. Subsequent reduction and lactonization yielded *cis*-lactone **34**, which can be reduced with Red-Al to provide 6-hydroxyrheadan (**35**), whose reversible etherification yields 11-methyl-2,3-methylenedioxy-4,6,7,8-tetramethoxyrheadan (**36**).

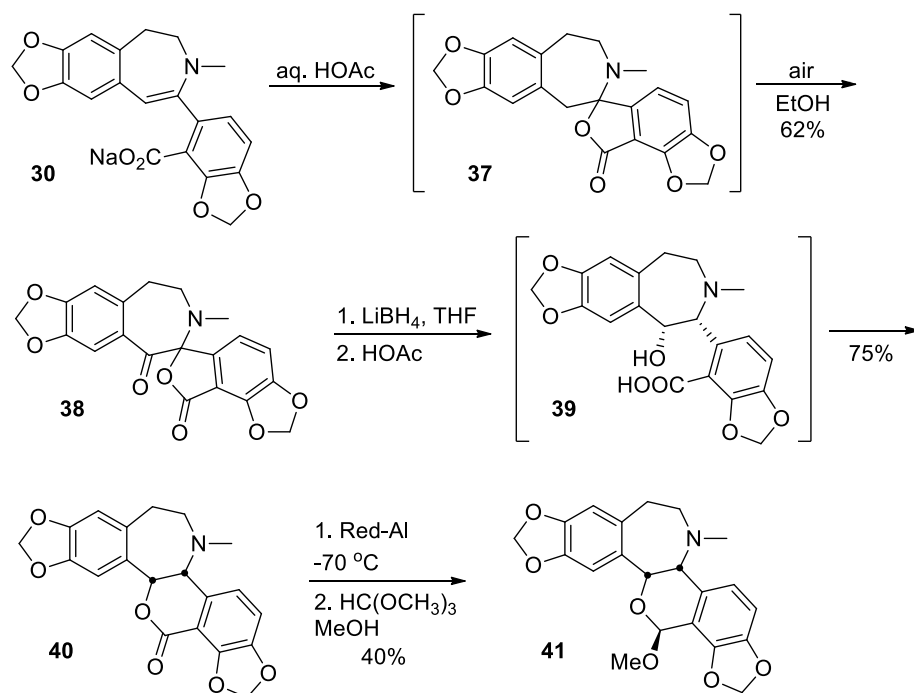


**Scheme 10.** Conversion of dihydrobenzazepine **27** into 11-methyl-2,3-methylenedioxy-4,6,7,8-tetramethoxyrheadan.

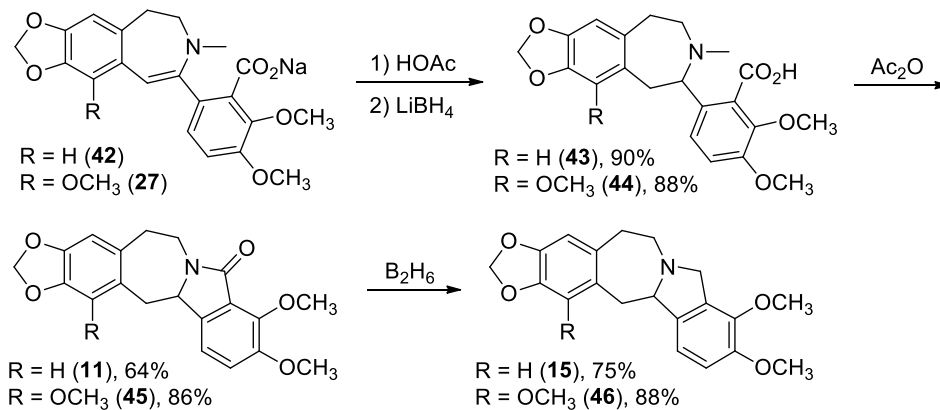
An analogous protocol with dihydrobenzazepine **30** afforded rheadine (Scheme 11).<sup>18</sup>

However, when treatment with acetic acid is followed immediately by reduction rather than air oxidation, the saturated amino acids **43** and **44** result (Scheme 12).<sup>19</sup> Acetic anhydride-induced lactamization yields lennoxamine (**11**) or its methoxy analog **45**. Finally, diborane reduction provides Schöpf's base VI (**15**) or its methoxy analog **46**.





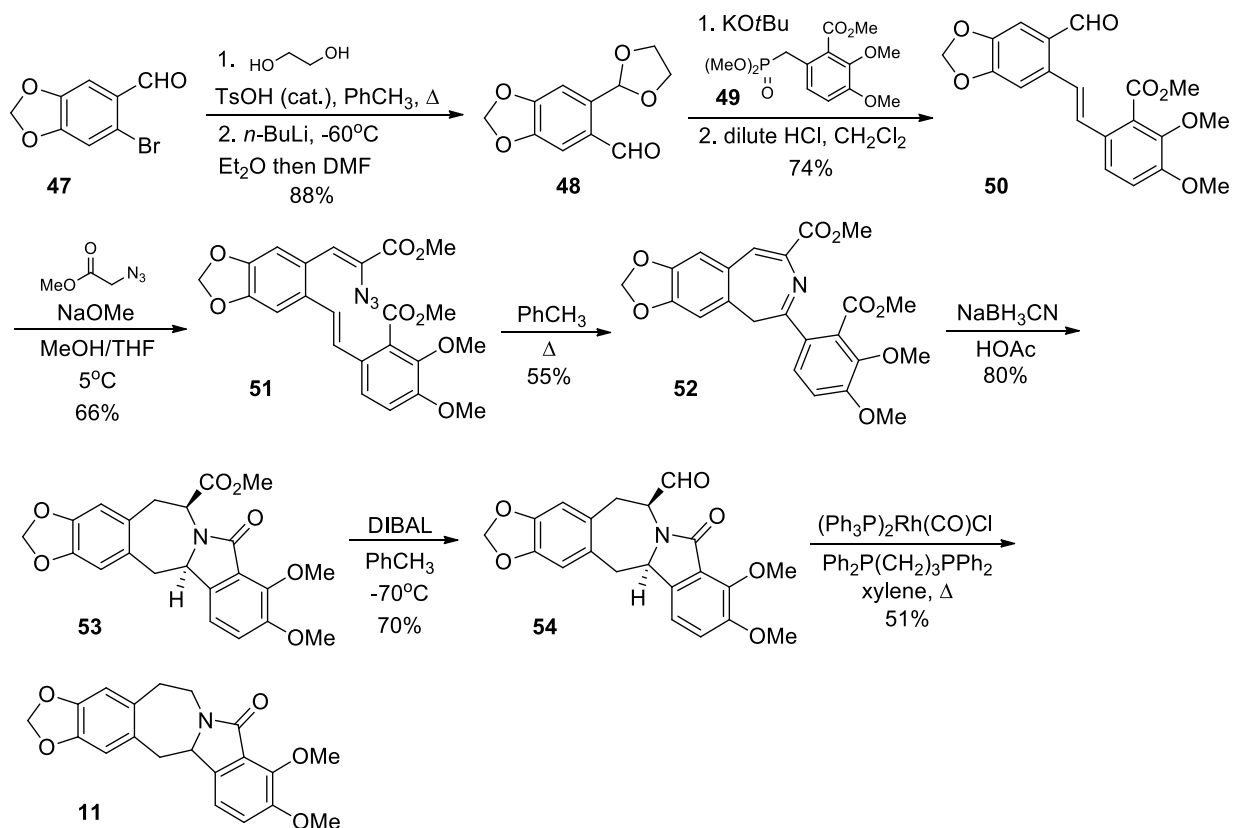
**Scheme 11.** Conversion of dihydrobenzazepine **30** to rhoeadine.



**Scheme 12.** Conversion of dihydrobenzazepines to lennoxamine, Schöpf's base VI, and their analogues.

Moody and Warrelow devised an approach to lennoxamine that also employs late-stage formation of the N7-C8 bond; however, their approach constructs the benzazepine system from simple substrates, rather than relying upon modification of a papaverrubine or phthalide alkaloid.<sup>20,21</sup> 6-Bromopiperonal (**47**) was converted to the mono-protected dialdehyde (**48**), followed by union with dimethoxybenzoate (**49**) under Wadsworth-Emmons conditions (Scheme 13). Liberation of the remaining aldehyde provided (*E*)-stilbene aldehyde **50**. Subsequent

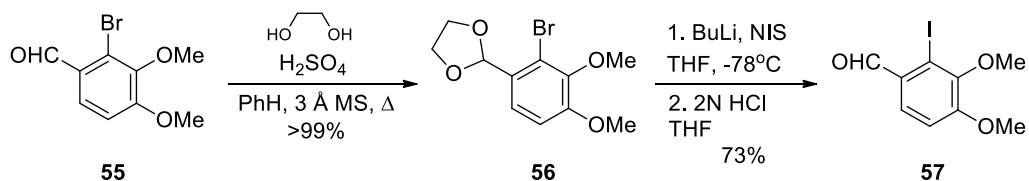
condensation with methyl azidoacetate provided an unstable azide (**51**) that could be heated to yield the critical benzazepine **52** in the key step of the synthesis. The benzazepine was accompanied by a 29% yield of an undesired benzyloquinoline side product. Reduction of both olefins of the benzazepine with sodium cyanoborohydride was accompanied by intramolecular cyclization that formed the N7-C8 bond giving the tetrahydroisindolobenzazepine core (**53**). The removal of the undesired ester at C6 was accomplished by DIBAL reduction to the aldehyde (**54**) and decarbonylation with bis(triphenylphosphine)rhodium(I) carbonyl chloride, ultimately yielding lennoxamine (**11**).



**Scheme 13.** Synthesis of lennoxamine via azide cyclization.

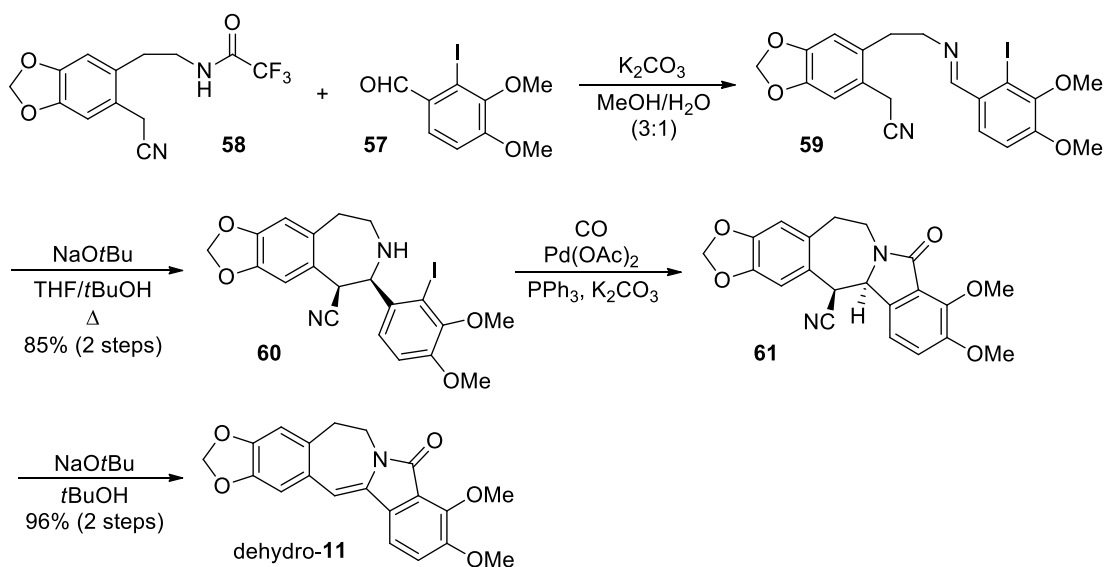
## 2.2. Formation of the N7-C8 and C8-C8a bonds

Orito and co-workers investigated the synthesis of dehydrolennoxamine (dehydro-**11**), and therefore the formal synthesis of lennoxamine,<sup>73,75</sup> and chilenine,<sup>54</sup> through palladium-catalyzed carbonylation.<sup>29</sup> Their route began with the preparation of aryl iodide **57** from aryl bromide **55** via protection of the aldehyde (**56**), halogen exchange, and deprotection (Scheme 14).



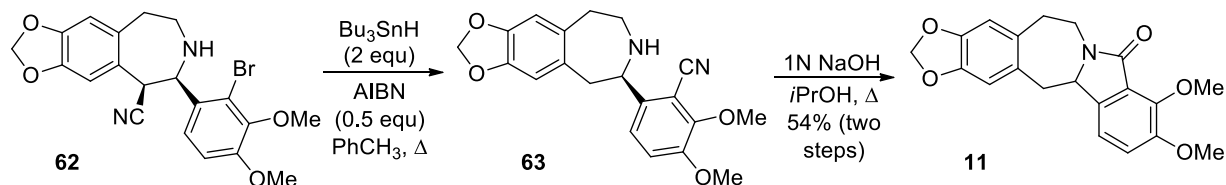
**Scheme 14.** Synthesis of aryl iodide **57**.

The aryl iodide was then coupled with trifluoroacetamide **58** (Scheme 15). Cyclization under basic conditions yielded benzazepine **60**, and at this stage palladium-catalyzed carbonylation formed the isoindolone ring of **61**, which was immediately subjected to elimination providing dehydrolennoxamine (dehydro-**11**).



**Scheme 15.** Synthesis of dehydrolennoxamine through carbonylation.

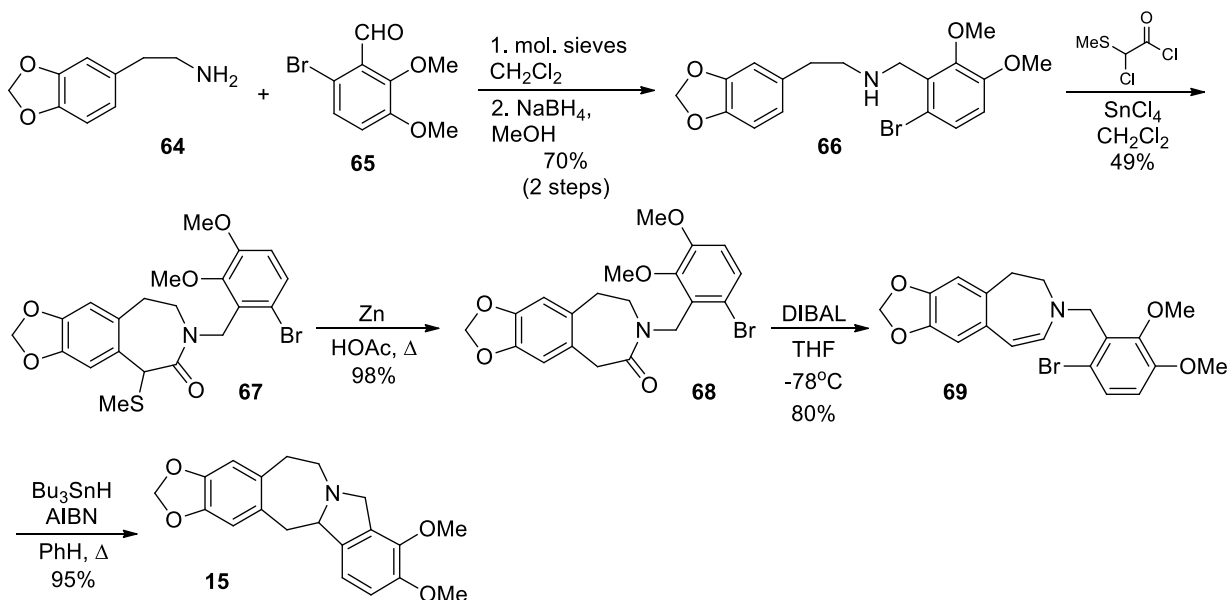
A bromo-substituted benzazepine (**62**, Scheme 16), prepared in an analogous fashion to its iodinated counterpart **60**, underwent migration of the cyano group under radical conditions (**63**), and subsequent basic cyclization afforded lennoxamine (**11**). This was the first reported synthesis of a natural product to employ cyano group migration.<sup>29</sup>



**Scheme 16.** Synthesis of lennoxamine through cyano migration.

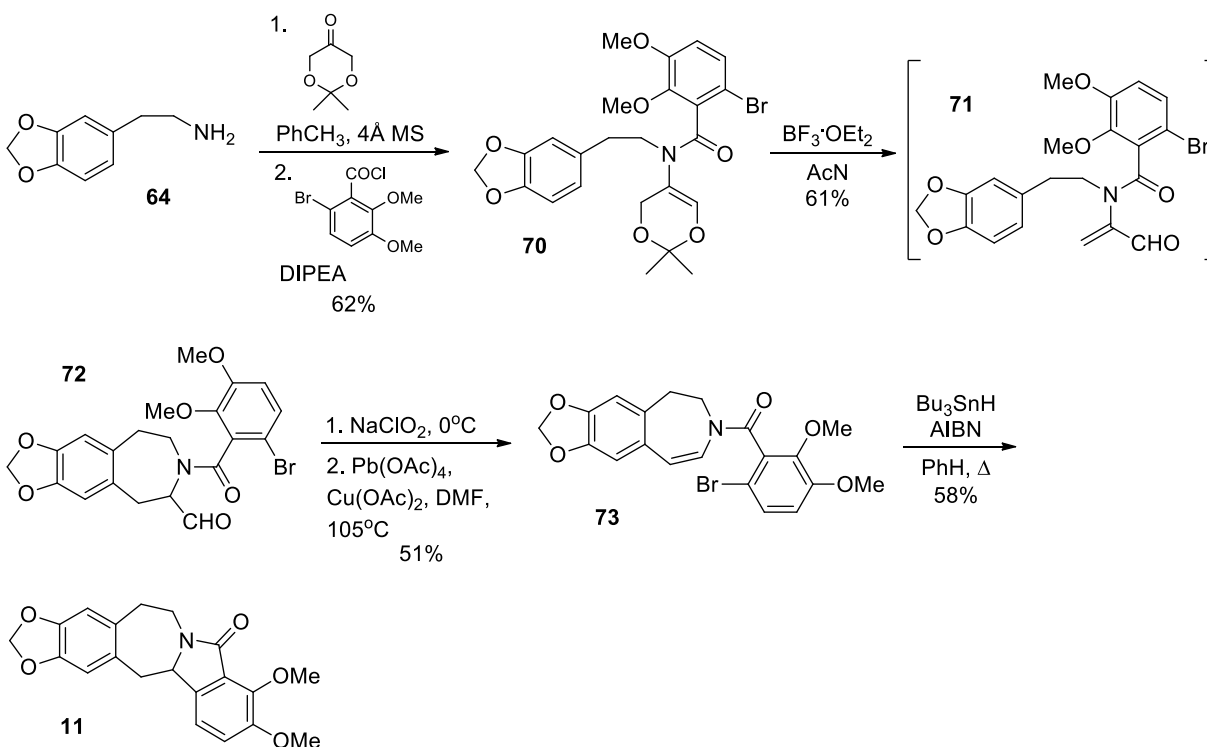
### 2.3. Formation of the C12a-C13 bond

Hanaoka and co-workers developed a synthesis of chilenamine (**15**) that built on their previous work using cyclization of sulfur-stabilized carbocations for the formation of alkaloids.<sup>22</sup> 3,4-Methylenedioxyphenethylamine (**64**) and 6-bromo-2,3-dimethoxybenzaldehyde (**65**) were condensed, and the resultant imine was reduced with sodium borohydride (**66**, Scheme 17). *N*-acylation using  $\alpha$ -chloro- $\alpha$ -methylthioacetyl chloride and cyclization of the sulfur-stabilized carbocation yielded lactam **67**. Desulfurization was performed with zinc in acetic acid (**68**), and reduction of the lactam afforded the enamine (**69**). Radical cyclization closed the isoindole ring and completed the synthesis of chilenamine (**15**).



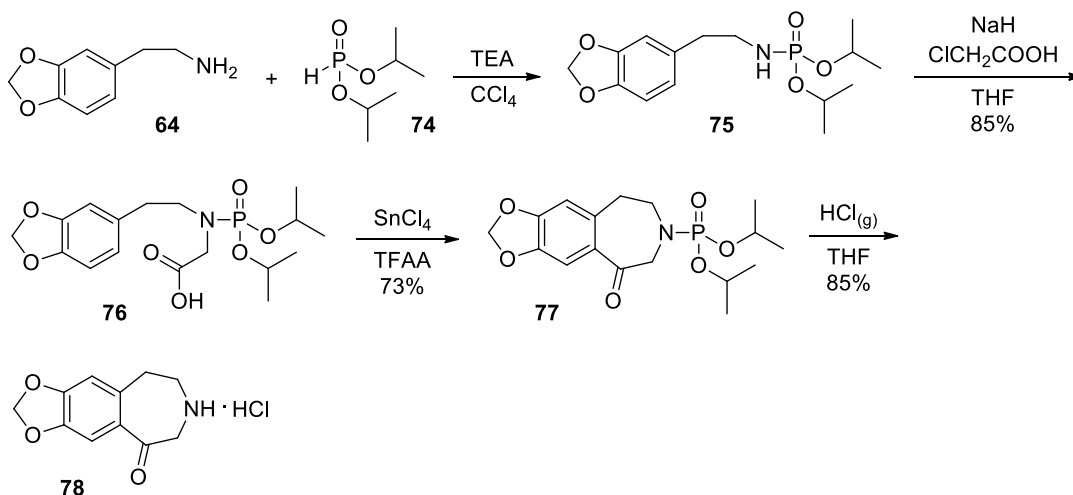
**Scheme 17.** Chilenamine synthesis employing cyclization of a sulfur-stabilized carbocation.

Fuchs and Funk developed an approach to the synthesis of lennoxamine (**11**) that relies upon an integral intramolecular EAS reaction of a 2-amidoacrolein formed via retrocycloaddition.<sup>23</sup> The synthesis began with phenethylamine **64**, which was condensed with 1,3-dioxin-5-one (Scheme 18). The imine thus formed was acylated to yield enamide **70**. Exposure to Lewis acid induced a retrocycloaddition to unveil the 2-amidoacrolein (**71**), which immediately underwent intramolecular EAS to provide the benzazepine (**72**). Oxidation of the aldehyde to its corresponding acid using sodium chlorite was followed by a Kochi reaction that installed the C13-C14 olefin (**73**). Finally, radical cyclization produced lennoxamine (**11**) in 58% yield along with 26% yield of the debrominated enamide.



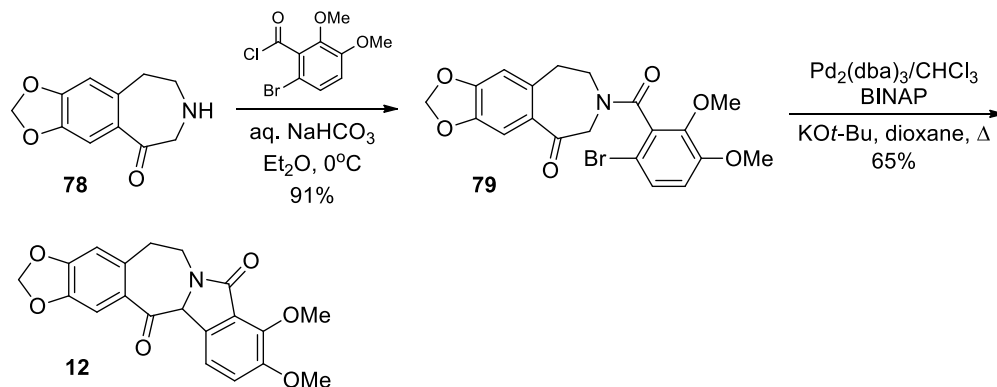
**Scheme 18.** Synthesis of lennoxamine through key cyclization of a 2-amidoacrolein.

Honda and Sakamaki reported a synthesis of 13-deoxychilenine (**12**), lennoxamine (**11**), and chilenine (**5**) that relies upon a palladium-catalyzed intramolecular  $\alpha$ -arylation of a ketone.<sup>24</sup> The benzazepinone (**78**) used as the starting material for this sequence was previously synthesized according to the method shown in Scheme 19.<sup>25</sup>



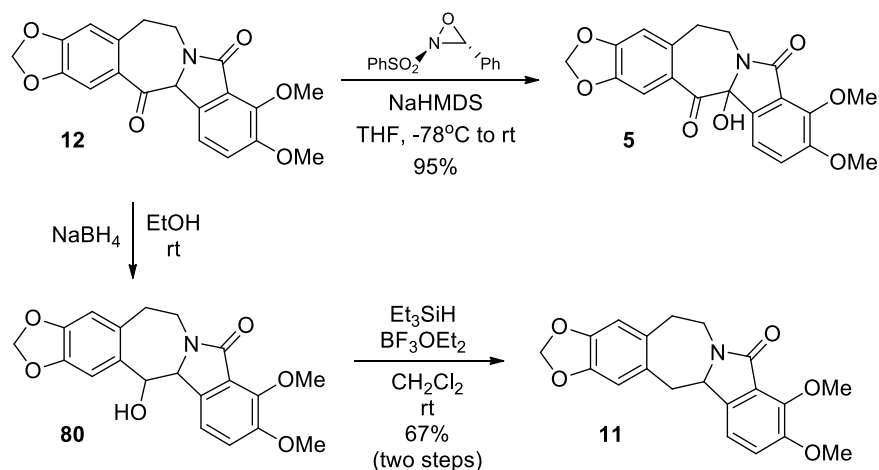
**Scheme 19.** Preparation of a benzazepinone to be used in the synthesis of 13-deoxychilenine.

Schotten-Baumann acylation of benzazepinone **78** yielded the amide **79** (Scheme 20). The key  $\alpha$ -arylation of the ketone then occurred using 5 mol%  $\text{Pd}_2(\text{dba})_3$ , 10 mol% racemic BINAP, and 1.5 equivalents of potassium *tert*-butoxide yielding the first synthesis of 13-deoxychilenine (**12**). The debrominated reactant was an accompanying byproduct (18%).



**Scheme 20.** Synthesis of 13-deoxychilenine.

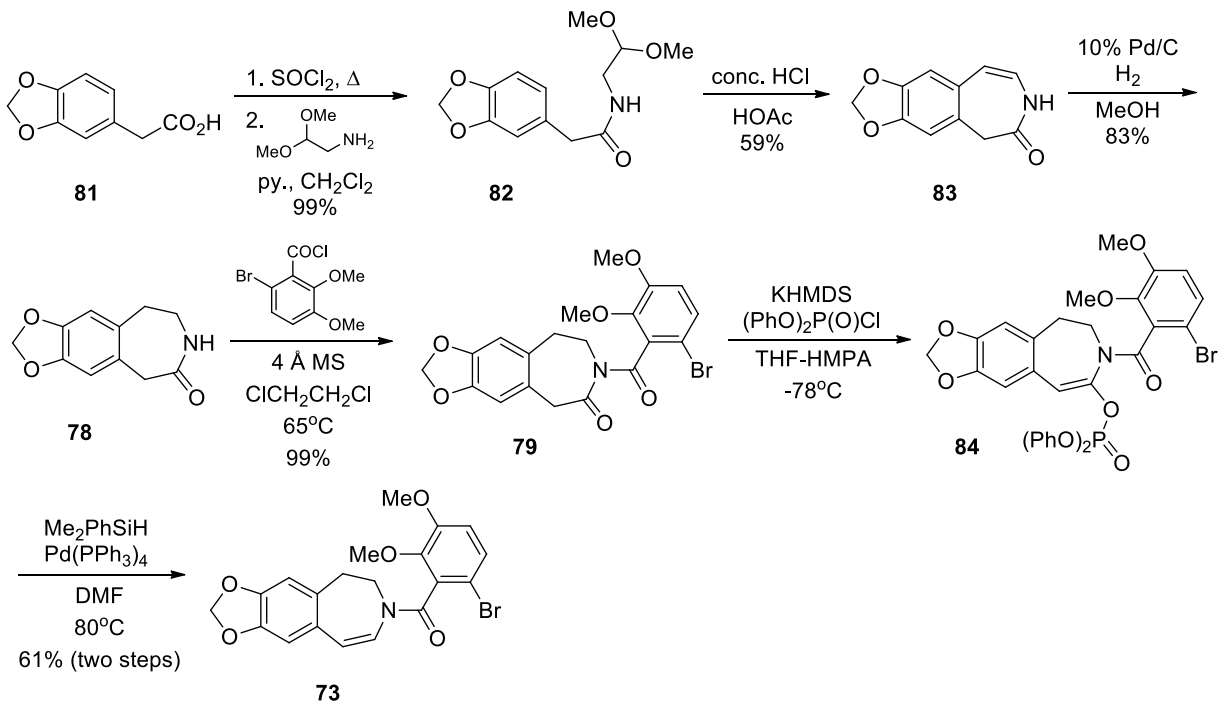
13-Deoxychilenine (**12**) could then be converted to lennoxamine (**11**) by sequential reduction with sodium borohydride and triethylsilane (Scheme 21). Alternatively, 13-deoxychilenine could be transformed into chilenine (**5**) by reaction with sodium hexamethyldisilazane and Davis's reagent.



**Scheme 21.** Synthesis of lennoxamine and chilenine from 13-deoxychilenine.

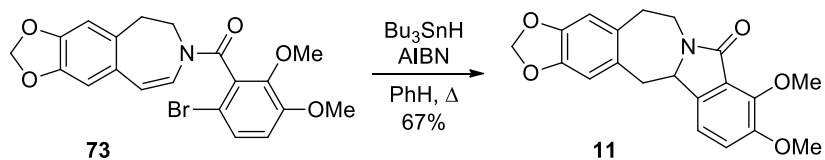
Fuwa and Sasaki developed a route to lennoxamine (**11**) and chilenine (**5**) that relies upon the catalytic hydrosilane reduction of an  $\alpha$ -phosphonoxy enamide (**84**).<sup>26,27</sup> Their synthesis began with 3,4-methylenedioxyphenylacetic acid (**81**), which was activated as the acid chloride and coupled with aminoacetaldehyde dimethyl acetal (Scheme 22). Pomeranz-Fritsch style

cyclization to yield benzazepinone **83** was followed by hydrogenation (**78**) and *N*-acylation (**79**). At this stage, the keystone  $\alpha$ -phosphonoxy enamide (**84**) was prepared. Chemoselective hydrosilane reduction provided the corresponding enamide (**73**).



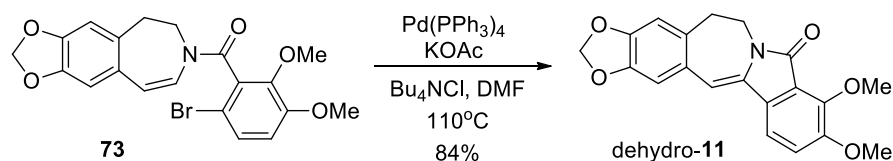
**Scheme 22.** Preparation of enamide **73** using hydrosilane reduction of an  $\alpha$ -phosphonoxy-enamide.

Enamide **73** was converted into lennoxamine (**11**) using the radical cyclization previously employed by Fuchs and Funk (Scheme 23).<sup>23</sup> Additionally, a 25% yield of the debrominated enamide was isolated as a byproduct of this reaction. This approach afforded lennoxamine in seven steps and 20% overall yield.



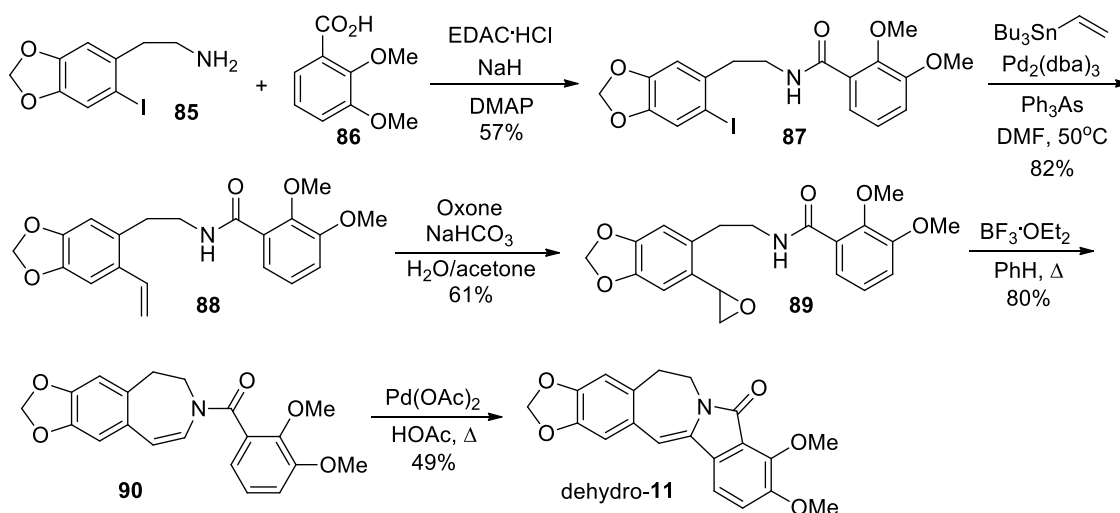
**Scheme 23.** Synthesis of lennoxamine from enamide **73**.

Alternatively, palladium-catalyzed cyclization provided dehydrolennoxamine (dehydro-**11**, Scheme 24), along with 9% recovered starting material. Dehydrolennoxamine has been converted by Fang and Danishefsky into chilene.<sup>54</sup> Consequently, this approach provides chilene in seven steps and 25% overall yield.



**Scheme 24.** Palladium-catalyzed cyclization of enamide **73** to yield dehydrolennoxamine.

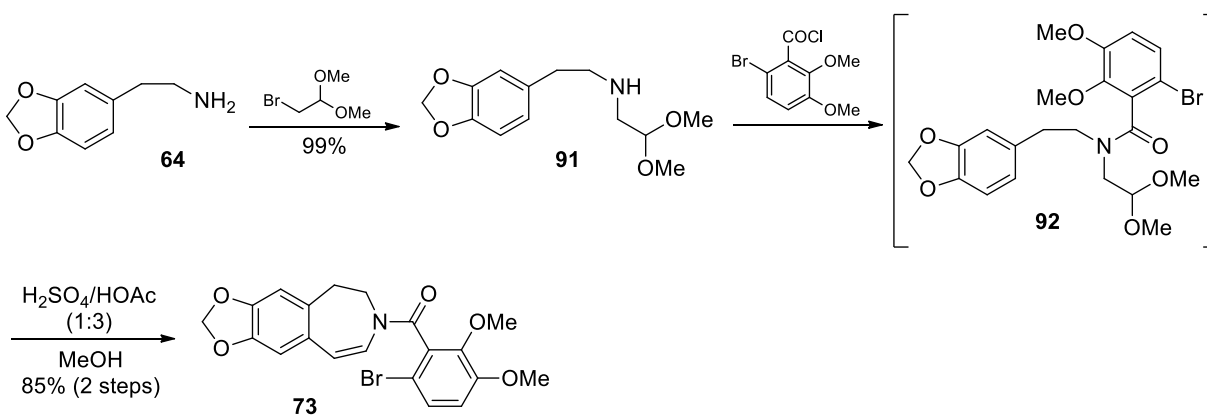
Kim and co-workers also engaged in palladium-mediated closure of the C12a-C13 bond. However, their approach did not require the use of an aryl halide for this cyclization.<sup>28</sup> Phenethylamine **85** and benzoic acid **86** were coupled. Then, Stille reaction with vinyltributylstannane yielded styrene **88**. Treatment with Oxone afforded the epoxide **89**, which was cyclized to the benzazepine (**90**) in the presence of Lewis acid. Finally, treatment with stoichiometric palladium acetate (2 equivalents) induced cyclization of the isoindolone ring giving dehydrolennoxamine (dehydro-**11**) that has been transformed into both lennoxamine,<sup>73,75</sup> and chilenine.<sup>54</sup>



**Scheme 25.** Palladium-catalyzed cyclization of an enamide without an aryl halide coupling partner to yield dehydrolennoxamine.

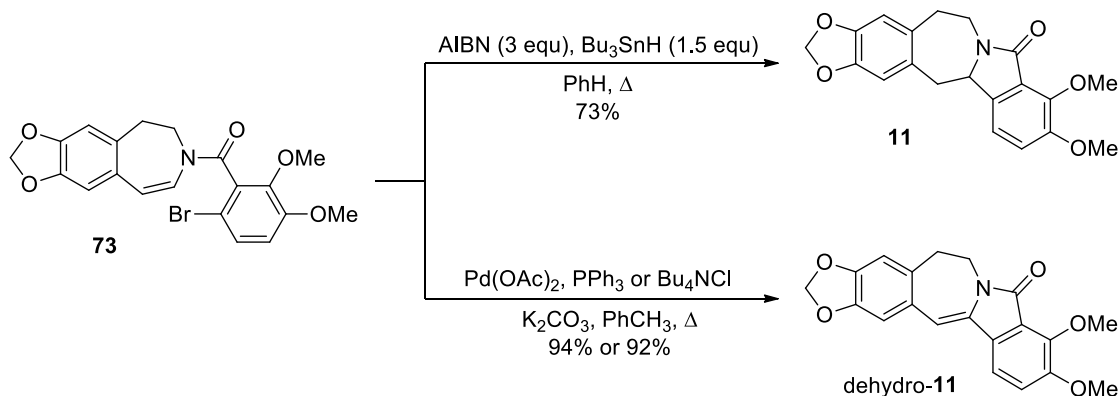
Orito and co-workers engaged in a comparison of radical and palladium-catalyzed cyclizations for formation of the C12a-C13 bond.<sup>29</sup> Both approaches relied upon a common enamide **73**. To initiate preparation of the enamide, *N*-alkylation of phenethylamine **64** with bromoacetaldehyde dimethyl acetal was followed by *N*-acylation with 6-bromo-2,3-dimethoxybenzoyl chloride. The amide thus formed (**92**) was then dissolved in a mixture of sulfuric and acetic acid (1:3) in methanol, which facilitated cyclization in 85% yield over two steps. (Scheme 26)





**Scheme 26.** Alternative preparation of enamide **73**.

Enamide **73** could be subjected to one of two cyclizations to form lennoxamine (**11**) or its dehydro analogue (dehydro-**11**). A radical cyclization, similar to that used by Fuchs and Funk,<sup>23</sup> yielded lennoxamine in 73% yield accompanied by 24% yield of the debrominated enamide. Alternatively, Heck cyclization, employing either triphenylphosphine as the ligand or tetrabutylammonium chloride as the additive, provided dehydrolennoxamine in greater than 90% yield. Since dehydrolennoxamine has been converted to both lennoxamine,<sup>73,75</sup> and chilenine,<sup>54</sup> this represents formal syntheses of these two as well.



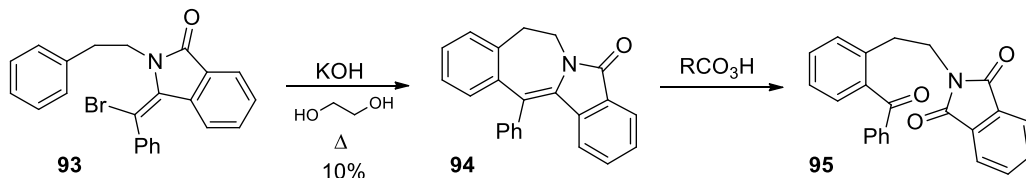
**Scheme 27.** Synthesis of lennoxamine or dehydrolennoxamine from enamide **73**.

### 3. Late-stage Synthesis of the Benzazepine

#### 3.1. Formation of the C14-C14a bond

Photochemistry has played a prominent role in this strategy for constructing the aporphoadane skeleton. For instance, early work by Scartoni and Marsili,<sup>30</sup> employed a vinyl bromide (**93**, Scheme 28) as a cyclization substrate, which provided the aporphoadane core in enlactam **94**, an

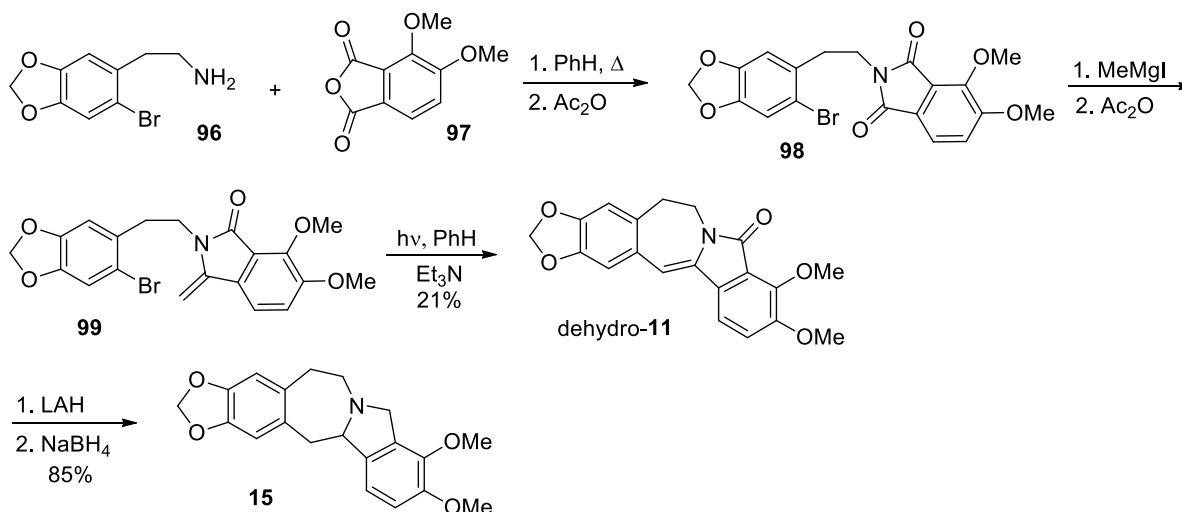
intermediate whose analogues recur in several syntheses of the aporphoadanes. The authors proposed a radical mechanism for the cyclization, which is supported by the observation that a good yield can be obtained by sunlight irradiation.<sup>31</sup>



**Scheme 28.** Benzazepine ring closure and oxidative cleavage.

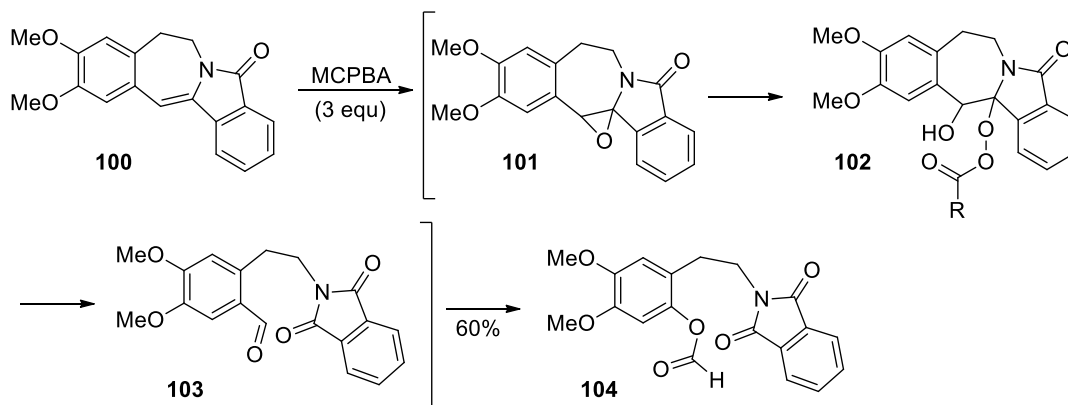
The oxidation of the enlactam with a peroxyacid afforded oxidative cleavage of the seven-membered ring (**95**). This was useful in assigning the structure of the enlactam but illustrates the difficulty of achieving additional oxygenation of the isoindolobenzazepine core.

In a strategically similar approach, Bernhard and Snieckus,<sup>32</sup> described the preparation of an aryl bromide (**99**) as a photocyclization substrate. Aryl bromides were used in this study because attempts to prepare vinyl bromides analogous to those used by Marsili and Scartoni resulted in the formation of angularly substituted isoquinoline derivatives from rapid Pictet-Spengler reaction, possibly due to the enhanced nucleophilicity of the aromatic ring now bearing a methylenedioxy bridge. Consequently, aryl bromides, such as **99**, were used as photocyclization substrates and were obtained through coupling of phenethylamine **96** and phthalic anhydride **97** followed by regioselective Grignard reaction and dehydration. Photocyclization yielded the enlactam dehydrolennoxamine (dehydro-**11**) in about 20% yield.



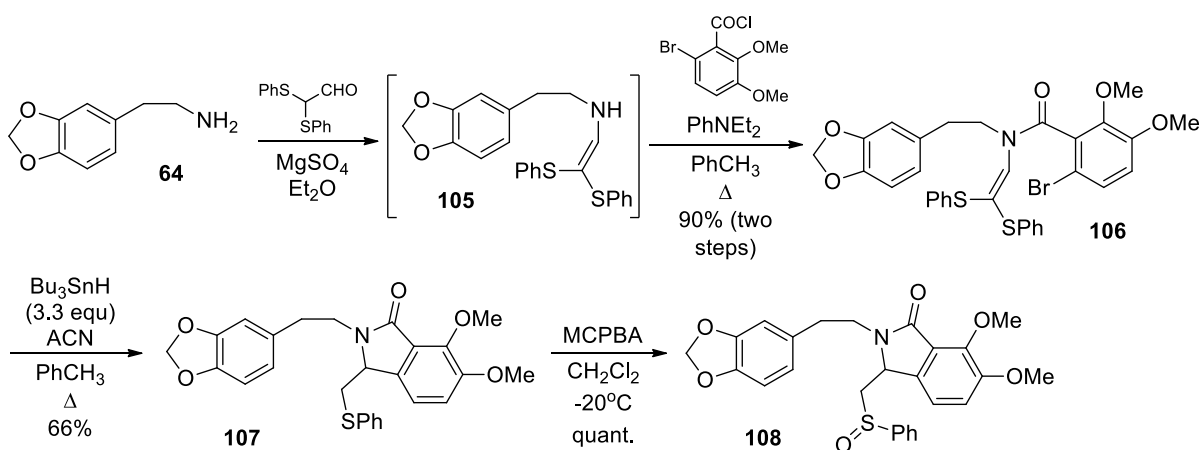
**Scheme 29.** Alternative photocyclization route to the seven-membered ring.

While enlactam dehydro-**11** can be fully reduced to Schöpf's base VI (**15**), attempts to oxidize the olefin of the enlactam, thereby installing the functionality found in chilenine, resulted only in undesired ring-opening as shown for related compounds in Scheme 30.<sup>33</sup>



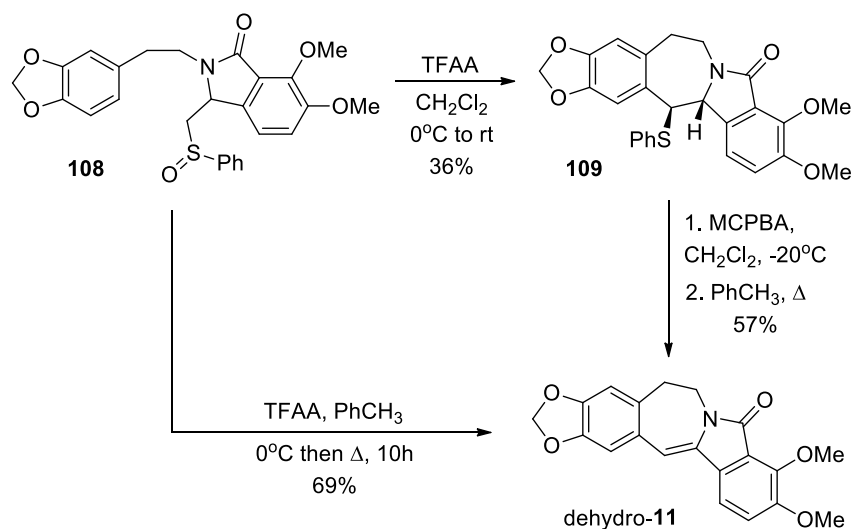
**Scheme 30.** Oxidative ring opening of enlactam **100**.

Ishibashi, Ikeda, and co-workers reported a synthesis of lennoxamine (**11**) and a formal synthesis of chilenine that had at their core a critical sulfur-directed regioselective aryl radical cyclization onto an enamide (**106**), which provided the isoindolone ring.<sup>34,35</sup> The radical cyclization substrate **106** was prepared in two steps from 3,4-methylenedioxyphenethylamine (**64**) by condensation with bis(phenylthio)acetaldehyde and *N*-acylation (Scheme 31). The radical cyclization proceeded with excess tributyltin hydride to afford 5-*exo-trig* ring closure and desulfurization (**107**). The corresponding sulfoxide **108** was prepared by oxidation with MCPBA.



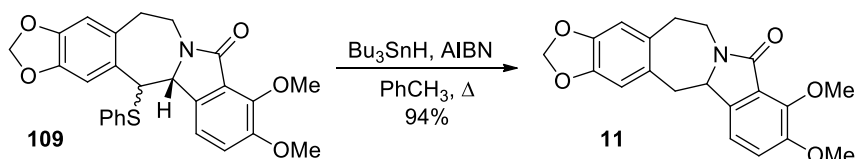
**Scheme 31.** Radical cyclization to prepare the isoindolone.

Pummerer rearrangement followed by intramolecular EAS converted sulfoxide **108** to the benzazepine (**109**) in 80% yield as a mixture of two diastereomers (Scheme 32). However, only one diastereomer (formed in 36% yield) was capable of undergoing *syn*-elimination upon oxidation and subsequent heating to give dehydrolennoxamine (dehydro-**11**). The other diastereomer was recovered unchanged after similar treatment. However, heating the sulfoxide (**108**) in the presence of trifluoroacetic anhydride yielded the enamide (dehydro-**11**) directly in 69% yield. Dehydrolennoxamine (dehydro-**11**) has been converted to chilenine by Fang and Danishefsky.<sup>54</sup>



**Scheme 32.** Pummerer rearrangement, intramolecular EAS, and elimination to prepare dehydrolennoxamine.

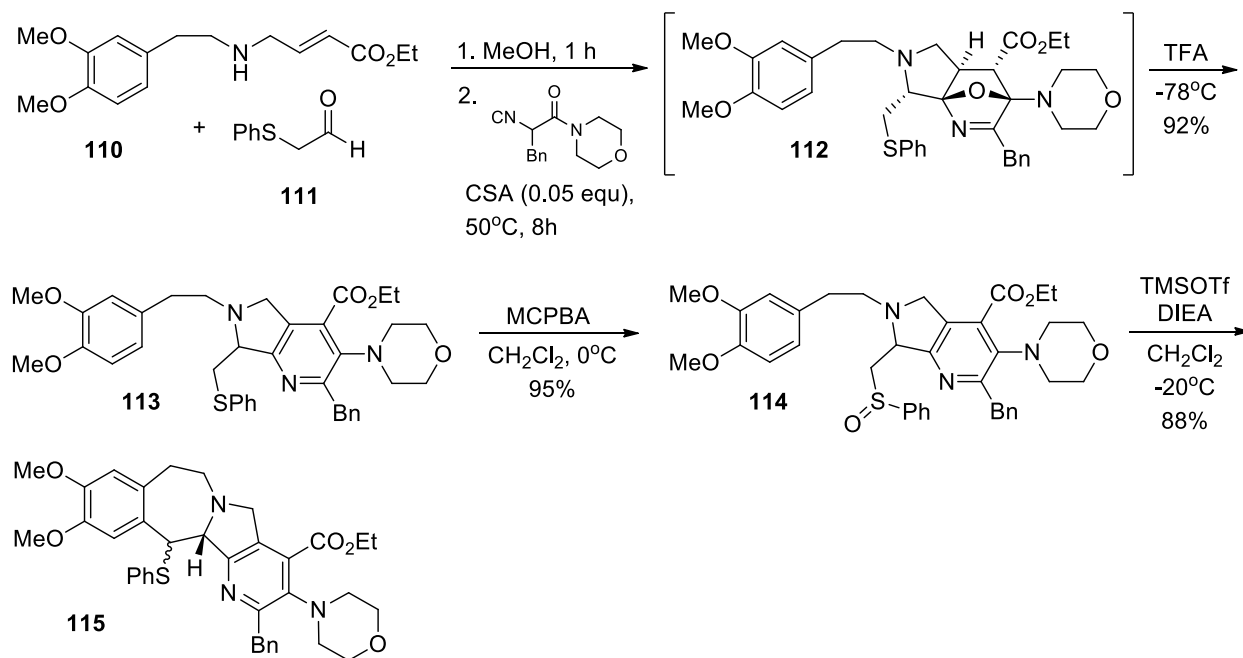
Both benzazepine diastereomers (**109**) could be converted to lennoxamine (**11**) via desulfurization (Scheme 33).



**Scheme 33.** Synthesis of lennoxamine via desulfurization.

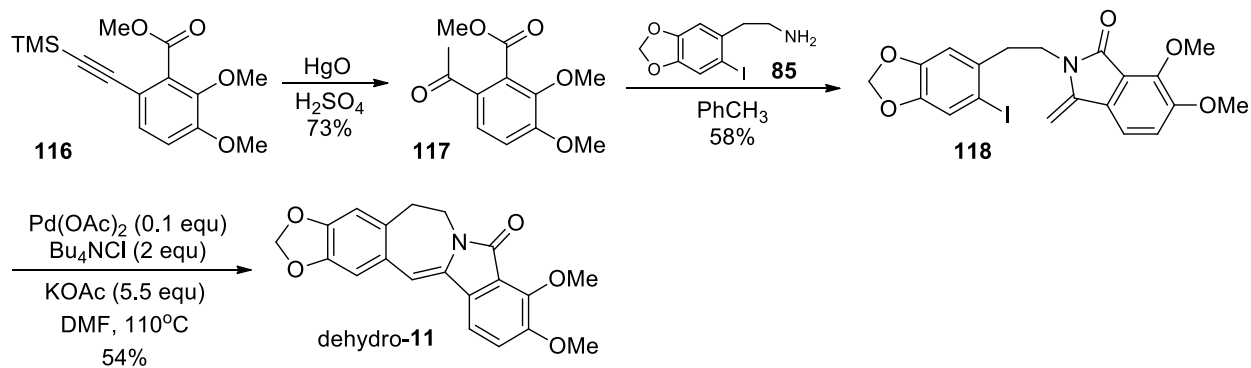
A similar Pummerer cyclization was used by Montaña and Zhu in their multi-component approach to a lennoxamine-type compound.<sup>36</sup> Initial reaction of allylamine **110** and aldehyde **111** was followed by addition of an isocyanoacetamide and camphorsulfonic acid (Scheme 34). The oxabridged tricycle thus formed (**112**) by domino three-component reaction and intramolecular Diels-Alder reaction was subjected to immediate fragmentation through addition of TFA at

reduced temperature. The resultant pyrrolopyridine (**113**) was oxidized to the corresponding sulfoxide (**114**) for Pummerer cyclization, which was facilitated by the use of excess TMSOTf and Hünig's base. A 2:1 ratio of diastereomeric tetracycles (**115**) was isolated with the major product having the (1*S*,2*R*) configuration.



**Scheme 34.** A multi-component reaction / Pummerer cyclization approach to a lennoxamine analogue.

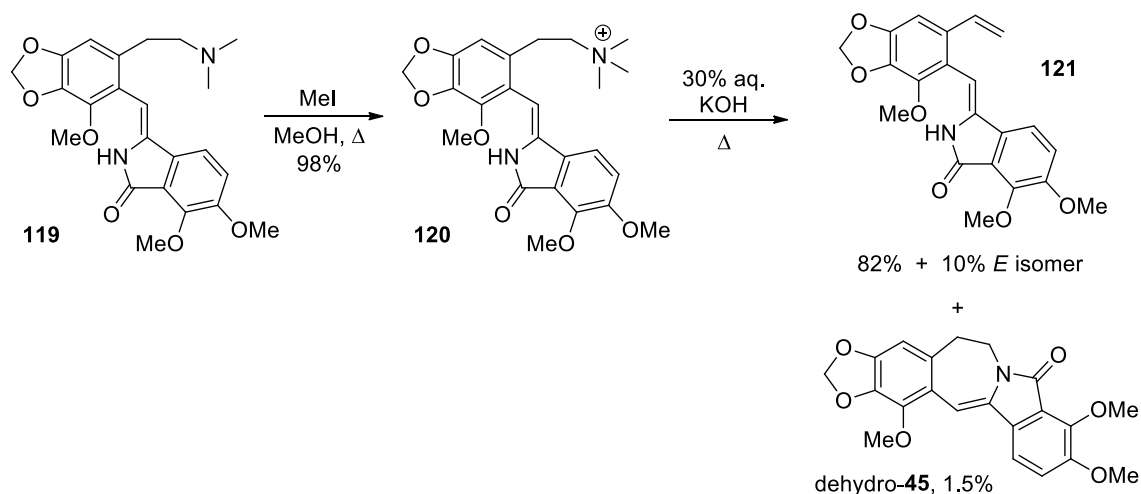
Kim and co-workers reported construction of the C14-C14a bond using intramolecular Heck reaction.<sup>37</sup> This approach relied upon the condensation of a keto ester (**117**) and an amine (**85**, Scheme 35). The TMS-acetylene reactant was prepared via modification of the reported protocol.<sup>47</sup> Hydration and desilylation yielded the keto ester fragment. Condensation with the phenethylamine yielded enelactam **118**, the cyclization precursor. Heck cyclization proceeded in the *endo* fashion when tetrabutylammonium chloride was used. In the absence of this additive, *exo* cyclization yielded the undesired isoindoloisoquinoline.



**Scheme 35.** Intramolecular Heck route to dehydrolennoxamine.

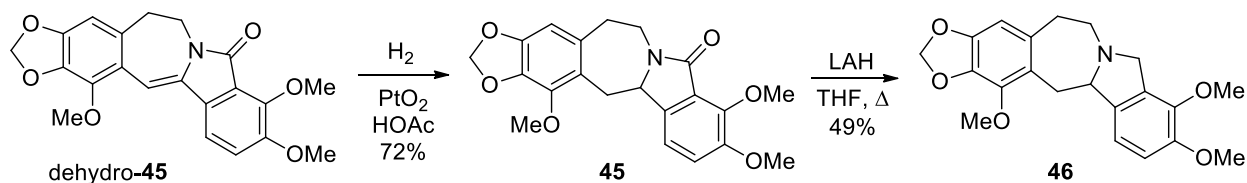
### 3.2. Formation of the C6-N7 bond

Narceine imide **119** has been used as a framework for building the aporphoeadane skeleton (Scheme 36).<sup>38</sup> Hofmann elimination yielded small quantities of enelactam dehydro-**45** in addition to the expected styrene derivative (**121**) and its *E* isomer. The enelactam dehydro-**45** is the C1-methoxy analogue of dehydrolennoxamine (dehydro-**11**), which was used in the Snieckus synthesis (Scheme 29).



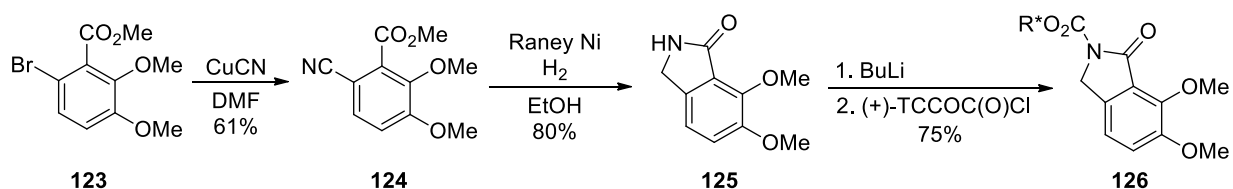
**Scheme 36.** Hofmann elimination of narceine imide.

Subsequent stepwise reduction of the olefin and lactam provided an analogue of Schöpf's base VI (**46**, Scheme 37). However, the hydrogenation of the olefin is difficult and is accompanied by small amounts of cleavage of the methylenedioxy bridge. Infrared analysis of **46** revealed peaks in the 2700 – 2800  $\text{cm}^{-1}$  region suggesting *trans* junction of the central rings.<sup>39</sup>



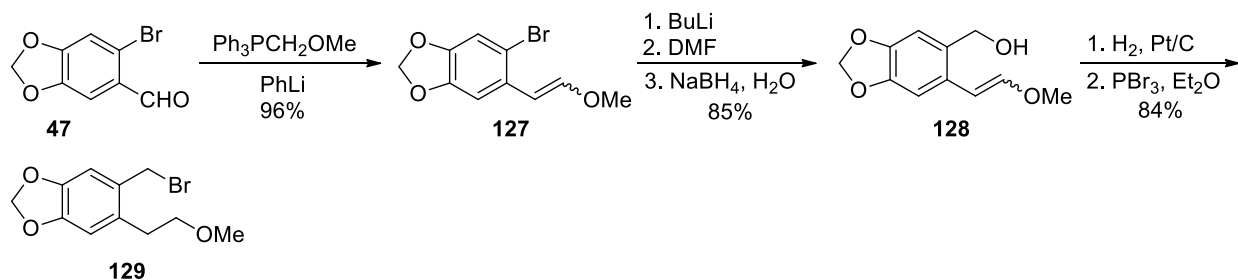
**Scheme 37.** Stepwise reduction of enelactam dehydro-45 to a Schöpf's base VI analogue.

Comins *et al.* reported the first asymmetric synthesis of (+)-lennoxamine.<sup>40</sup> The known isoindolone **125** was prepared from benzoate **123** through addition of cyanide and reduction, which led to lactamization (Scheme 38).<sup>41</sup> At this stage, the chiral auxiliary, (+)-*trans*-2-( $\alpha$ -cumyl)cyclohexanol (TCC), was installed through acylation with its chloroformate.



**Scheme 38.** Preparation of isoindolone bearing a chiral auxiliary.

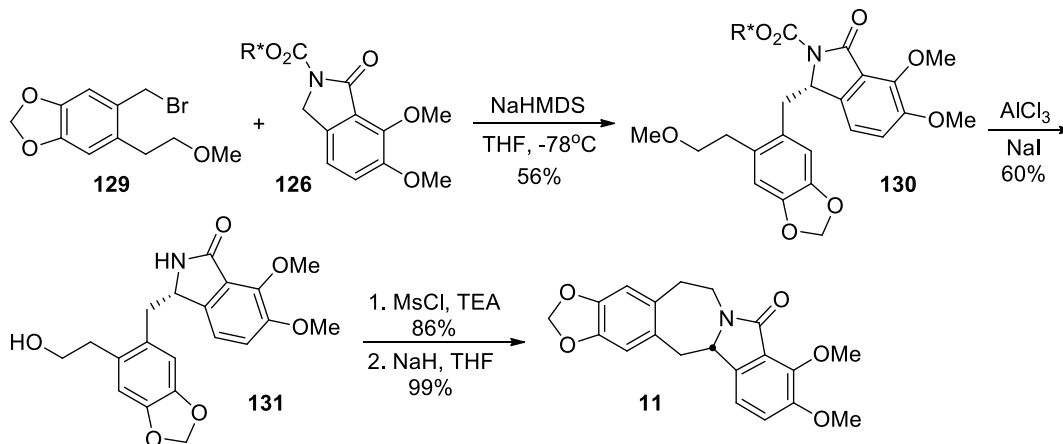
This isoindolone (**126**) required a benzylic bromide coupling partner (**129**), which was prepared from 6-bromopiperonal (**47**, Scheme 39). The Levine reagent was used in olefination of the starting aldehyde. This was followed by a three-step one-pot procedure in which lithium-bromide exchange, formylation, and reduction occurred to afford the benzylic alcohol (**128**). Hydrogenation and bromination yielded the benzylic bromide fragment (**129**).



**Scheme 39.** Synthesis of the benzylic bromide fragment.

Union of the fragments occurred upon exposure to NaHMDS at low temperatures (Scheme 40). The electron-rich nature of the isoindolone ring rendered the anion somewhat unstable, making this coupling challenging. Aluminum trichloride and sodium iodide cleaved only the

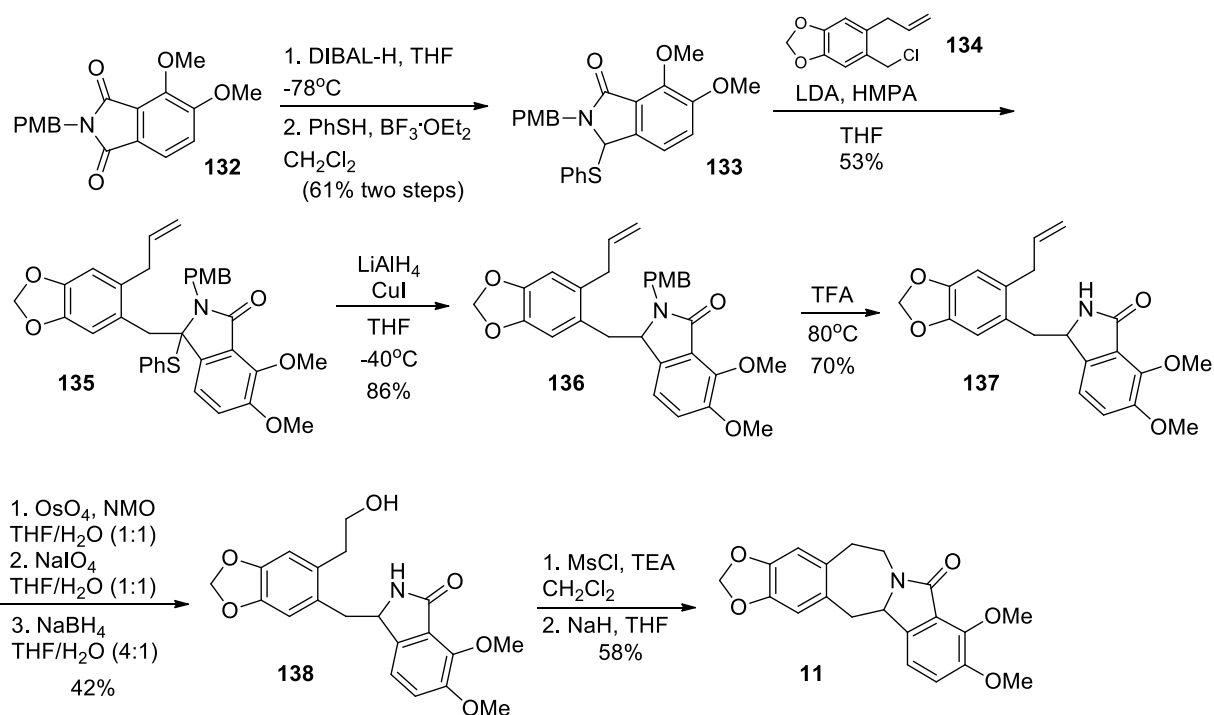
methyl alkyl ether and the auxiliary, which allowed the C6-N7 bond to be formed when the alcohol (**131**) was converted to its mesylate and the nitrogen was deprotonated with sodium hydride.



**Scheme 40.** Synthesis of (+)-lennoxamine.

Yoda and co-workers developed a synthesis of lennoxamine that hinged upon the chemoselective desulfurization of a  $\gamma$ -phenylthio-substituted aromatic lactam (**135**) using lithium aluminum hydride in the presence of copper(I) iodide (Scheme 41).<sup>42</sup> The synthesis began with *N*-PMB-3,4-dimethoxyphthalimide (**132**), which was reduced to the hydroxylactam using DIBAL-H and immediately converted to the  $\gamma$ -phenylthiolactam **133**. This phenylthiolactam was then coupled with benzylic chloride **134** (prepared from 6-bromopiperonal) under basic conditions. The  $\gamma$ -phenylthio-substituted lactam thus formed (**135**) underwent chemoselective desulfurization (**136**). The isoindolone was then deprotected (**137**), and the olefin was dihydroxylated, oxidatively cleaved, and reduced to alcohol **138**. The alcohol was converted to its mesylate and displaced by the isoindolone nitrogen upon treatment with base to yield lennoxamine (**11**).

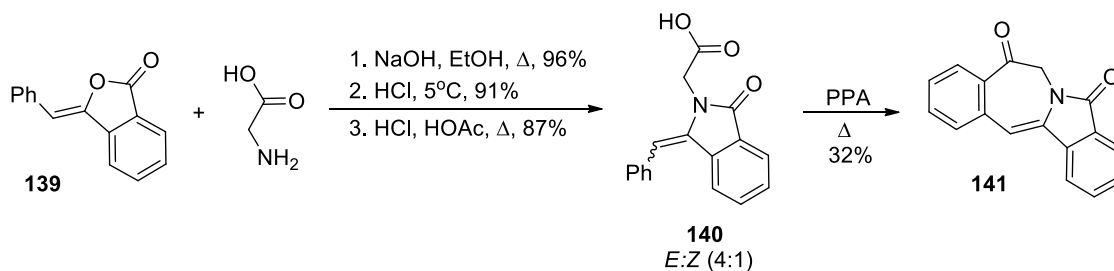




**Scheme 41.** Lennoxamine synthesis relying upon chemoselective desulfurization.

### 3.3. Formation of the C4a-C5 bond

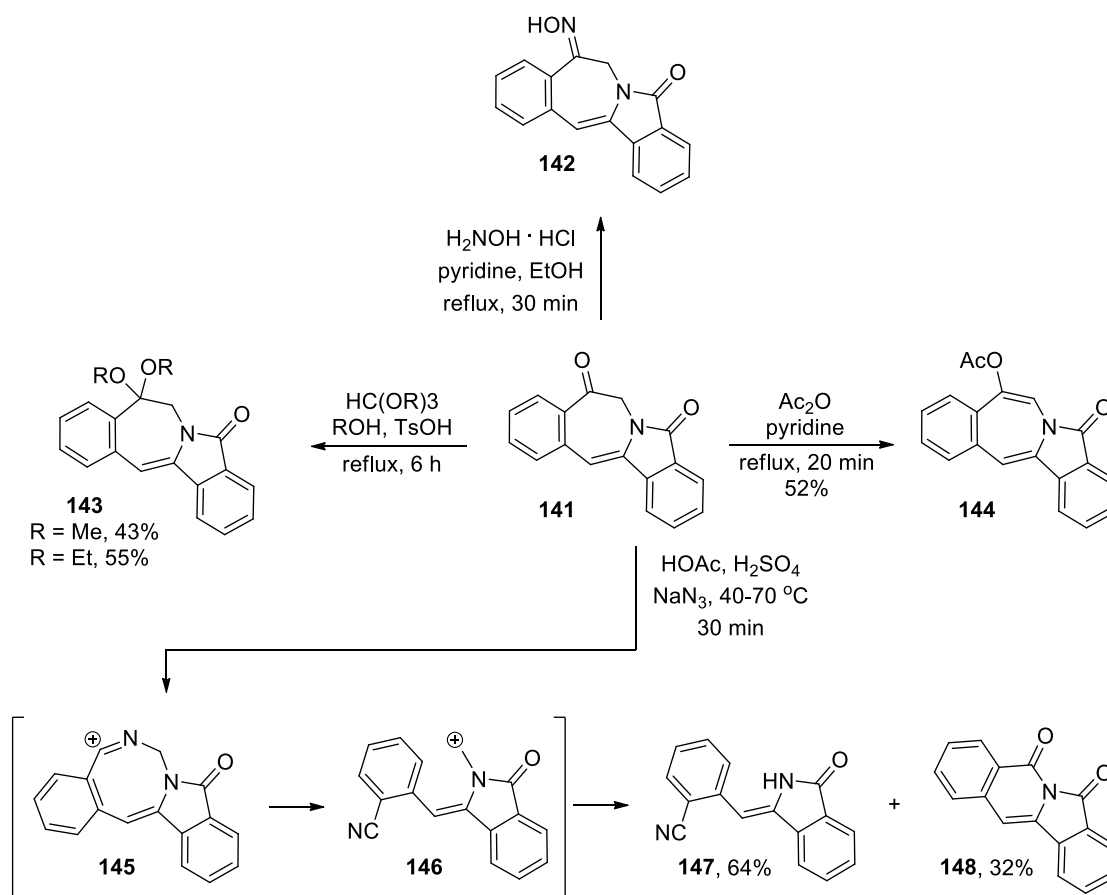
Scartoni and co-workers pioneered this approach, which first establishes the phthalimide ring through reaction of 3-benzylidenephthalide (**139**) with glycine in basic media (Scheme 42).<sup>43</sup> This yields sodium 3-benzyl-3-hydroxyphthalimidin-2-ylacetate, which is then protonated with HCl at reduced temperature to give the corresponding carboxylic acid. Dehydration provides 3-benzylidenephthalimidin-2-ylacetic acid (**140**) as a 4:1 mixture of its *E* and *Z* isomers. Subsequent intramolecular electrophilic aromatic substitution in polyphosphoric acid forms the benzazepine system of **141**.



**Scheme 42.** Stepwise formation of the isoindole and benzazepine systems.

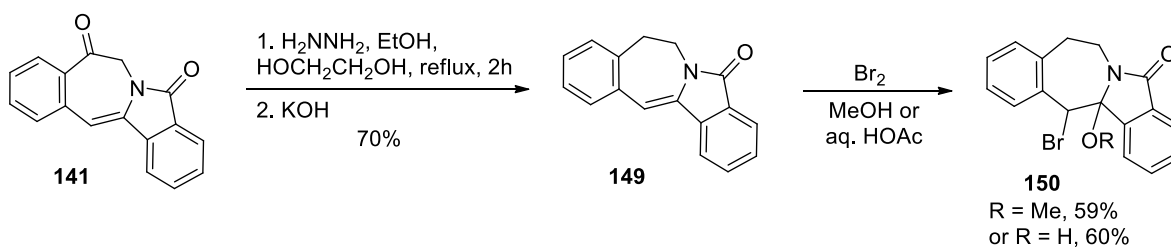
The tetracycle **141** can then undergo a variety of transformations (Scheme 43) to the enol acetate (**144**), the acetal (**143**), or the oxime (**142**). Additionally, Schmidt reaction with hydrazoic

acid ultimately induces fragmentation of the seven-membered ring to the phthalimidine (**147**) and contraction of the seven-membered ring to the isoindoloisoquinolinedione (**148**).



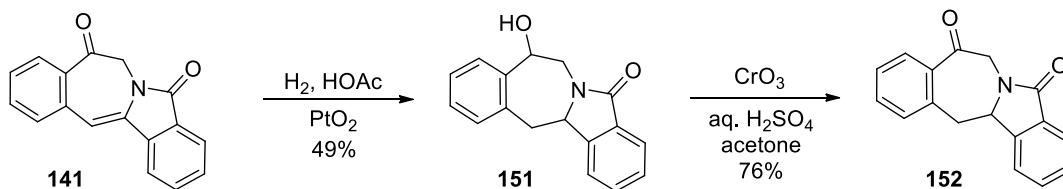
**Scheme 43.** Reactions of the benzylic ketone.

Significantly, the oxidation state of various sites on the seven-five system can be manipulated. Wolff-Kishner reduction of the benzylic ketone of **141** yielded enlactam **149**, which can undergo addition of bromine and a nucleophilic solvent across the olefin (**150**, Scheme 44).



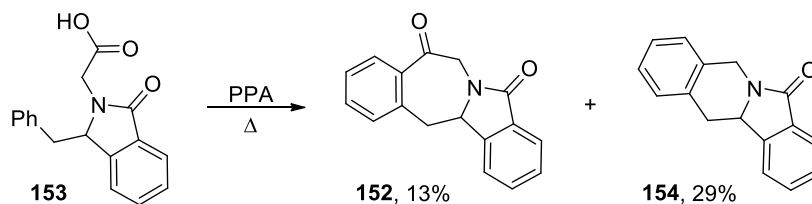
**Scheme 44.** Wolff-Kishner reduction and electrophilic addition.

Alternatively, hydrogenation reduces both the benzylic ketone and the olefin (**151**), while the resultant alcohol can be readily reoxidized using Jones' reagent (**152**, Scheme 45).



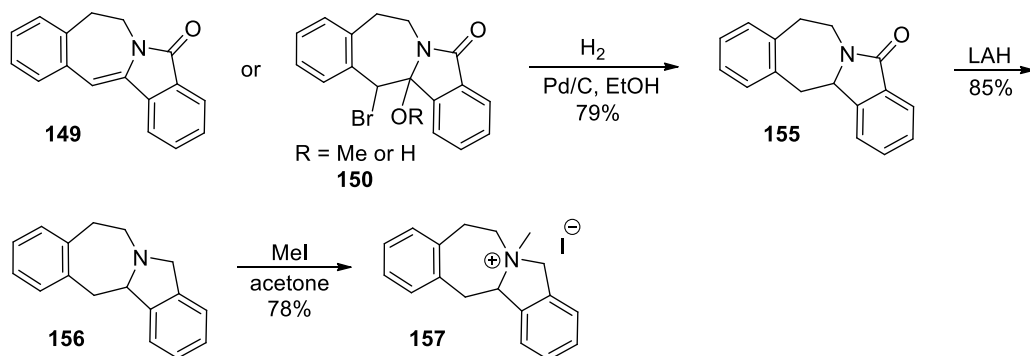
**Scheme 45.** A reduction-oxidation route to an isoindolobenzazepinedione.

The same product (**152**) results directly from intramolecular electrophilic aromatic substitution of phthalimidine **153** (Scheme 46). However, this cyclization suffers a reduction in yield due to the formation of isoindoloisoquinolinone **154** via the extrusion of carbon monoxide from the intermediate acylium ion.



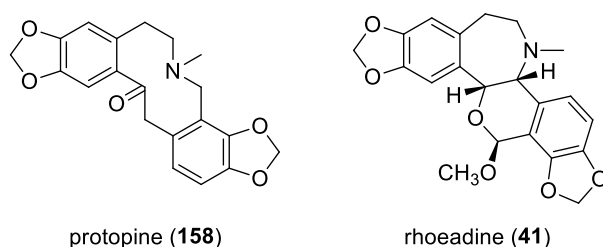
**Scheme 46.** An EAS route to an isoindolobenzazepinedione.

Notably, both the Wolff-Kishner reduction product **149** and the electrophilic addition products **150** can be reduced to the isoindolobenzazepinone (**155**) via catalytic hydrogenation (Scheme 47). Subsequent lithium aluminum hydride reduction of the lactam yields an unstable isoindolobenzazepine (**156**), which can be alkylated to produce the methiodide **157**.



**Scheme 47.** Further reduction of enlactam **149**.

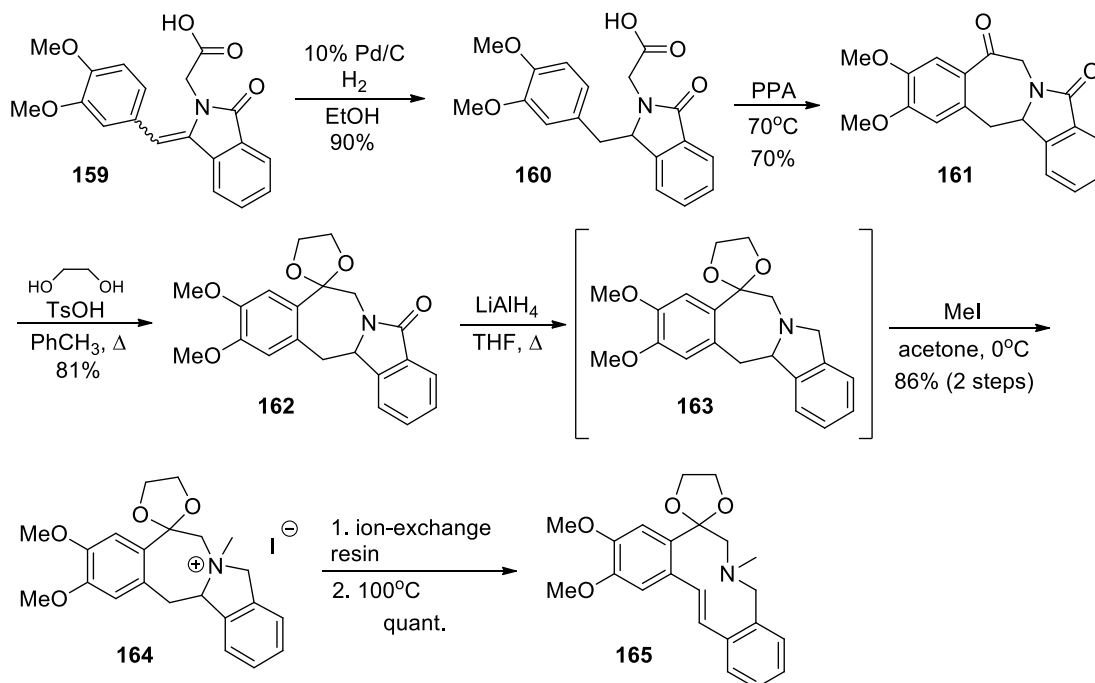
Others<sup>44</sup> have commented on the tantalizing statement at the conclusion of the manuscript by Scartoni, *et al.* stating that “Work is in progress to test whether the series of reactions described above can be applied to similar products, bearing appropriate substituents in the benzene rings, in the hope of finding a new route to alkaloids of the protopine, and possibly of the rhoeadine series” (Figure 5). Therein lies an opportunity for further investigation that would tremendously enhance the synthetic utility of this pathway.



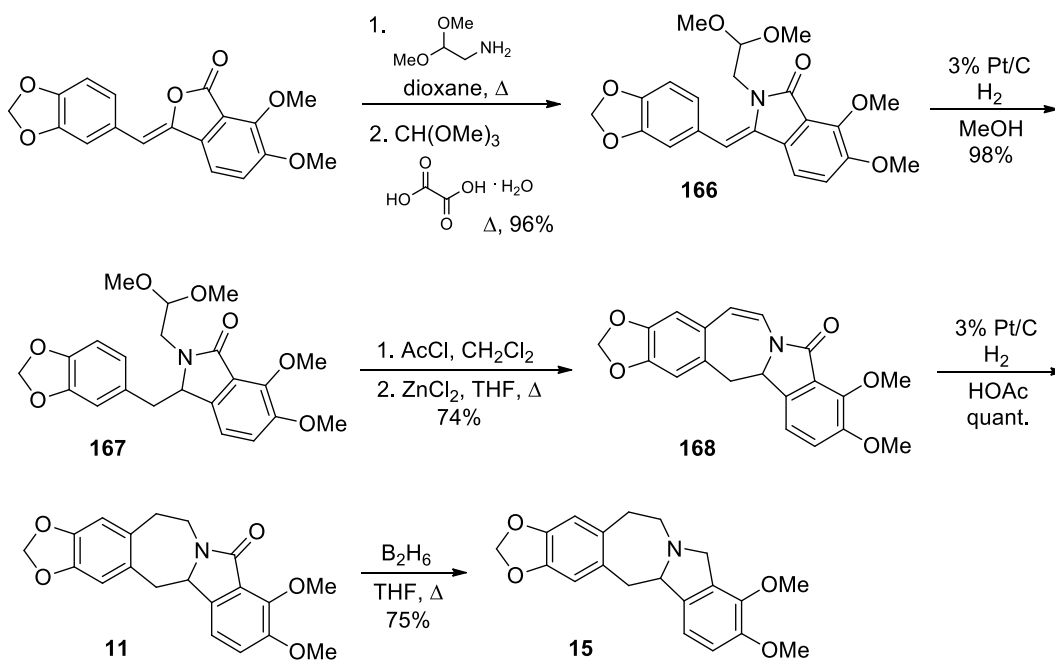
**Figure 5.** Protopine and rhoeadine.

Some progress was made toward this goal by Marsili and co-workers.<sup>45</sup> Phthalimide derivative **159** (Scheme 48) was prepared, as a mixture of its *E* and *Z* isomers, in a fashion similar to that reported previously (refer to Scheme 42).<sup>43</sup> Hydrogenation and cyclization, also accomplished in the familiar fashion, provided the isoindolobenzazepinedione (**161**), which was subsequently protected as its acetal (**162**). Reduction of the lactam using lithium aluminum hydride yielded an unstable amine (**163**) that was immediately converted to its methiodide (**164**). The methiodide was passed over an ion-exchange resin pretreated with sodium hydroxide and then heated to induce degradation to compound **165**, which could be considered a protopine analogue.

Napolitano *et al.* devised a synthesis of lennoxamine and chilenamamine that relies upon a key intramolecular cyclization through alkylation (Scheme 49).<sup>46</sup> Their synthesis began with a phthalide, which was condensed with aminoacetaldehyde dimethyl acetal to yield phthalimide **166**. Reduction of the olefin yielded the cyclization substrate (**167**), and cyclization was achieved by treatment with acetyl chloride followed by zinc chloride. An additional hydrogenation yielded lennoxamine (**11**), and literature precedent,<sup>19</sup> allowed conversion to chilenamamine (**15**).

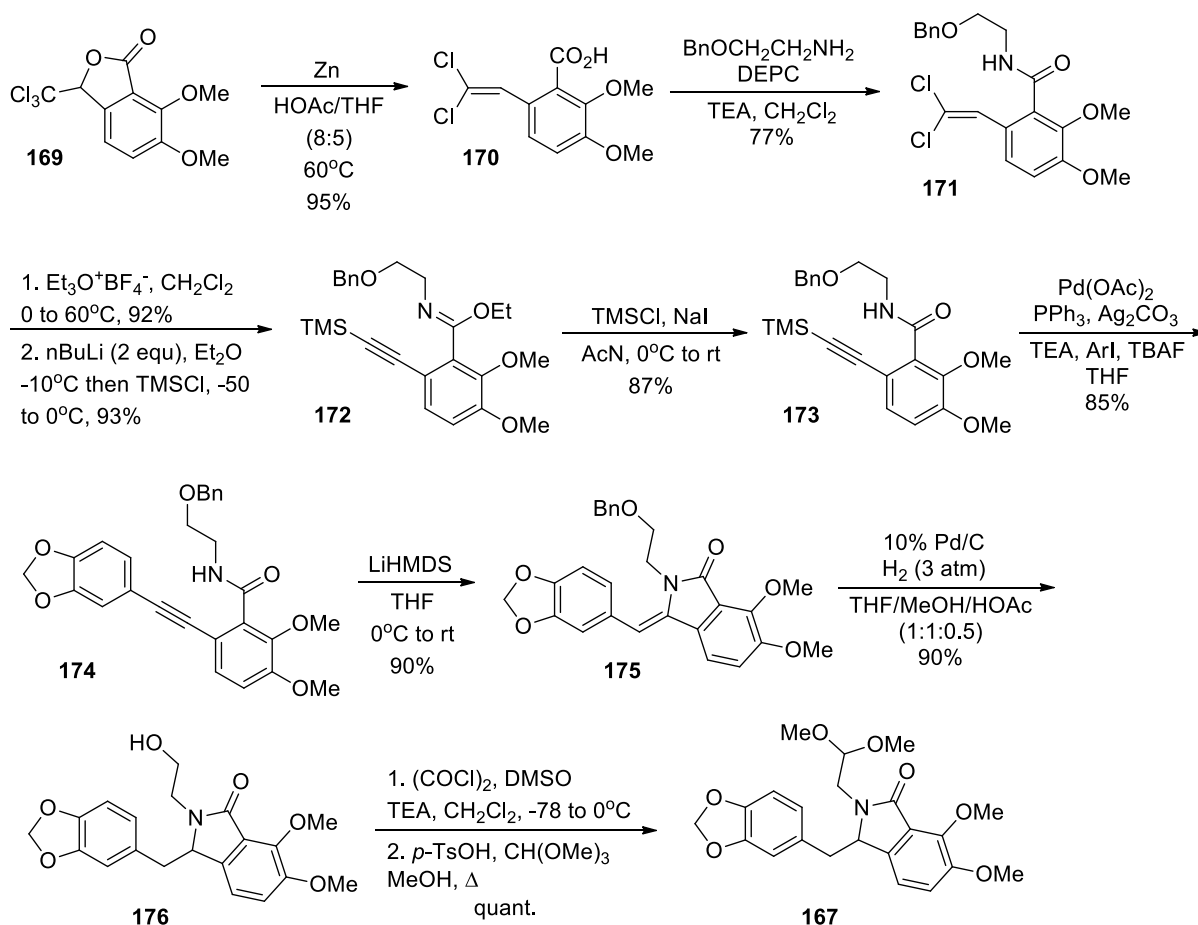


**Scheme 48.** Preparation of a protopine analogue via an aporphoadane.



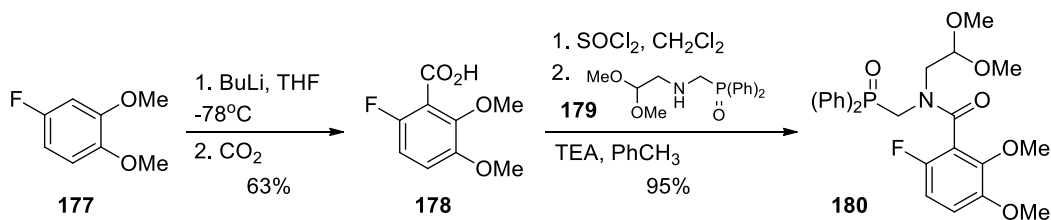
**Scheme 49.** Synthesis of lennoxamine and chilenamamine.

Koseki and Nagasaka reported a formal synthesis of lennoxamine in which the key steps include palladium-catalyzed arylation and subsequent intramolecular cyclization of an *o*-ethynylbenzamide (**174**).<sup>47</sup> Their synthesis began with the reduction of lactone **169** (Scheme 50). The resultant acid (**170**) was coupled with 2-(benzyloxy)ethylamine using diethyl pyrocarbonate. The amide (**171**) was protected using Meerwein's reagent, and then the trimethylsilylacetylene was installed. Subsequent deprotection of the amide yielded the substrate for palladium-catalyzed arylation (**173**). The arylation product (**174**) was treated with LiHMDS to induce intramolecular cyclization giving isoindolone **175**. The isoindolone could also be prepared in 61% yield via a one-pot procedure in which palladium-catalyzed arylation was followed immediately by the addition of 2 equivalents LiHMDS. The benzyl group was removed via hydrogenolysis, which also reduced the olefin. Swern oxidation and immediate formation of the dimethyl acetal yielded **167**, which was previously converted to lennoxamine (refer to Scheme 49).<sup>48</sup>



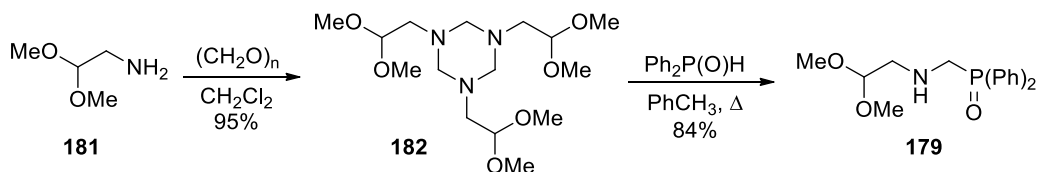
**Scheme 50.** Alternative preparation of the dimethyl acetal **167**.

Couture *et al.* reported a synthesis of lennoxamine that has at its core a basic cyclization of a phosphorylated benzamide (**180**) followed by a Horner coupling.<sup>48</sup> Regioselective metallation of 4-fluoroveratrole (**177**) and trapping with carbon dioxide yielded benzoic acid **178** (Scheme 51). After activation as the acid chloride, this fragment was coupled with phosphorylated amine **179**



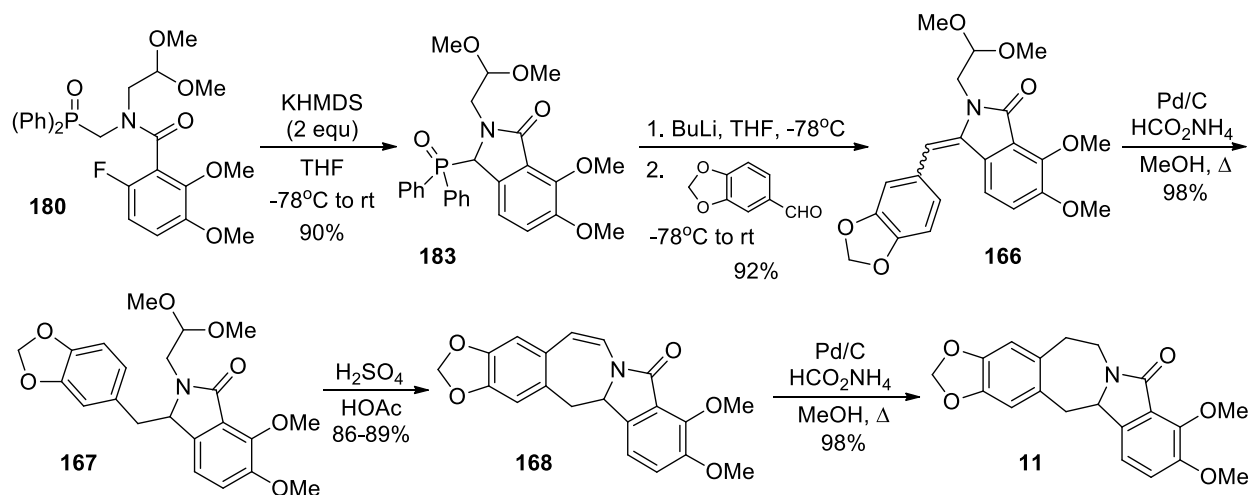
**Scheme 51.** Phosphorylated benzamide synthesis.

The phosphorylated amine (**179**) was prepared from aminoacetaldehyde dimethyl acetal (**181**) in two steps: Mannich reaction to form the hexahydrotriazine (**182**) and fragmentation through exposure to diphenylphosphine oxide (Scheme 52).



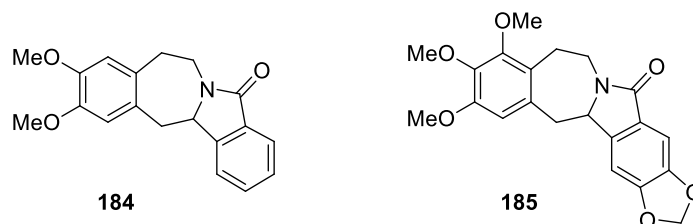
**Scheme 52.** Phosphorylated amine synthesis

The benzamide (**180**) thus derived underwent regioselective cyclization to form the isoindolone **183** (Scheme 53). This phosphorylated isoindole was united with piperonal through a Horner reaction (**166**). The olefin was reduced, and cyclization under acidic conditions yielded the benzazepinone (**168**). One further hydrogenation produced lennoxamine (**11**).



**Scheme 53.** Conversion of a phosphorylated benzamide to lennoxamine.

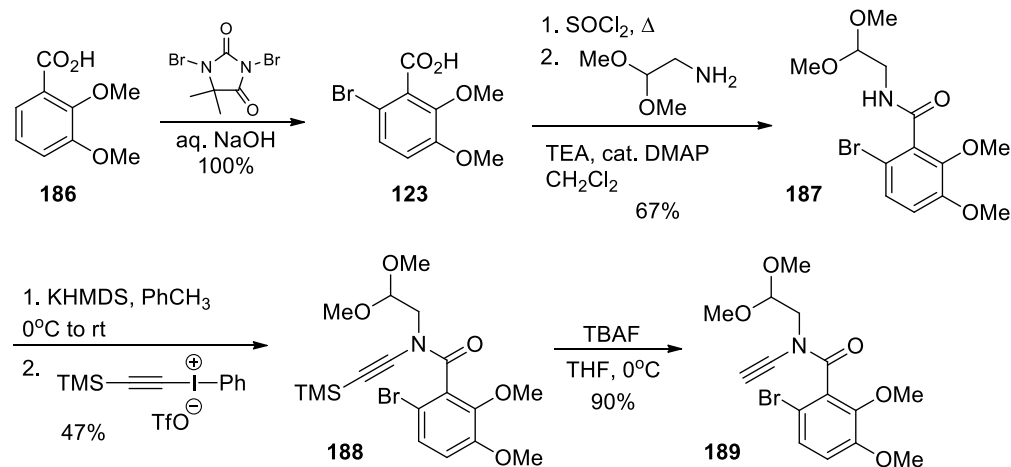
Two analogues of lennoxamine (**184** and **185**, Figure 6) were also prepared in an analogous fashion, from phosphorylated *o*-bromobenzamides.



**Figure 6.** Lennoxamine analogues prepared from phosphorylated *o*-bromobenzamides.

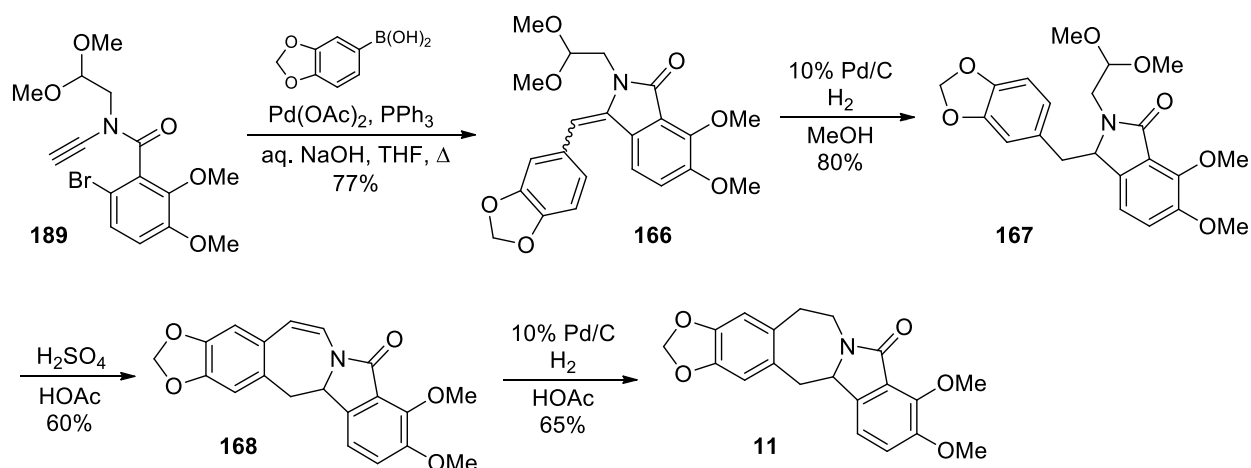
Meyer, Cossy, and co-workers described a synthesis of lennoxamine in which Heck-Suzuki-Miyara domino reactions were used to construct the isoindolone and add the framework for the benzazepine.<sup>49,50</sup> The necessary ynamide (**189**) was prepared from 2,3-dimethoxybenzoic acid (**186**, Scheme 54). Bromination using 1,3-dibromo-5,5-dimethylhydantoin was followed by coupling with aminoacetaldehyde dimethyl acetal via the acid chloride. The secondary amide thus formed (**187**) was deprotonated with KHMDS, and TMS-acetylene was then installed using the alkynylidonium salt. Desilylation of **188** provided the desired ynamide (**189**).





**Scheme 54.** Synthesis of the ynamide for Heck-Suzuki-Miyara domino reaction.

When treated with 3,4-(methylenedioxy)phenylboronic acid in the presence of catalytic palladium acetate and triphenylphosphine the domino sequence provided the isoindolone (**166**, Scheme 55) as an 85:15 mixture of the *E* and *Z* isomers. Hydrogenation was followed by ring closure in acid<sup>48</sup> to yield enamide **168**, and an additional hydrogenation provided lennoxamine (**11**) in eight steps and 7% overall yield.

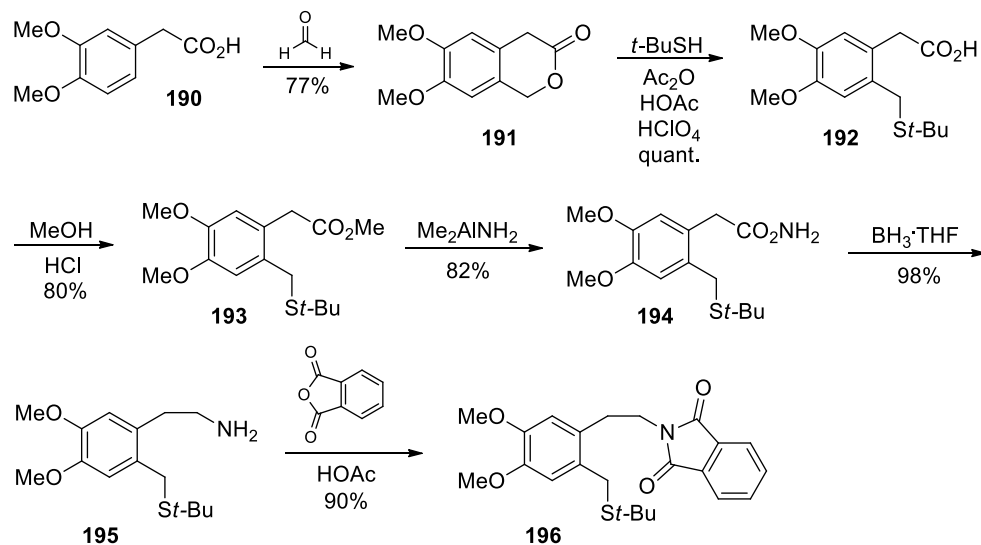


**Scheme 55.** Heck-Suzuki-Miyara domino reaction and completion of the lennoxamine synthesis.

### 3.4. Formation of the C13-C14 bond

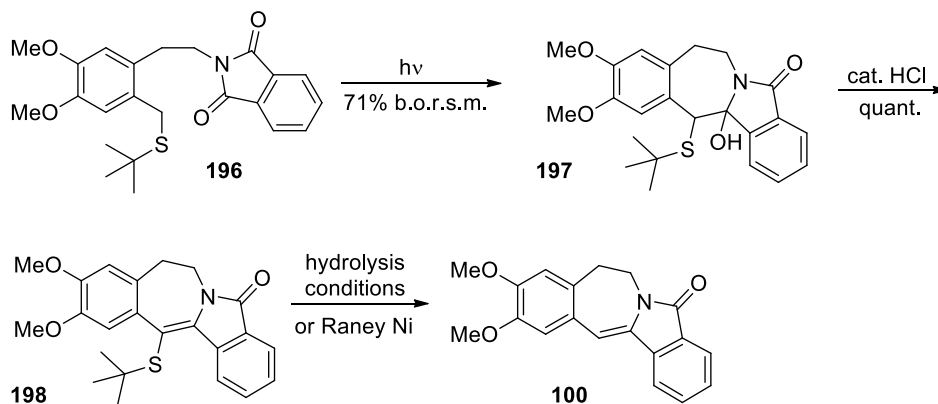
Building on the inspiration provided by earlier photochemical attempts, King and Mazzocchi revisited this strategy utilizing benzyl thioethers, benzyl phenyl ethers, and benzyl diphenyl amines as photocyclization substrates.<sup>44</sup> Of these, the benzyl thioethers proved to be the most promising substrates. A benzyl *t*-butyl thioether substrate (**196**) was prepared in six steps from homoveratric acid (**190**, Scheme 56). Electrophilic aromatic substitution and concomitant

cyclization provided isochromanone (**191**). Ring opening with *t*-butyl thiol in the presence of acetic anhydride, acetic acid, and perchloric acid provided a benzyl *t*-butyl thioether (**192**). Subsequent esterification, amidation, and reduction yielded phenethylamine **195** that was condensed with phthalic anhydride to install the phthalimide fragment.



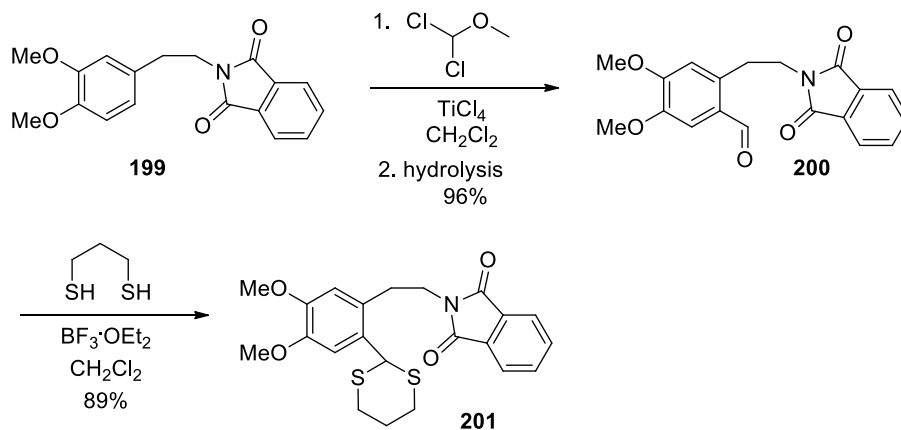
**Scheme 56.** Preparation of a benzyl *t*-butyl thioether photocyclization substrate.

Photocyclization successfully formed the seven-membered ring in 71% yield (**197**, Scheme 57) as a diastereomeric mixture in which the *cis* arrangement predominated and was expected to be more stable due the potential for the *trans* isomer to undergo spontaneous epoxide formation. Dehydration yielded a thioenol ether (**198**) that was expected to be a critical intermediate for the subsequent installation of the ketone and hydroxyl groups of chilenine. However, attempts to hydrolyze the thioenol ether yielded only the enlactam (**100**) familiar from the Snieckus approach (refer to Scheme 30).<sup>33</sup>



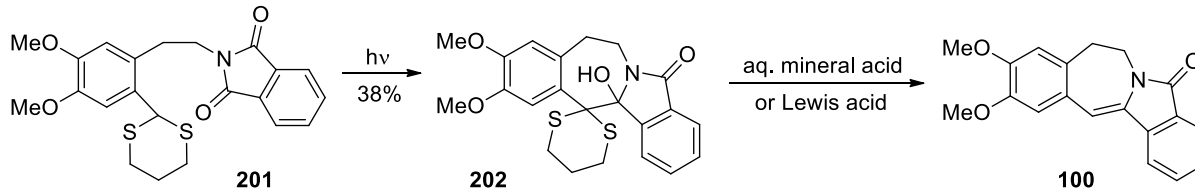
**Scheme 57.** Photocyclization of a benzyl *t*-butyl thioether.

An alternative approach employed a benzaldehyde derivative masked as its dithiane (**201**, Scheme 58), which was prepared in two steps from an appropriate phthalimide (**199**).



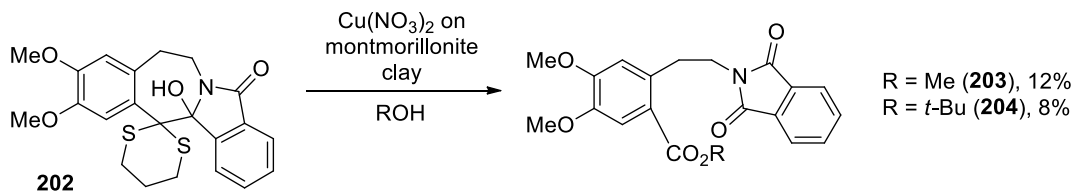
**Scheme 58.** Preparation of a dithiane photocyclization substrate.

Photocyclization successfully installed the seven-membered ring in 38% yield (**202**, Scheme 59); however, yet again most attempts to hydrolyze the dithiane met with formation of the familiar enelactam (**100**).



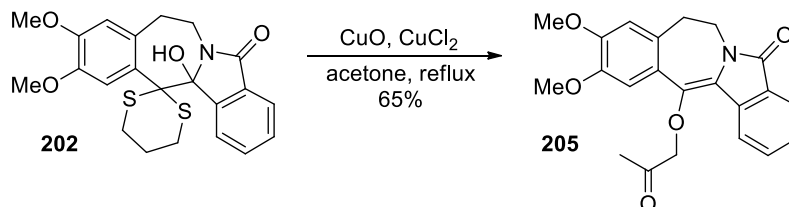
**Scheme 59.** Photocyclization of a dithiane.

Treatment with cupric nitrate on montmorillonite clay led to seven-membered ring scission (Scheme 60).



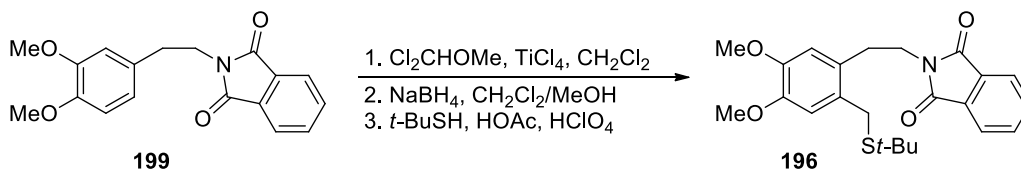
**Scheme 60.** Ring cleavage of the benzazepine.

However, exposure of dithiane **202** to cupric oxide and cupric chloride in acetone at reflux produced an enol ether (**205**) through hydrolysis, solvent incorporation, and [3,3]-sigmatropic rearrangement (Scheme 61). Unfortunately, hydrolysis of this enol ether or its analogue derived from acetophenone was not successful.



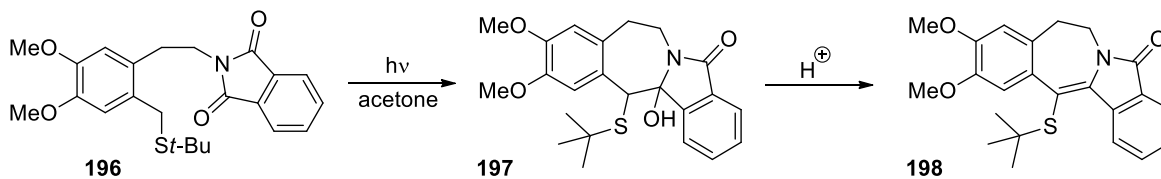
**Scheme 61.** Enol ether formation.

Despite the setbacks in functionalizing the photocyclization product as desired, the preparation of dithiane **201** suggested to the investigators that a more efficient synthesis of the initial benzyl *t*-butyl thioether photocyclization substrate (**196**) could be accomplished as outlined in Scheme 62. Compound **199**, which is readily prepared from 3,4-dimethoxyphenethylamine and phthalic anhydride, could be converted into the photocyclization substrate via formylation, reduction, and condensation with *t*-butyl thiol.<sup>51</sup>



**Scheme 62.** More efficient preparation of benzyl *t*-butyl thioether photocyclization substrate.

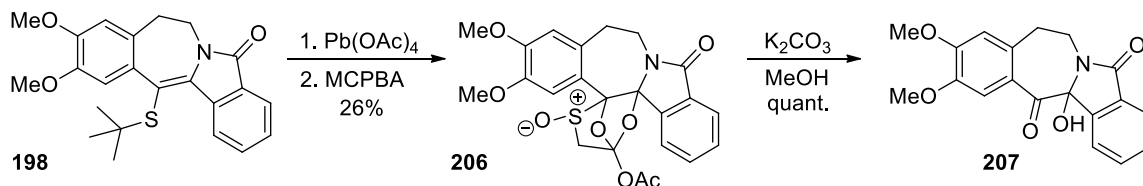
Photocyclization and subsequent acid-catalyzed dehydration provided the thioenol ether (**198**, Scheme 63) in 68% overall yield from phthalimide **199**.



**Scheme 63.** Photocyclization and dehydration of a benzyl *t*-butyl thioether.

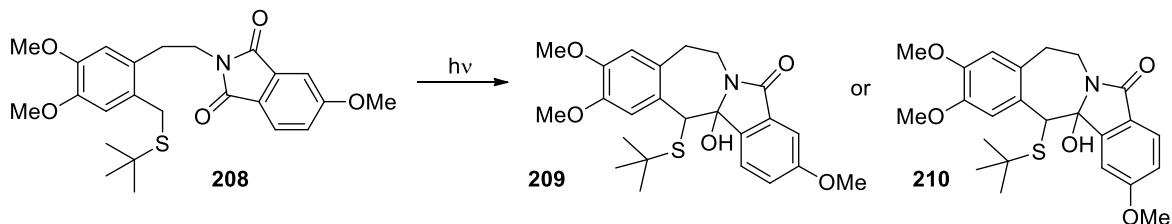
Their return to this photochemical substrate and the resultant thioenol ether **198** prompted the examination of alternative methods of transforming the thioenol ether into the desired hydroxyketone (**207**). Treatment with lead tetraacetate followed by MCPBA produced an

unusual hexacyclic orthoester (**206**, Scheme 64), the structure of which was elucidated via X-ray crystal analysis. This orthoester effectively served as a protecting group for the desired functionality, and indeed cleavage of the orthoester with potassium carbonate in methanol yielded the much sought after hydroxyketone (**207**), in seven steps and 17.7% overall yield.<sup>51</sup>



**Scheme 64.** Formation of the hydroxyketone via a hexacyclic orthoester.

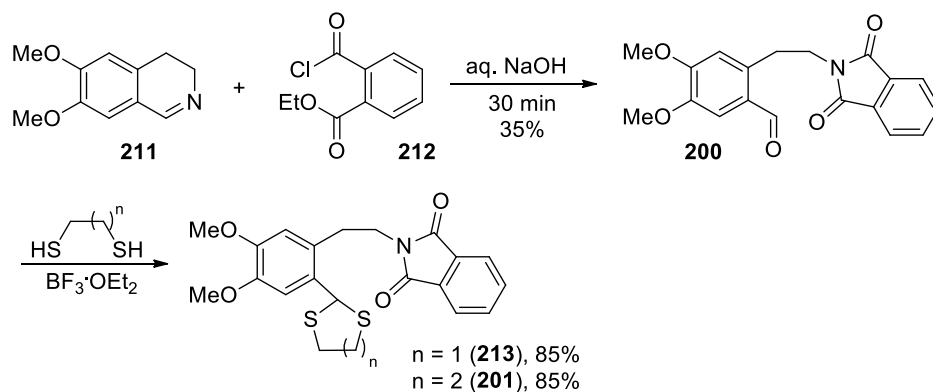
This success naturally prompted King and Mazzocchi to examine photocyclization substrates with substitution on the phthalimide ring, which could potentially yield a structure all but identical to the natural product chilenine. With a single methoxy group on the phthalimide ring (**208**), photocyclization was still successful, although which isomeric product (**209** or **210**) was formed was unclear (Scheme 65).<sup>44</sup>



**Scheme 65.** Photocyclization of a substrate bearing a single methoxy group on the phthalimide.

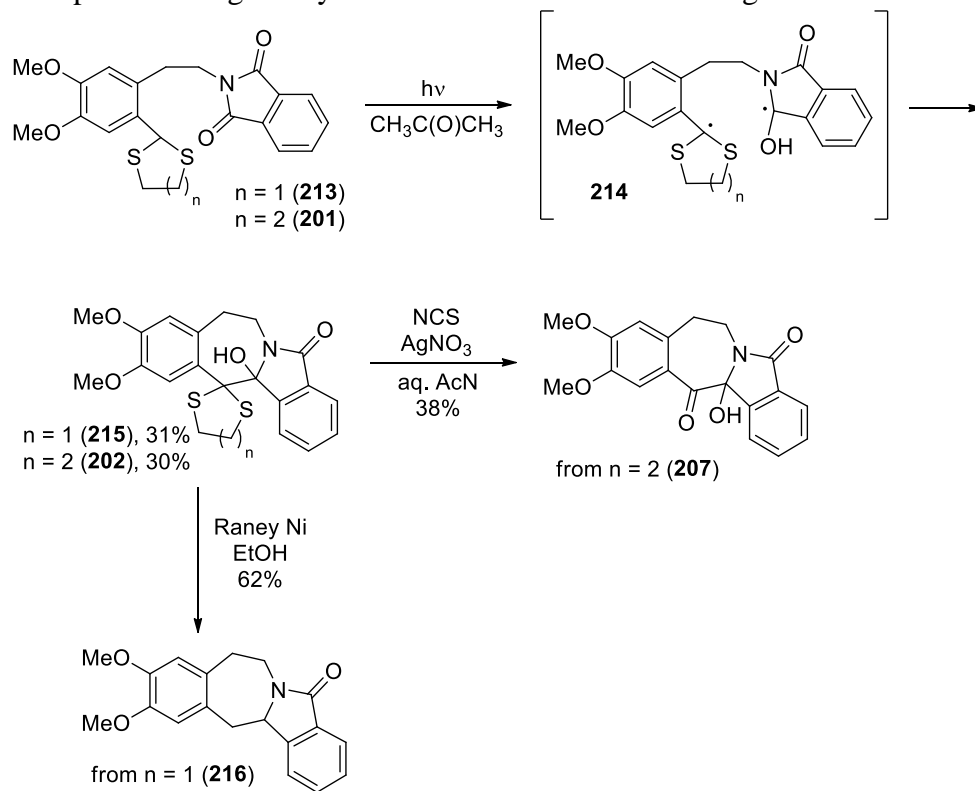
Disappointingly, the analogous reaction with a dimethoxysubstituted phthalimide was unsuccessful. The authors proposed that the reduction potential of the phthalimide is altered by the substitution such that electron transfer is no longer a favorable process or such that back electron transfer becomes more favorable.

An analogous photochemical approach to the aporphoadane skeleton was investigated by Kessar and co-workers.<sup>52,53</sup> In this instance, the photochemical substrates were derived from a dihydroisoquinoline (**211**, Scheme 66) by reaction with 2-carboethoxybenzoyl chloride (**212**) and subsequent masking of the benzaldehyde (**200**) with ethane-1,2-thiol or propane-1,3-thiol (**213** or **201**, respectively).



**Scheme 66.** Preparation of photochemical substrates from a dihydroisoquinoline.

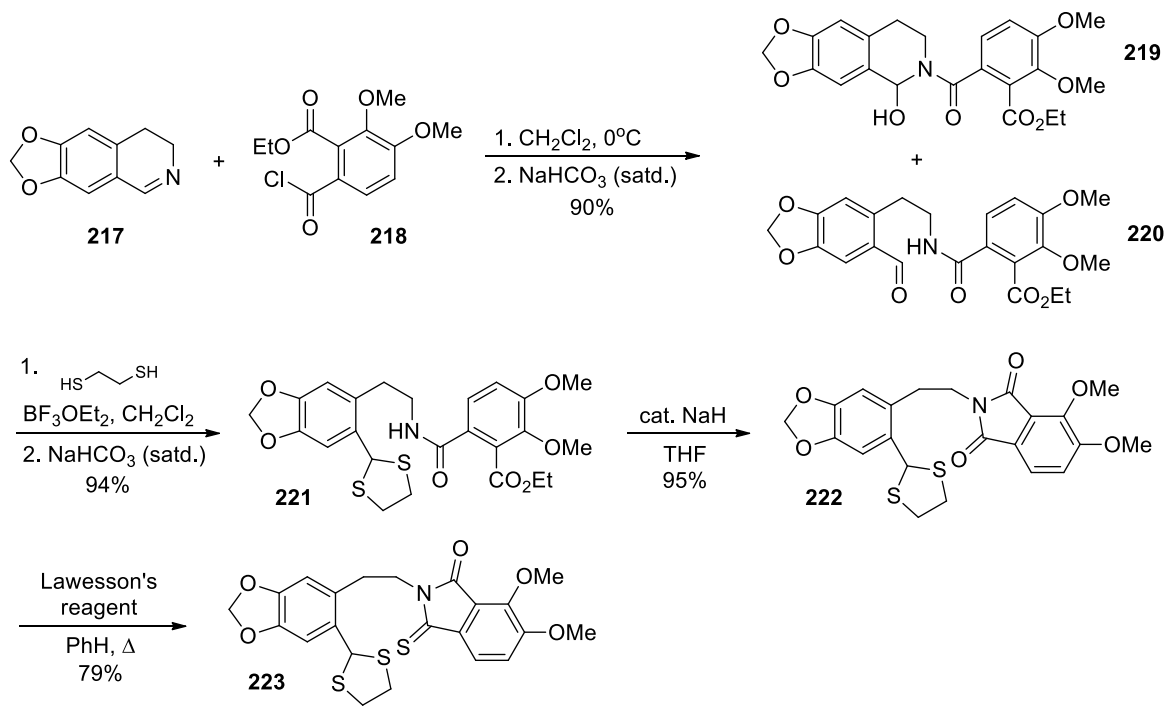
Photochemical substrate **201** was the same as that used by King and Mazzocchi.<sup>44</sup> In this case, photocyclization was followed by successful deprotection of the ketone using *N*-chlorosuccinimide and silver nitrate in aqueous acetonitrile to give chilenine analogue **207** (Scheme 67). Alternatively, complete reduction of both the dithiane and the hydroxyl group could be accomplished using Raney Ni to afford lennoxamine analogue **216**.



**Scheme 67.** Photocyclization and deprotection or reduction of the masked hydroxyketone.

The absence of substrates bearing a substituted phthalimide suggests that, as with King's work, the photocyclization may have been detrimentally affected by the presence of electron-donating groups on this ring.

Fang and Danishefsky employed reductive coupling mediated by either tungsten hexacarbonyl or rhodium(II) acetate to form the C13-C14 bond.<sup>54</sup> Their synthesis began with the acylation of dihydroisoquinoline **217** to provide an inseparable mixture of **219** and **220**, both of which were converted to the corresponding dithiolane **221** (Scheme 68). Catalytic base incited phthalimide ring closure (**222**), and Lawesson's reagent provided the desired monothiophthalimide **223**.

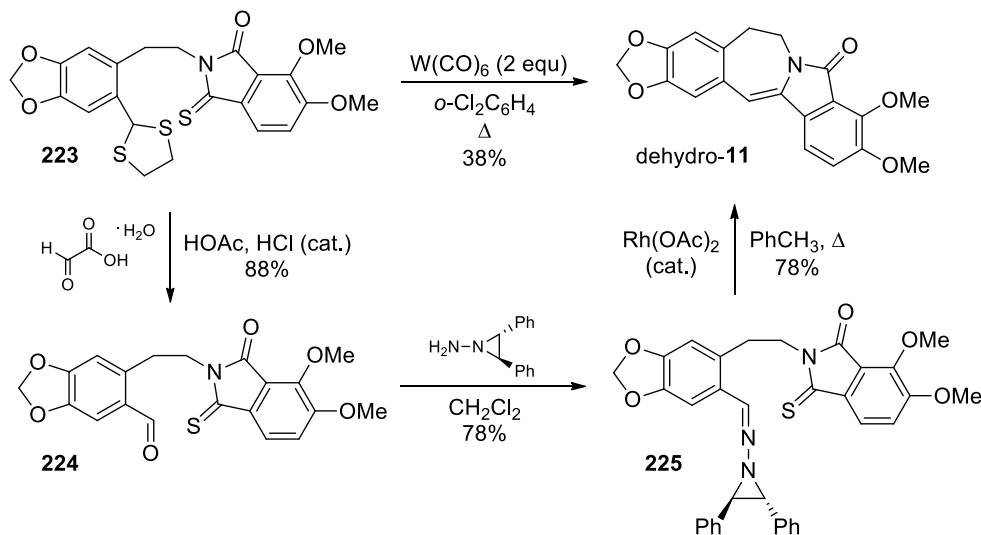


**Scheme 68.** Preparation of a monothiophthalimide.

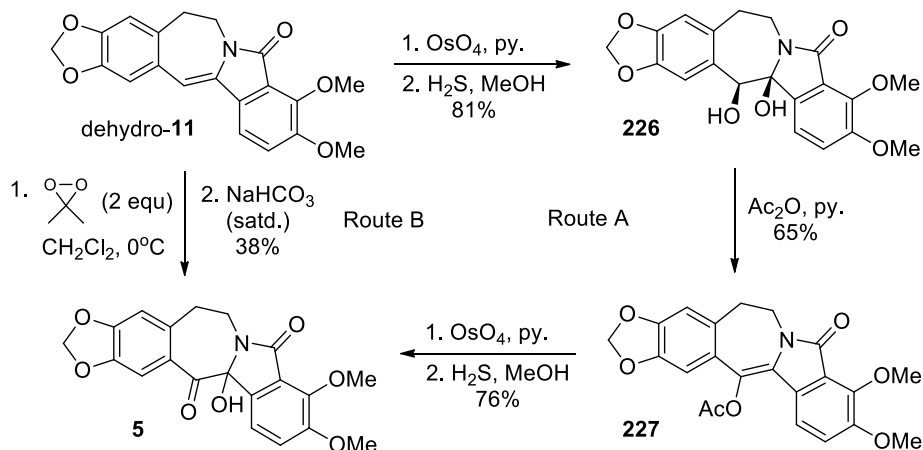
Treating the dithiolane directly with tungsten hexacarbonyl yielded the enelactam dehydrolennoxamine (dehydro-**11**, Scheme 69) in 38% yield. However, an alternative approach to the enelactam unveiled the aldehyde (**224**), converted it to the hydrazone (**225**), and employed rhodium(II) acetate for the reductive coupling yielding the enelactam in 53.5% yield over the three-step sequence.

The authors circumvented the C13-C14 bond cleavage that had been previously observed<sup>33</sup> when using MCPBA in an attempt to install the C13 and C14 oxygenation. In one route, treatment with osmium tetroxide followed by workup with hydrogen sulfide yielded the *cis*-diol **226** (Scheme 70). Treatment with acetic anhydride in pyridine led to dehydration, giving the enol acetate (**227**). This enol acetate yielded chilenine (**5**, in 40% yield over the three-step sequence)

when oxidized with osmium tetroxide, again using a hydrogen sulfide workup. Alternatively, direct exposure of enlactam dehydro-**11** to two equivalents of dimethyl dioxirane, followed by addition of saturated aqueous sodium bicarbonate, provided chilenine directly in 38% yield. The authors attributed the success of this method to the non-nucleophilic nature of dimethyl dioxirane, as opposed to the peroxy acids used in previous reports (refer to Scheme 30) which opened the intermediate epoxide before it could rearrange to a ketone or enol whose subsequent oxidation would yield chilenine.



**Scheme 69.** Intramolecular reductive coupling of the monothiophthalimide.

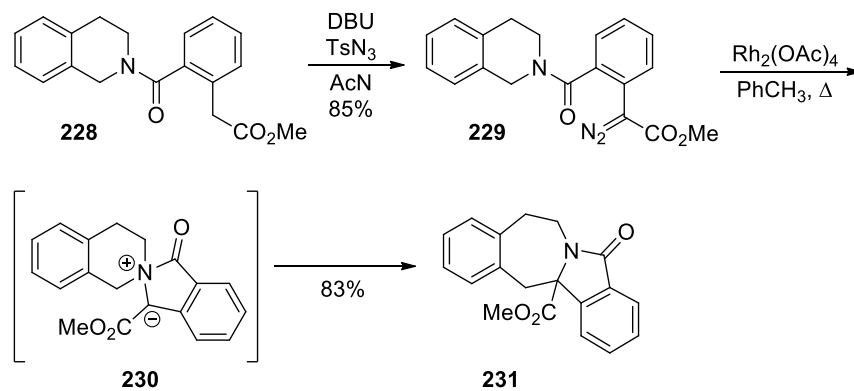


**Scheme 70.** Oxidation of dehydrolennoxamine.

Padwa *et al.* demonstrated the utility of Stevens [1,2]-rearrangement in the synthesis of the isoindolobenzazepine core (Scheme 71).<sup>55</sup> In a model study, amido ester **228** was converted to

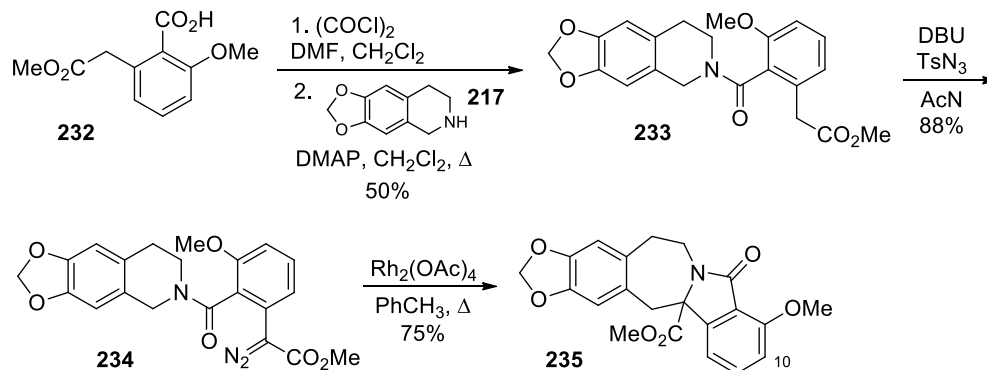


the diazo amide (**229**) through addition of DBU and tosyl azide. Subsequent treatment with rhodium(II) acetate dimer in refluxing toluene provided the aporphoadane core (**231**), presumably through the formation of a spriocyclic ammonium ylide (**230**), which then underwent Stevens [1,2]-rearrangement in which the benzylic carbon migrated preferentially.



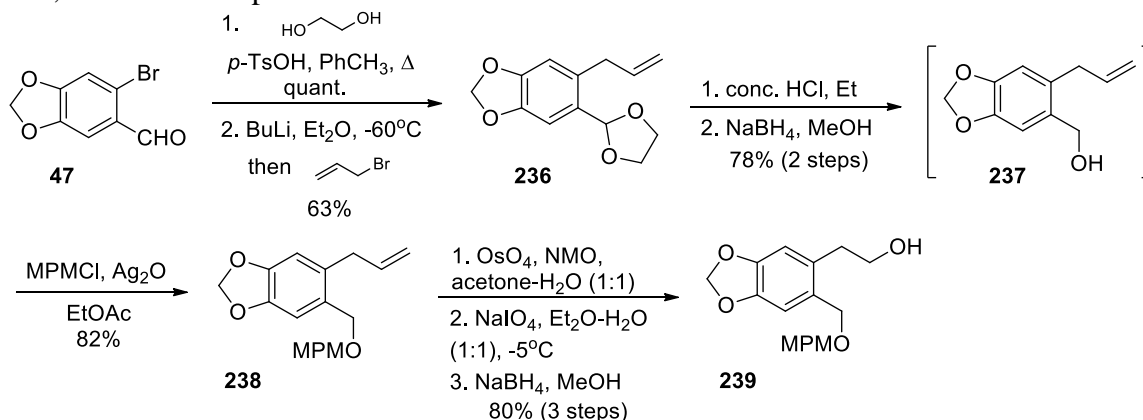
**Scheme 71.** Synthesis of aporphoadane core through Stevens rearrangement.

This method could be applied to substrates with some, but not all, of the substituents present in the natural product lennoxamine (Scheme 72). Benzoic acid **232** was converted to the corresponding acid chloride and coupled with isoquinoline **217** to yield amido ester **233**. This amido ester could be transformed into the diazo compound (**234**); however, attempts to do the same with an amido ester bearing a second methoxy substituent that would lead to the requisite C10 methoxy substitution of lennoxamine were unsuccessful. The additional methoxy group diminished the acidity of the benzylic hydrogens, which rendered diazo transfer ineffective. Nevertheless, diazo amide **234** did successfully undergo the Stevens rearrangement to yield a more fully elaborated aporphoadane (**235**).



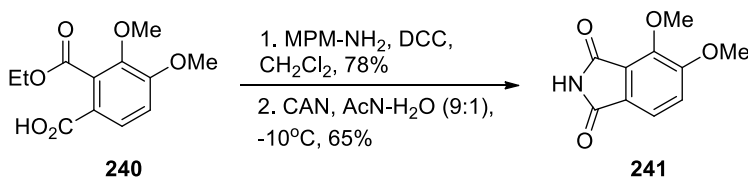
**Scheme 72.** Synthesis of a lennoxamine analogue through Stevens rearrangement.

Yoda *et al.* constructed the C13-C14 bond using a samarium iodide-mediated pinacol coupling as the key step.<sup>56</sup> The synthesis began with bromopiperonal (**47**), which was protected as its acetal and then subjected to aromatic allylation to yield **236** (Scheme 73). Removal of the acetal was followed by reduction of the aldehyde. The incipient alcohol (**237**) was then protected as its 4-methoxybenzyl (MPM) ether (**238**), after which dihydroxylation, oxidative cleavage of the diol, and reduction provided alcohol **239**.



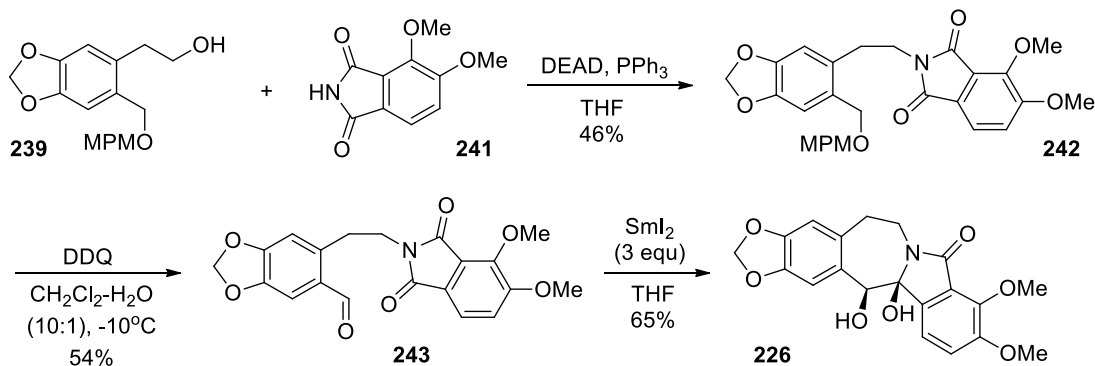
**Scheme 73.** Synthesis of the benzodioxole fragment.

The other building block was derived from 3,4-dimethoxy-2-ethoxycarbonylbenzoic acid (**240**), which was coupled with MPM-amine using DCC (Scheme 74). Removal of the protecting group led to ring closure, providing phthalimide **241**.



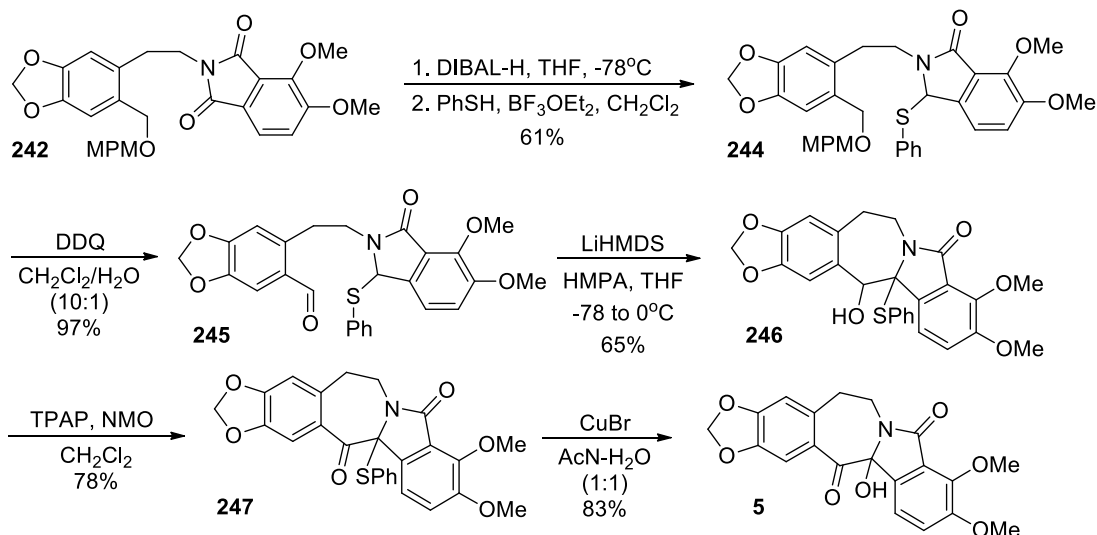
**Scheme 74.** Synthesis of the phthalimide fragment.

The two fragments were united using Mitsunobu conditions (Scheme 75), after which DDQ removed the remaining MPM group and oxidized the benzyl alcohol. The aldehyde thus formed (**243**) underwent an intramolecular pinacol coupling when treated with samarium iodide to yield diol **226** as a 3:1 mixture of the *cis* and *trans* diastereomers. Since Danishefsky and co-workers had previously converted this diol into chilenine,<sup>54</sup> the work of Yoda *et al.* constitutes a formal total synthesis of chilenine.



**Scheme 75.** Union of the fragments and pinacol ring closure.

Yoda and co-workers also utilized a Lewis acid-mediated tandem reaction of  $\gamma$ -phenylthio-substituted lactams to prepare chilenine.<sup>57</sup> Their synthesis began with phthalimide **242** (Scheme 76), whose synthesis they had previously reported (refer to Scheme 75).<sup>56</sup> Regioselective DIBAL-H reduction provided the hydroxylactam as an intermediate that was treated directly with thiophenol to yield the  $\gamma$ -phenylthiolactam **244**. Removal of the MPM protecting group with DDQ proceeded with concomitant oxidation of the newly liberated benzyl alcohol to give aldehyde **245**. Base-induced cyclization installed the benzazepine ring (**246**), and TPAP selectively oxidized the alcohol to the ketone (**247**) without oxidation of the sulfur. Finally, the tandem desulfurization and hydroxylation developed by these investigators provided chilenine (**5**).

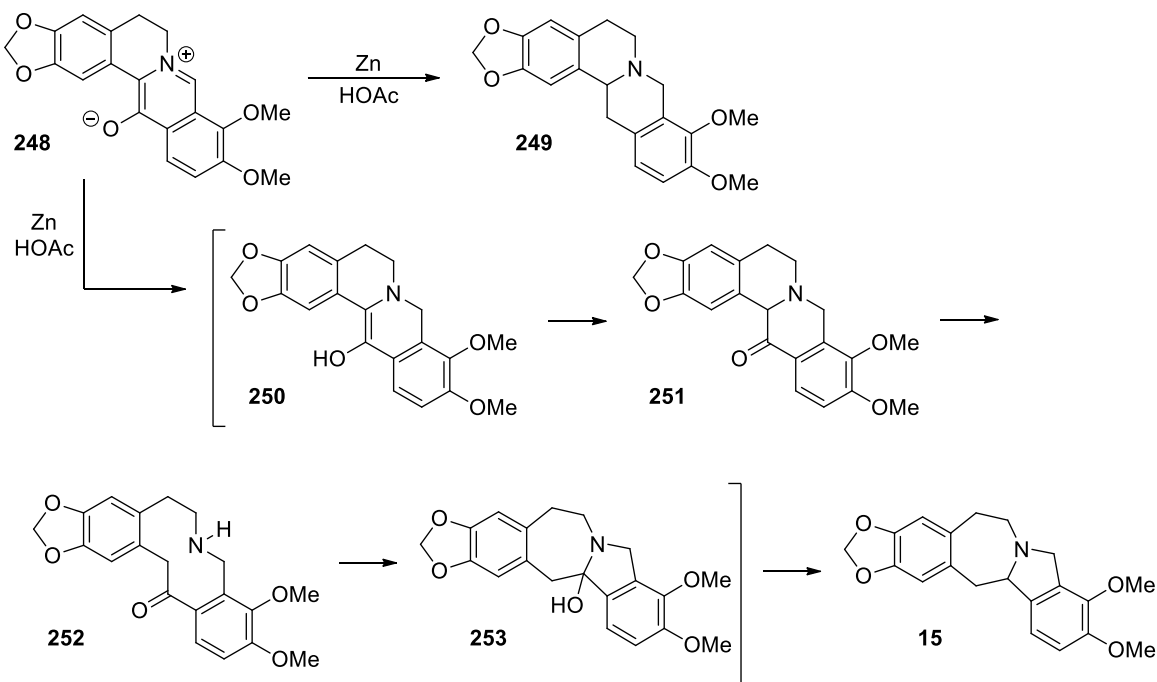


**Scheme 76.** Synthesis of chilenine using tandem desulfurization and hydroxylation

## 4. Concurrent Synthesis of the Seven/Five Ring System

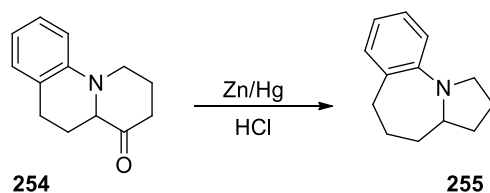
### 4.1. Formation of the N7-C13 bond

Schöpf and Schweikert reported that the reduction of berberine-phenol (**248**) in zinc and acetic acid provided two products, a tetrahydroberberine (**249**) as well as the rearrangement product bearing a fused seven/five ring system at its core (**15**, Scheme 77).<sup>58</sup> This was the first reported synthesis of chilenamine, which occurred nearly twenty years before its isolation.



**Scheme 77.** Reduction of berberine-phenol in zinc and acetic acid.

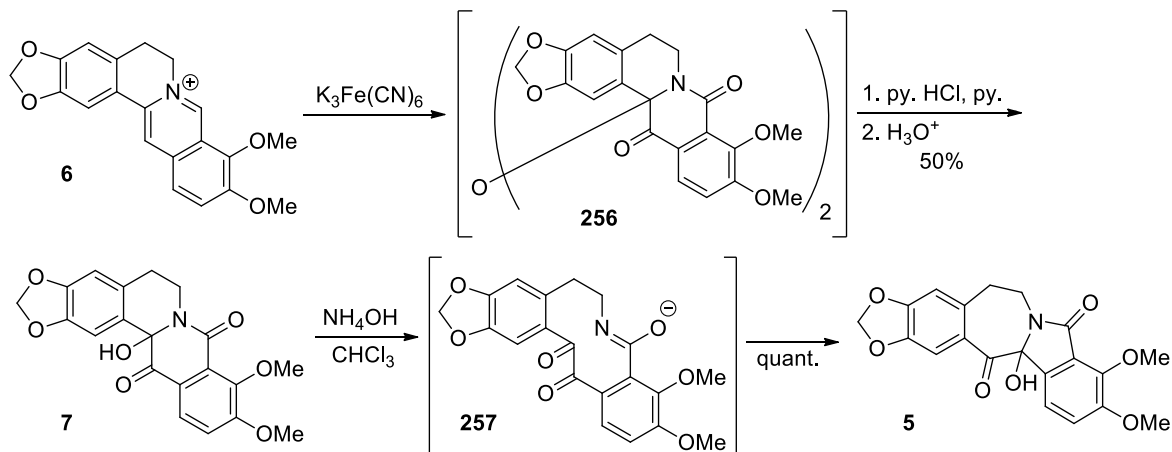
It has been noted<sup>59</sup> that the rearrangement is analogous to that observed in the rearrangement of the  $\alpha$ -amino ketone **254** under Clemmensen reduction conditions (Scheme 78).<sup>60</sup>



**Scheme 78.** Clemmensen reduction of an  $\alpha$ -amino ketone.

Shamma and co-workers also reported a method for the synthesis of aporphoadanes, but this time from berberine itself.<sup>6,61</sup> Berberine (**6**, Scheme 79) was dimerized to oxybisberberine (**256**)

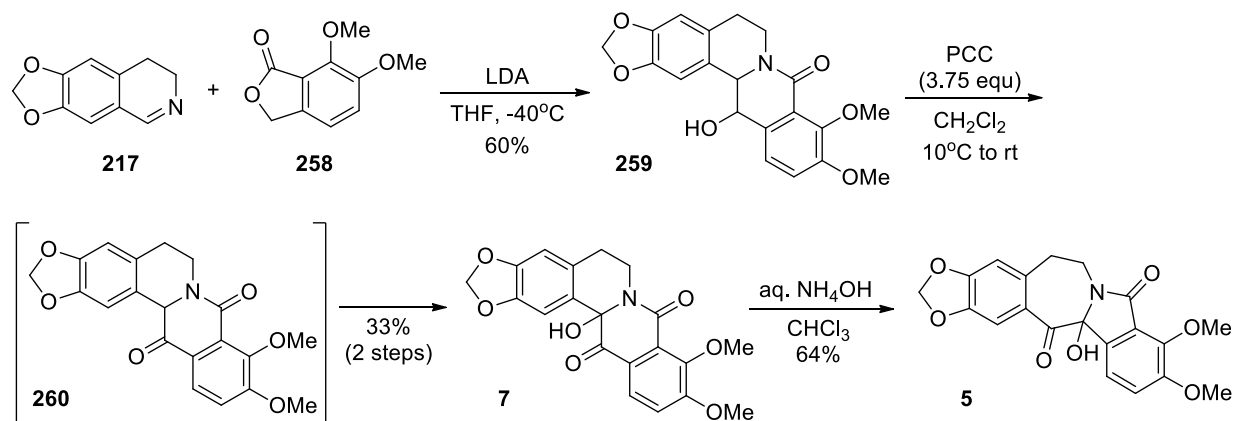
using potassium ferricyanide. The dimer could be cleaved nearly quantitatively with pyridine hydrochloride in pyridine to yield the homoannular  $\alpha$ -ketocarbinolamide **7** (which could also be called prechilenine or 8,13-dioxo-14-hydroxycanadine) along with recovered berberine in a 1:1 ratio. Treatment of **7** with ammonium hydroxide in chloroform resulted in a carbinol-carbonyl transposition. This likely proceeds through deprotonation of the hydroxyl group followed by fragmentation to yield **257**, which can undergo transannular cyclization onto the closer ketone, forming the N7-C13 bond and providing chilenine (**5**) five years prior to its isolation.



**Scheme 79.** Synthesis of chilenine from berberine.

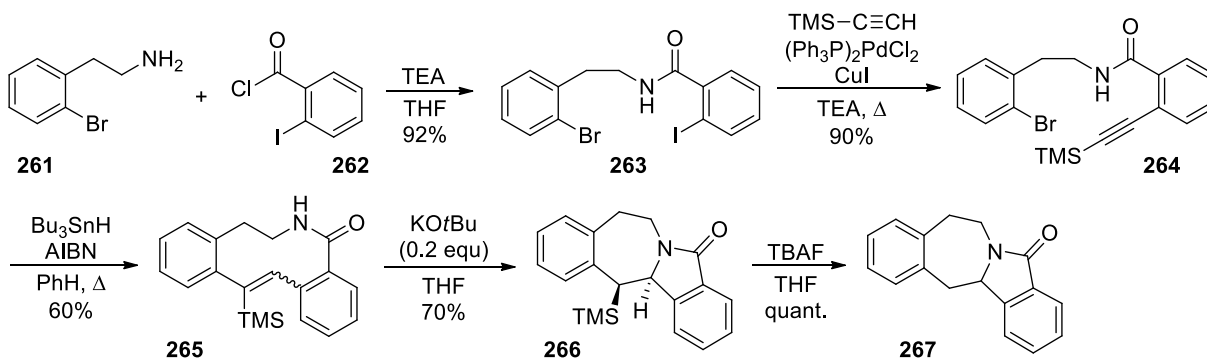
As an aside, chilenine has also been prepared as a very minor side product (2%) of the pyrolysis of 8,13-dioxo-14-methoxycanadine (i.e. prechilenine, **7**) via an analogous mechanism.<sup>62</sup>

While the methods outlined above utilized a natural product derivative as the starting material, some other approaches have built the framework from simpler substrates. In one example, Kessar *et al.* described a chilenine synthesis that used the known base induced carbinol-carbonyl transposition,<sup>6,61</sup> but constructed the substrate, prechilenine, from simple building blocks (Scheme 80).<sup>63</sup> Their synthesis began with the known condensation<sup>64</sup> of dihydroisoquinoline **217** and 6,7-dimethoxyphthalide (**258**), which was prepared from *o*-vanillin.<sup>65</sup> The lactam that resulted (**259**) could be oxidized to ketone **260**, however, since the ketone was unstable, the lactam was oxidized directly to hydroxyketone **7** using excess PCC and longer reaction times. The method of Shamma,<sup>6,61</sup> was used to convert hydroxyketone **7** to chilenine (**5**).



**Scheme 80.** Synthesis of chilenine using controlled oxygenation and carbinol-carbonyl transposition.

In another example of building the core from simple substrates, Castedo and co-workers built the unsubstituted aporphoeadane core using a novel transannular cyclization of an azamacrocycle (**265**, Scheme 81).<sup>66</sup> Condensation of *o*-bromophenethylamine (**261**) and *o*-iodobenzoylchloride (**262**) yielded amide **263**, which underwent Sonogashira coupling with trimethylsilylacetylene. While desilylation and radical cyclization was an option, it was lower yielding than direct radical cyclization of the silylated acetylene (**264**). The vinylsilane thus formed (**265**) underwent transannular cyclization at the  $\beta$ -position in base to yield the isoindolobenzazepinone **266** as the *syn* diastereomer. Subsequent desilylation yielded the aporphoeadane core (**267**).

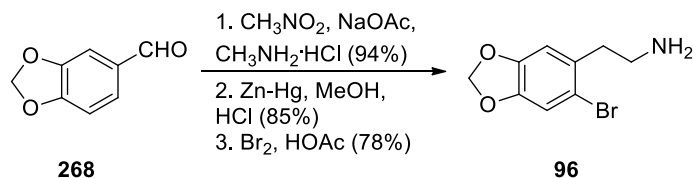


**Scheme 81.** Synthesis of the aporphoeadane core via transannular cyclization.

On the other hand, epoxidation of the vinylsilane followed by acidic workup led instead to the berberine architecture, presumably through rearrangement of the  $\alpha$ -epoxysilane to a ketone that underwent transannular cyclization with the lactam.

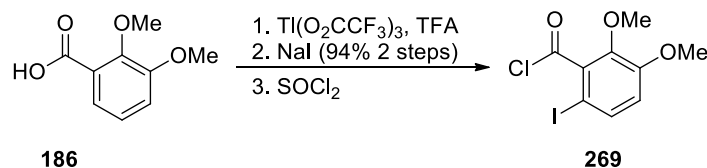
These same investigators (Castedo, Domínguez, and co-workers) utilized the vinylsilane methodology in a synthesis of lennoxamine.<sup>67</sup> To construct the cyclization precursor, two

fragments were needed. The phenethylamine fragment (**96**) was prepared from piperonal (**268**) through Henry reaction, reduction of the nitro group, and bromination (Scheme 82).



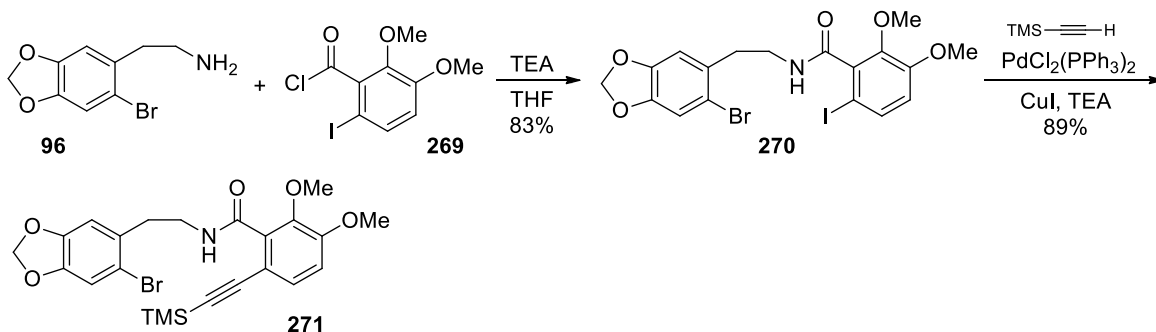
**Scheme 82.** Synthesis of the phenethylamine fragment.

2,3-Dimethoxybenzoic acid (**186**) provided the acid chloride fragment (**269**) after iodination and treatment with thionyl chloride (Scheme 83).



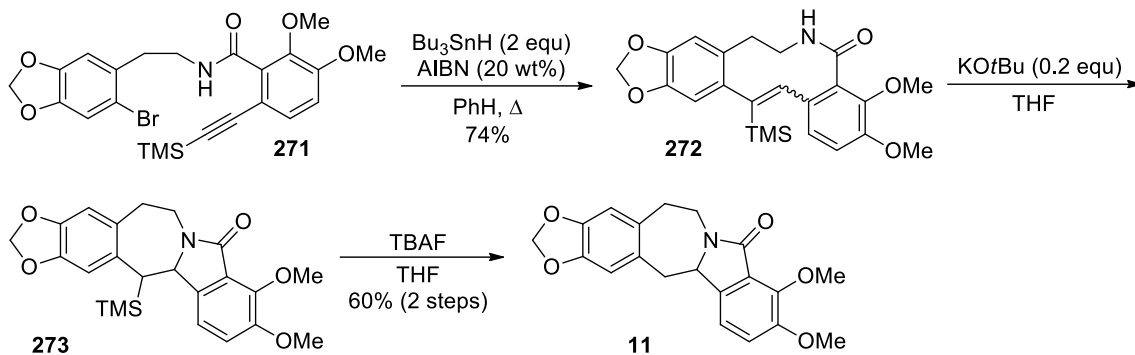
**Scheme 83.** Synthesis of the acid chloride fragment.

The fragments were smoothly united (Scheme 84), and then trimethylsilylacetylene was chemoselectively coupled to the benzamide (**270**), yielding the critical cyclization precursor (**271**) that would actually be used in two distinct routes to lennoxamine.



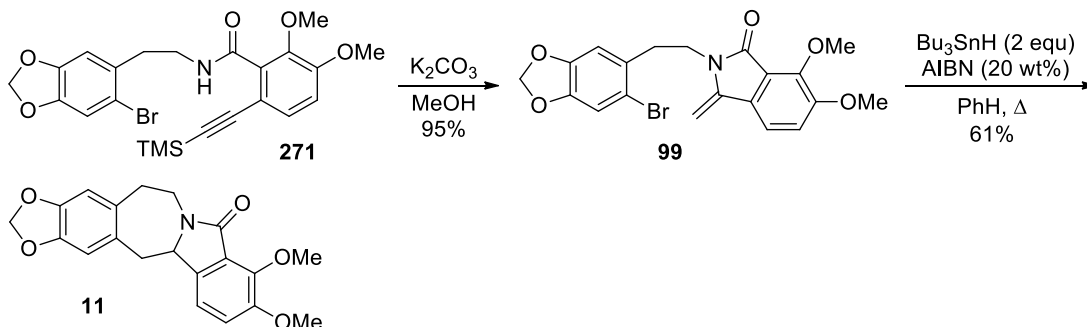
**Scheme 84.** Synthesis of the radical cyclization precursor.

First, macrocycle formation (**272**) occurred through intramolecular radical addition to the alkyne (Scheme 85). A single geometric isomer was isolated but its configuration was unknown and irrelevant for the remainder of the synthesis. Transannular base-induced cyclization created the aporphoadane core (**273**), which was readily desilylated to provide lennoxamine (**11**).



**Scheme 85.** Macrocycle formation and transannular cyclization to form lennoxamine.

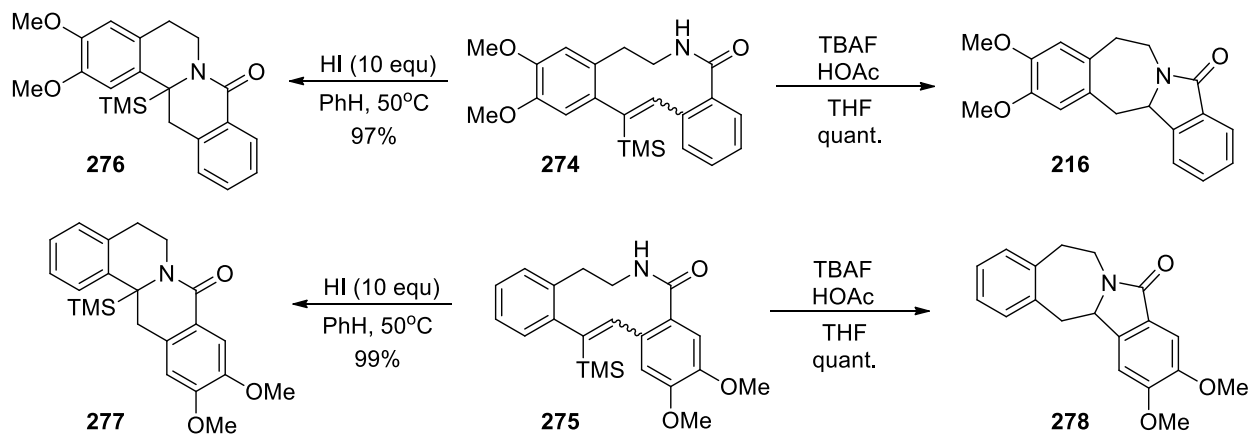
Alternatively, the same critical intermediate **271** readily underwent desilylation and cyclization in base (Scheme 86). The methylenephthalimide thus formed (**99**) was also a viable radical cyclization precursor yielding lennoxamine (**11**) upon closure of the benzazepine ring through formation of the C14-C14a bond instead.



**Scheme 86.** Alternative use of the radical cyclization precursor to yield lennoxamine via a different strategy.

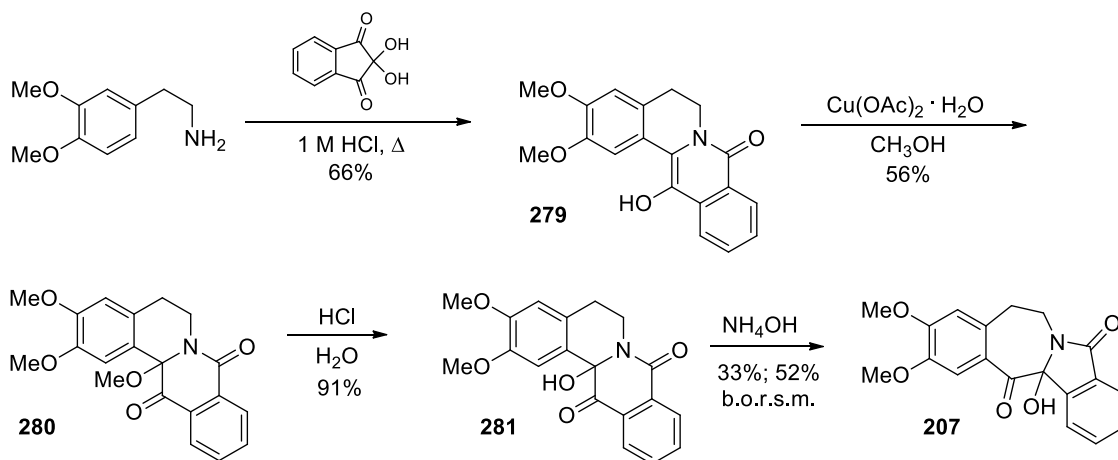
This same research group (Domínguez, Saá, and co-workers) later reported that vinylsilanes **274** and **275** could be cyclized in one of two ways to yield protoberberines or aporphoadanes (Scheme 87).<sup>68</sup> Treatment of vinylsilane **274** or **275** with a moderate excess of hydroiodic acid in benzene at 50 °C yielded the tetrahydroprotoberberines **276** or **277**, respectively, in nearly quantitative yield. It appears that these reactions proceed via protonation  $\beta$  to the vinylsilane and transannular attack of the amide nitrogen on the  $\alpha$  carbocation. However, treatment of the same vinylsilanes with TBAF buffered with acetic acid yielded the isoindolobenzazepinones **216** or **278** instead. This reversal of regioselectivity is attributed to fluoride promoted transannular attack of the amide nitrogen on the  $\beta$ -position of the vinylsilane.





**Scheme 87.** Formation of protoberberines or aporphoadanes from macrocyclic vinylsilanes.

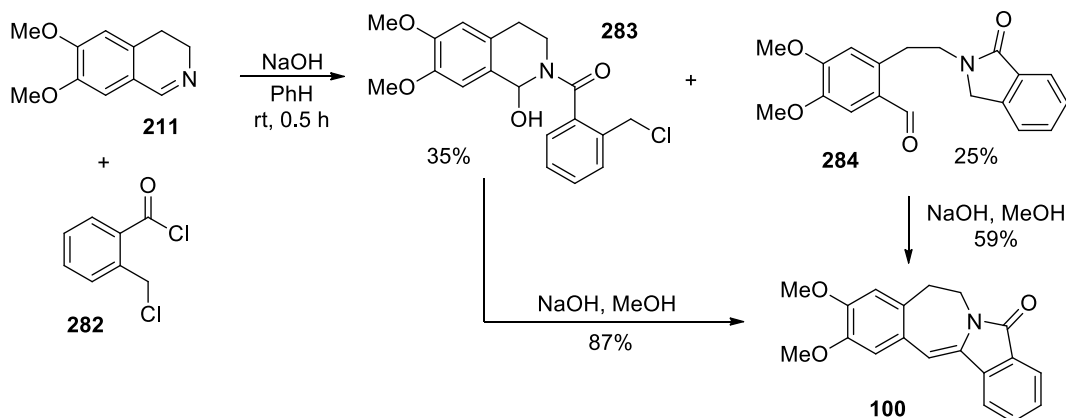
In another example, homoveratrylamine and ninhydrin can be condensed in acidic media in a process involving tandem Pictet–Spengler reaction and rearrangement of the spirocyclic adduct to ultimately provide oxyprotoberberine **279** (Scheme 88). Cupric acetate-mediated oxidation provides the methoxy ketone **280**,<sup>69</sup> and conversion to the hydroxyl ketone (**281**) proceeds smoothly in aqueous acid. Base-induced carbinol-carbonyl transposition<sup>6,61</sup> converts the homoannular  $\alpha$ -keto carbinolamide to the heteroannular  $\alpha$ -keto carbinolamide **207**, which is the same chilene analogue made by Mazzocchi and co-workers (see Scheme 64). This method consists of 4 steps and provides 11% overall yield (17.5% based on recovered starting material in the final step).<sup>70</sup>



**Scheme 88.** Synthesis of a chilene analogue from 3,4-dimethoxyphenethylamine and ninhydrin.

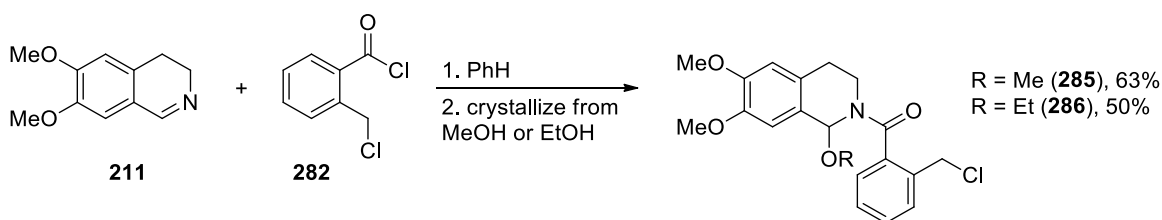
#### 4.2. Formation of the N7-C13 and C13-C14 bonds

Ruchirawat and co-workers reported a one-pot method for the construction of the aporphoeadane skeleton from dihydroisoquinolines and 2-chloromethylbenzoyl chloride (Scheme 89).<sup>71</sup> This method was based on the preliminary observation that dihydroisoquinoline **211** and 2-chloromethylbenzoyl chloride (**282**) reacted in the presence of base so as to provide a somewhat unstable pseudobase **283** and aldehyde **284**, both of which could subsequently be converted to enelactam **100** in methanolic sodium hydroxide.



**Scheme 89.** Formation of enelactam **100** from a dihydroisoquinoline and 2-chloromethylbenzoyl chloride.

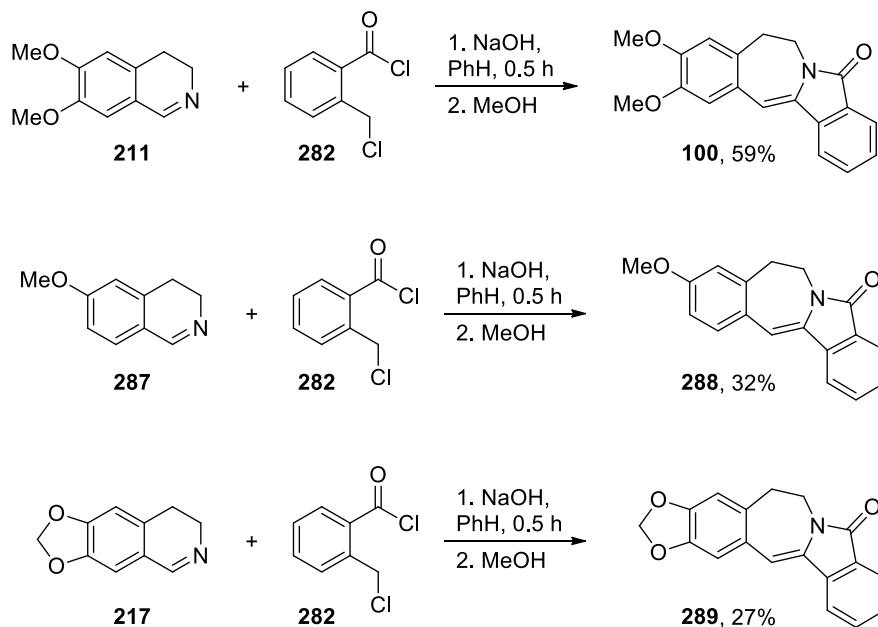
It was also observed that condensation of the dihydroisoquinoline and 2-chloromethylbenzoyl chloride followed by recrystallization from an alcoholic solvent simply provided the addition products **285** or **286** (Scheme 90).



**Scheme 90.** Condensation of a dihydroisoquinoline and 2-chloromethylbenzoyl chloride followed by recrystallization.

These observations enabled the formulation of a one-pot approach to enelactams that included initial exposure of a dihydroisoquinoline and 2-chloromethylbenzoyl chloride (**282**) to sodium hydroxide in benzene, followed by removal of the solvent and addition of methanol (Scheme 91). This one-pot procedure was amenable to varying substitution on the dihydroisoquinoline (e.g. **211**, **287**, or **217**). The identity of the hydroxide counterion was

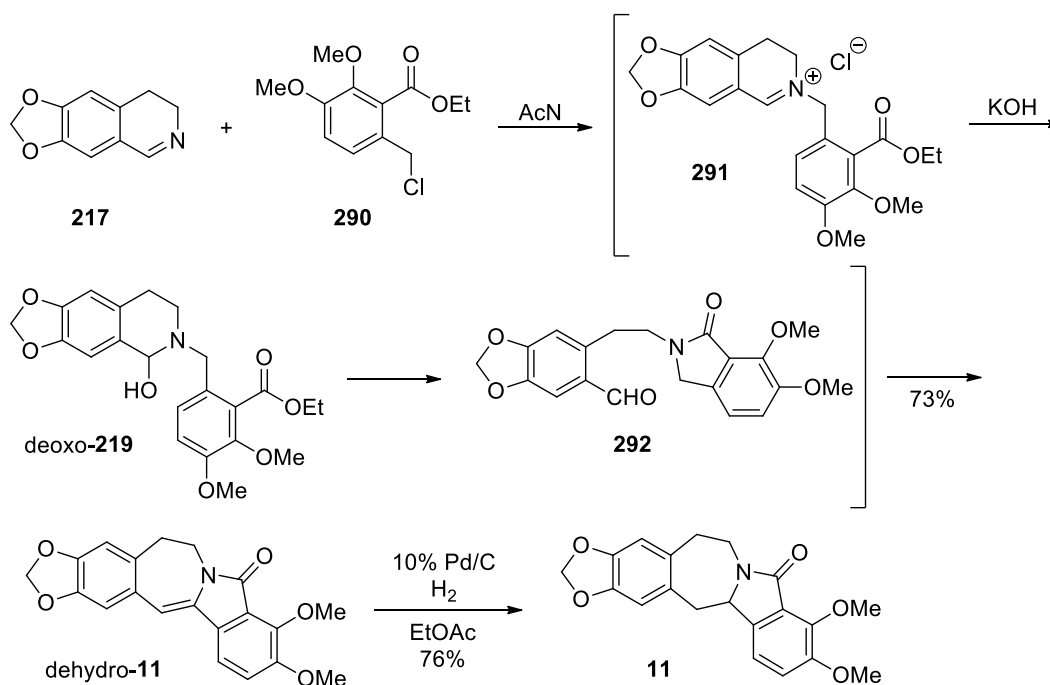
deemed critical.<sup>73</sup> Furthermore, an alkoxy group at the 6 position was necessary, presumably to facilitate fragmentation to the aldehyde and amide ion needed for cyclization to form the lactam ring of **100**, **288**, or **289**.<sup>72</sup>



**Scheme 91.** One-pot approach to the aporphoeadane core.

#### 4.3. Formation of the N7-C8 and C13-C14 bonds

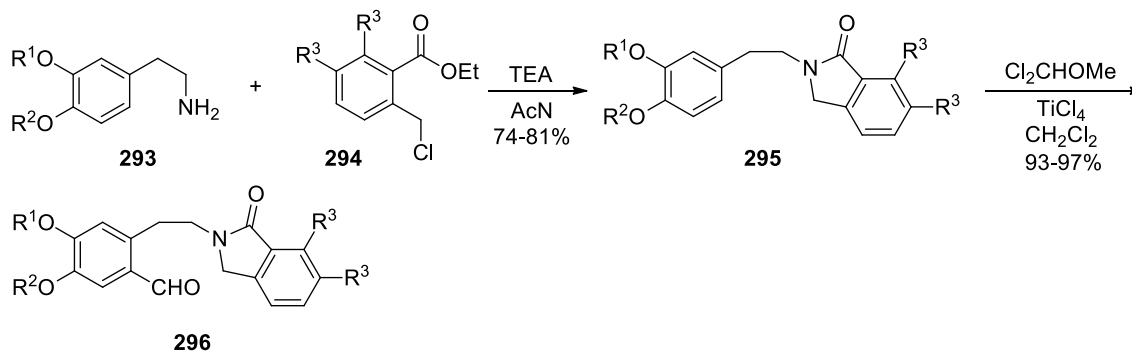
The Ruchiwarat group revised its approach<sup>73</sup> due to two principal challenges associated with the original route: the need for halomethylbenzoyl chlorides that are not readily accessible and the disappointing yield provided by 6,7-methylenedioxy-3,4-dihydroisoquinoline (**217**) in reaction with chloromethylbenzoyl chloride (**282**, refer to Scheme 91). This second-generation approach (Scheme 92) constructed the lactam ring through intramolecular attack of an amine on ester, as opposed to the intramolecular attack of an amide on a benzyl chloride used in the original approach. It was expected that the enhanced nucleophilicity of the amine would render the cyclization more facile in the second-generation approach. 6,7-Methylenedioxy-3,4-dihydroisoquinoline (**217**) was alkylated with the more easily obtained ethyl 6-chloromethyl-2,3-dimethoxybenzoate (**290**) to yield an iminium ion (**291**) that was not isolated but was instead treated directly with potassium or sodium hydroxide. Dehydrolennoxamine (dehydro-**11**) was obtained directly without isolation of the putative pseudobase and aldehyde intermediates, deoxo-**219** and **292** respectively. The 15% lower yield obtained when using sodium hydroxide reinforces the earlier observation about the significance of the counterion. Finally, hydrogenation smoothly provided lennoxamine (**11**).



**Scheme 92.** Second-generation approach to the one-pot synthesis of aporphoeadanes.

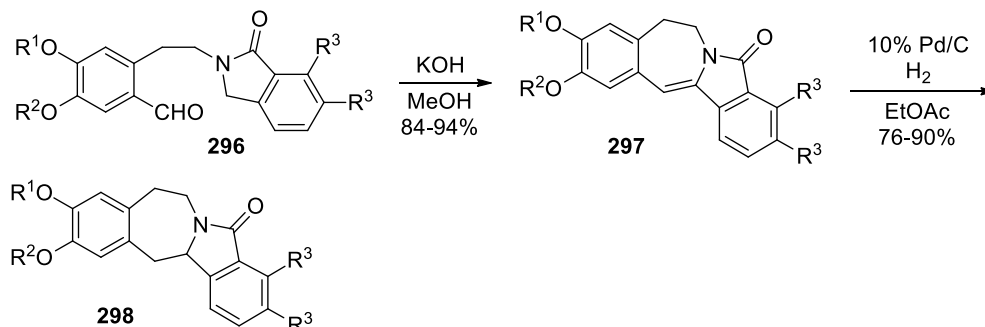
In this approach, a methoxy group *ortho* to the ethyl ester is essential, presumably to enhance the leaving group ability.<sup>72</sup>

Given the critical nature of the pattern of oxygenation on both the dihydroisoquinoline and benzoate fragments, Sahakitpichan and Ruchirawat sought a method that would be efficient regardless of the substituent pattern. This third-generation approach<sup>72</sup> (Scheme 93) sequentially prepares the five-membered ring, forming an isolable intermediate, before making the seven-membered ring; however, it is included in this section for continuity. The seven-membered ring formation relies upon the use of an aldehyde isoindolone prepared in two steps from a phenethylamine of type **293** and a chloromethylbenzoate ester of type **294**. An alkylation-acylation sequence provides the isoindolone **295**, while subsequent formylation with dichloromethyl methyl ether and titanium tetrachloride yields the aldehyde isoindolone **296**.



**Scheme 93.** Preparation of aldehyde isoindolones.

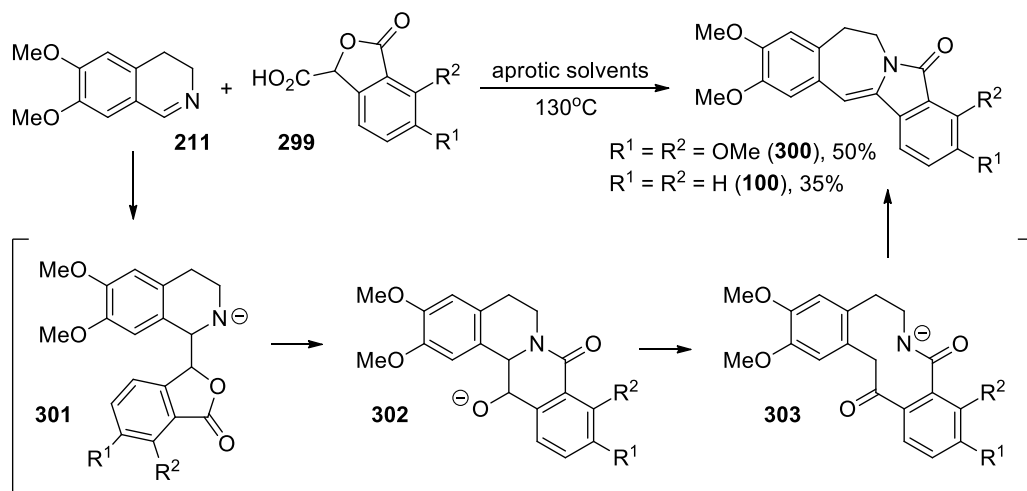
Yields were good for both steps regardless of whether a 3,4-methylenedioxy ( $R^1 = R^2 = \text{CH}_2$ ) or 3,4-dimethoxyphenethylamine ( $R^1 = R^2 = \text{Me}$ ) was used. Additionally, the presence of either methoxy groups ( $R^3 = \text{OMe}$ ) or hydrogens ( $R^3 = \text{H}$ ) on the chloromethylbenzoate ring had little impact on yield. The cyclization of the aldehyde isoindolone (**296**) in methanolic potassium hydroxide also proceeded smoothly in all cases with little, if any, noticeable impact of the substitution pattern on yield (Scheme 94). Finally, hydrogenation of the enlactam yielded lennoxamine or its analogues (**298**).



**Scheme 94.** Cyclization and hydrogenation of the aldehyde isoindolone.

#### 4.4. Formation of the N7-C8, N7-C13, and C13-C14 bonds

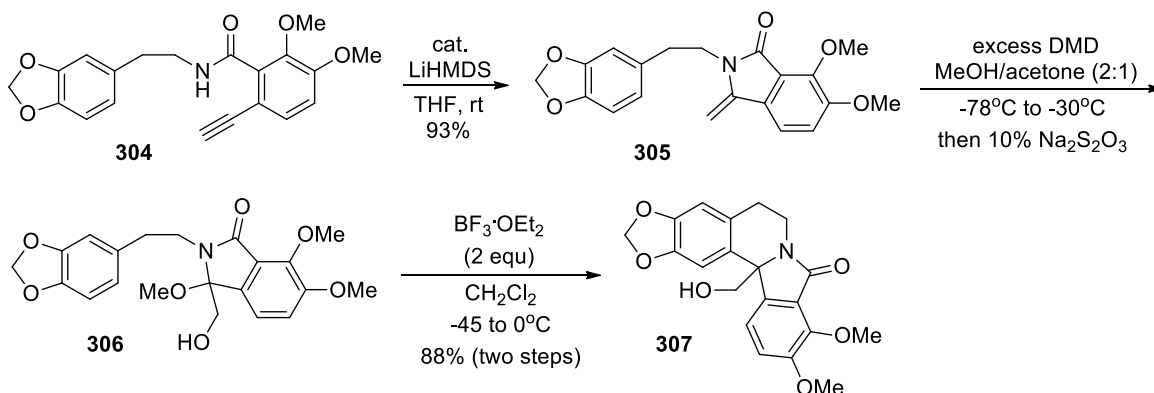
Chiefari, Janowski, and Prager utilized decarboxylation of phthalidecarboxylic acids (**299**) in the presence of imine electrophiles to devise a strikingly concise synthesis of the aporphoadane core (Scheme 95).<sup>74</sup> When the imine was a dihydroisoquinoline (e.g. **211**), the product of the condensation was an isoindolobenzazepinone (e.g. **100** or **300**). The product is likely formed by initial decarboxylation and attack on the imine to give **301** followed by lactamization (**302**), ketone formation (**303**), and transannular cyclization. While the yields are modest, the brevity of the synthesis is a distinct advantage.



**Scheme 95.** Synthesis of the aporphoadane core based on the decarboxylation of phthalidecarboxylic acids.

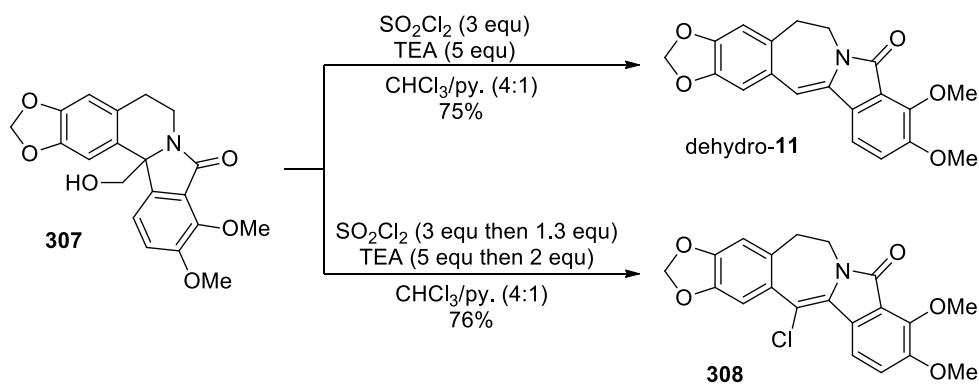
#### 4.5. Formation of the C14a-C14 bond

Nagasaka and co-workers reported a unique ring expansion of an isoindoloisoquinolone, which ultimately afforded both lennoxamine and chilenine.<sup>75,76</sup> Their approach began with the *o*-ethynylbenzamide **304** (Scheme 96), which was prepared according to the previously reported protocol.<sup>47</sup> Intramolecular cyclization proceeded in the presence of catalytic LiHMDS to yield methyldeneisoindolone **305**. On treatment with excess dimethyldioxirane in methanol and acetone, the methoxylactam **306** was formed. This methoxylactam underwent cyclization to the isoindoloisoquinolone **307** upon exposure to boron trifluoride diethyl etherate.



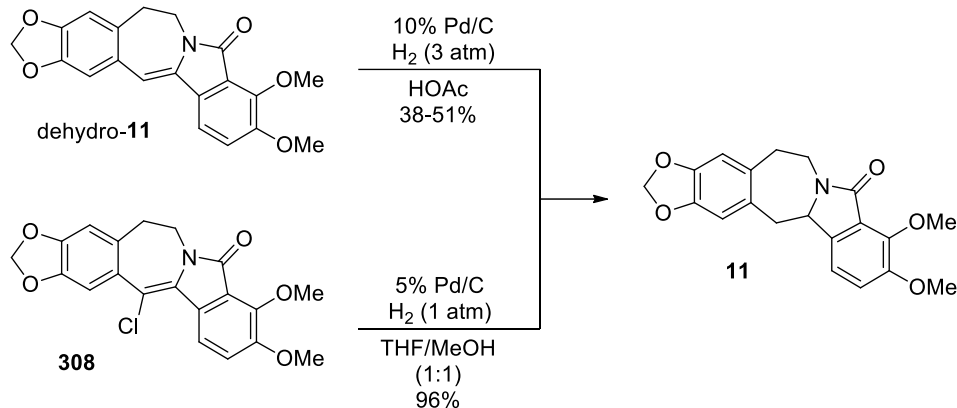
**Scheme 96.** Synthesis of the isoindoloisoquinolone ring expansion substrate.

Ring expansion occurred under two sets of conditions yielding related enolactams dehydro-**11** or **308** in nearly identical yield (Scheme 97).



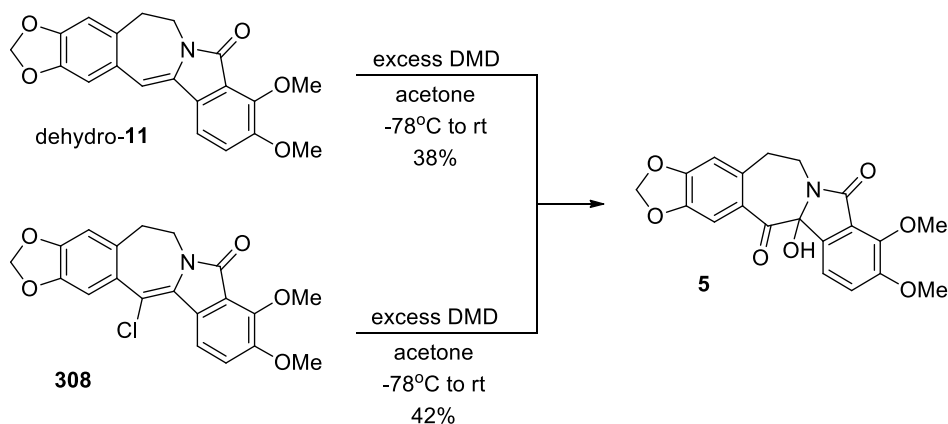
**Scheme 97.** Ring expansion of the isoindoloisoquinoline.

Chloroenolactam (**308**) could be reduced to lennoxamine (**11**, Scheme 98) in much higher yield (96%) than that which resulted from the reduction of dehydrolennoxamine (dehydro-**11**, 38-51%).



**Scheme 98.** Reduction to form lennoxamine.

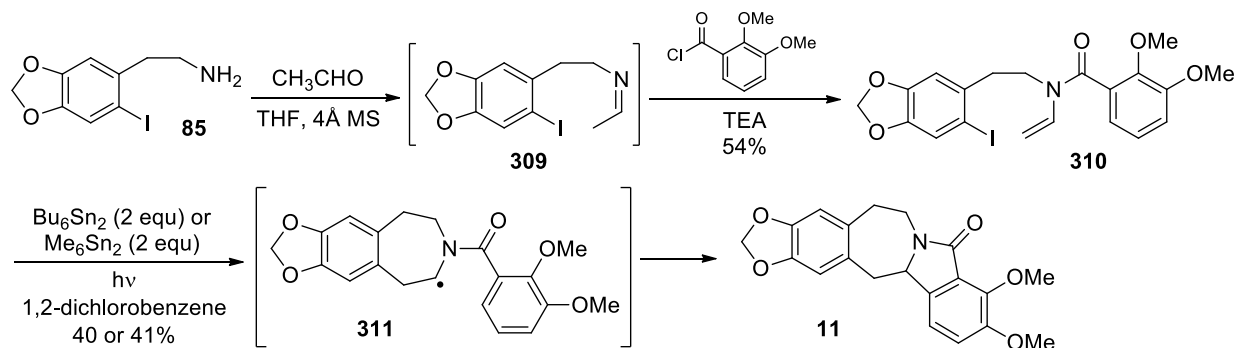
Enolactams dehydro-11 and 308 were both converted to chilenine (5) in 38 and 42% yield, respectively, using the method of Fang and Danishefsky (Scheme 99).<sup>54</sup>



**Scheme 99.** Conversion to chilenine.

#### 4.6. Formation of the C12a-C13 and C14-C14a bonds

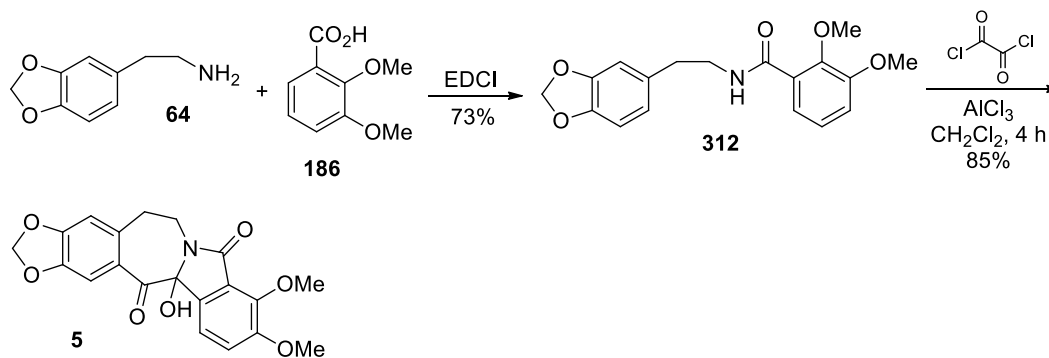
Ishibashi and co-workers presented a concise synthesis of lennoxamine that relies upon a radical cascade involving aryl radical-induced 7-*endo* cyclization followed by homolytic aromatic substitution (Scheme 100).<sup>77</sup> Phenethylamine 85 was condensed with acetaldehyde, and the imine thus formed (309) was immediately acylated to yield enamide 310. Radical initiation, using conditions carefully selected to suppress hydrogen abstraction by the intermediate radicals, yielded lennoxamine (11) via benzazepine radical 311 in a total of three steps and 22% overall yield.



**Scheme 100.** Radical cascade synthesis of lennoxamine.

#### 4.7. Formation of the N7-C13, C12a-C13, and C14-C14a bonds

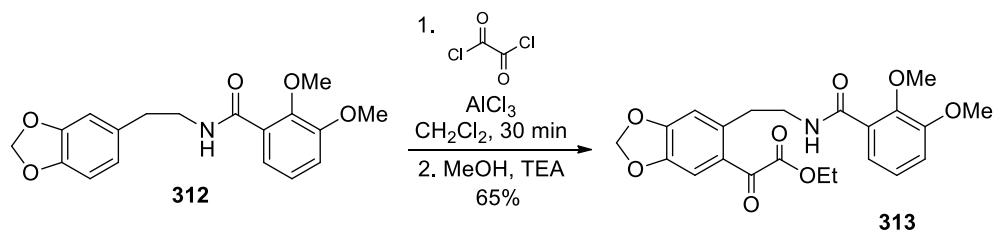
Kim and co-workers devised another stunningly concise synthesis of chilenine that employed oxalyl chloride as a two-carbon synthetic equivalent for C13 and C14 of the natural product (Scheme 101).<sup>78</sup> Their synthesis began with the straightforward coupling of phenethylamine **64** and benzoic acid **186**. With amide **312** in hand, the chilenine synthesis was expected to proceed via sequential: Friedel-Crafts acylation to form the C14-C14a bond; cyclization of the amide nitrogen onto the remaining acid chloride to form the benzazepine through installation of the N7-C13 bond; and Friedel-Crafts type reaction to close the isoindolone through the formation of C12a-C13.



**Scheme 101.** Two-step synthesis of chilenine using oxalyl chloride as a synthetic equivalent.

This two-step synthesis of chilenine (**5**) provides 62% overall yield. Some evidence for the proposed mechanism of the one-pot procedure was obtained by premature quenching of the reaction with methanol and triethylamine (Scheme 102). This yielded keto ester **313**, which provides support for initial Friedel-Crafts acylation to form the C14-C14a bond.



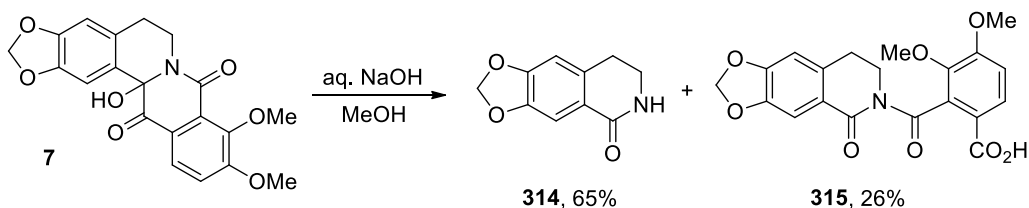


**Scheme 102.** Evidence for initial Friedel-Crafts acylation to form the C14-C14a bond.

## 5. Reactions of Aporphoeadanes

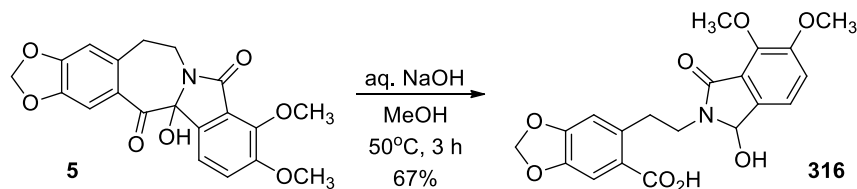
### 5.1. Reactions in base

Shamma and co-workers have extensively studied the reactions of aporphoeadanes including chilenine. Some of the earliest observations included comparisons to the reactivity of its homoannular  $\alpha$ -ketocarbinolamide counterpart prechilenine (**7**). For instance, the heteroannular  $\alpha$ -ketocarbinolamide chilenine is more stable to base than its homoannular counterpart.<sup>61</sup> Treatment of the homoannular  $\alpha$ -ketocarbinolamide (**7**) with aqueous sodium hydroxide readily yields noroxyhydrastine (**314**) as the major product, along with Perkin's anhydroberberilic acid (**315**, Scheme 103).<sup>6</sup>



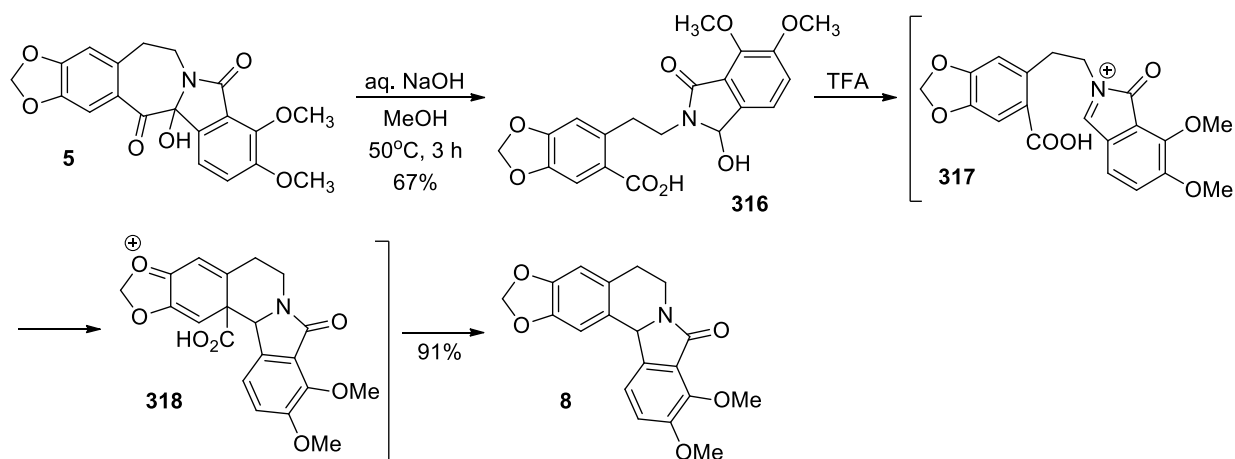
**Scheme 103.** Oxidative cleavage of the homoannular  $\alpha$ -ketocarbinolamide prechilenine.

However, alkaline hydrolysis of the heteroannular  $\alpha$ -ketocarbinolamide chilenine (**5**) requires prolonged warming, ultimately leading to cleavage of the C13 to C14 bond to form imidol **316** (Scheme 104).<sup>1</sup> This process is akin to Haller-Bauer reaction of the ketone of chilenine.



**Scheme 104.** Alkaline hydrolysis of chilenine.

This reaction was an important part of the synthesis of nuevamine (**8**), which occurred five years before it was isolated.<sup>1</sup> Basic cleavage of the azepine ring was followed by treatment with trifluoroacetic acid, which initially formed iminium ion **317** (Scheme 105). Intramolecular Friedel-Crafts alkylation (**318**) preceded extrusion of carbon dioxide to provide nuevamine.

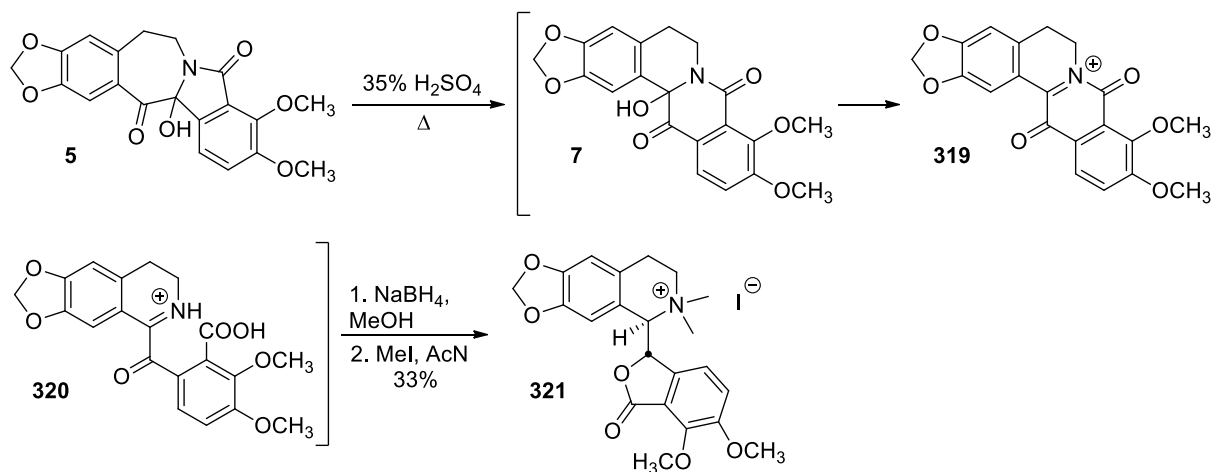


**Scheme 105.** Conversion of chilenine to nuevamine.

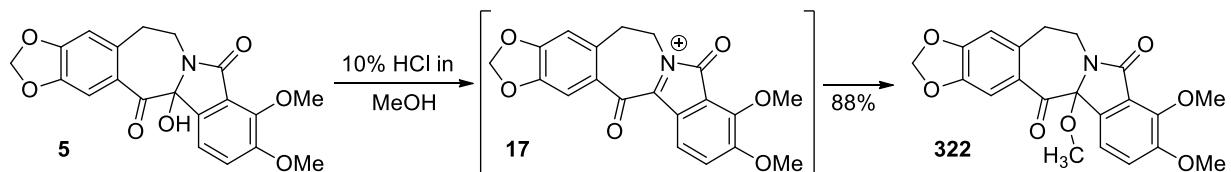
## 5.2. Reactions in acid

On the other hand, treatment of chilenine with strong acid at elevated temperatures leads to ring contraction and amide bond scission (Scheme 106).<sup>1</sup> When chilenine (**5**) is heated at reflux in 35% sulfuric acid, the reaction is understood to proceed through initial formation of the homoannular  $\alpha$ -ketocarbinolamide **7**. As an aside, this is significant because treatment of the homoannular  $\alpha$ -ketocarbinolamide with ammonium hydroxide incites the reverse reaction.<sup>6,61</sup> The hydroxyl group is lost to give the violet iminium salt **319**, and the lactam is subsequently cleaved. Sodium borohydride was then used to reduce the  $\alpha$ -ketoiminium ion (**320**) to the corresponding amino alcohol, which spontaneously lactonized. Finally, methylation with excess methyl iodide yielded  $\beta$ -hydrastine methiodide (**321**).

Chilenine is, however, amenable to nucleophilic exchange much like its homoannular counterpart. Treatment with methanol in >28% sulfuric acid induces the exchange.<sup>61</sup> Alternatively, treatment with 10% methanolic hydrogen chloride accomplishes the same result (Scheme 107).<sup>6</sup> The drastic color change that occurs during the reaction suggests the intermediacy of iminium ion **17**, which is blue-black in color.

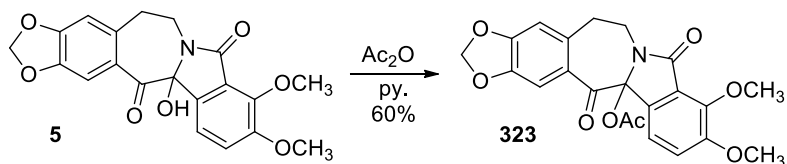


**Scheme 106.** Ring contraction and amide bond scission of chilenine.



**Scheme 107.** Nucleophilic exchange with methanol.

Nucleophilic exchange also happens readily in acetic anhydride and pyridine upon standing at room temperature (Scheme 108). Given the mild reaction conditions and the tertiary nature of the hydroxyl group, it is presumed that the same iminium ion (**17**) is an intermediate and that it adds acetate to yield **323**.<sup>1</sup>

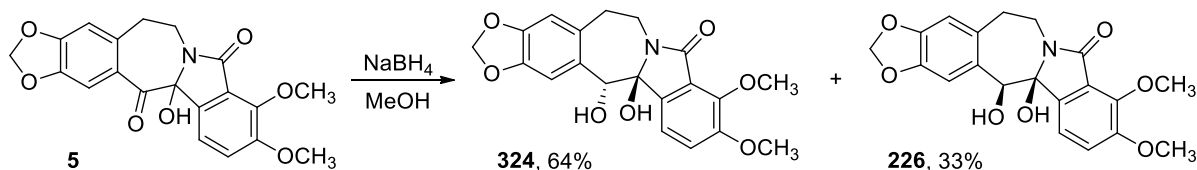


**Scheme 108.** Nucleophilic exchange with acetic anhydride.

### 5.3. Reactions with reducing agents

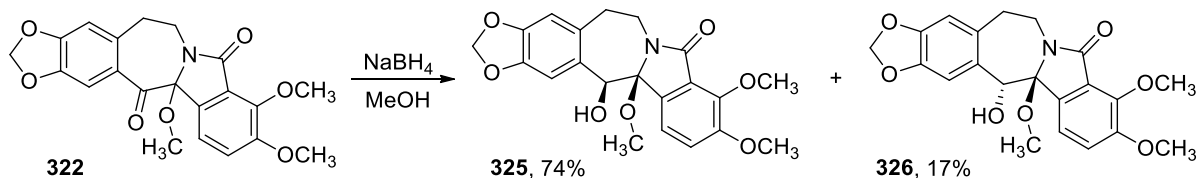
Mild reducing conditions convert the ketone of chilenine or its C13 methoxy analogue to the *cis* or *trans*-diol or  $\alpha$ -hydroxyether, respectively. Conditions that preclude intramolecular participation lead to the *cis* products, while those that allow intramolecular participation result in *trans* products.<sup>1</sup> For instance, when chilenine is treated with sodium borohydride in methanol the *trans*-diol (**324**) is the predominant product (Scheme 109). It is probable that the C13 hydroxyl

group of chilenine complexes with borohydride and that intramolecular addition of hydride to the carbonyl then necessarily occurs from the same side as the hydroxyl group affording the *trans* product. Acidification of the aqueous layers during workup provides the *cis*-diol **226** as the minor product. The necessity of acidification to isolate the *cis*-diol suggests that it was present as the cyclic borate ester.



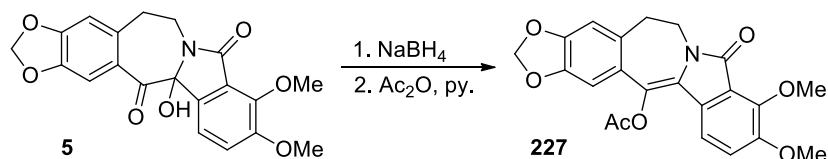
**Scheme 109.** Sodium borohydride reduction of chilenine.

On the other hand, the C13 methoxy analogue of chilenine (**322**) undergoes reduction in the same conditions to provide the *cis*-hydroxyether **325** as the major product (Scheme 110). In this case, intramolecular participation is precluded, so attack of hydride simply occurs from the less hindered face, opposite the methoxy group. A comparatively small amount of the *trans*-hydroxyether (**326**) was isolated as a minor product.



**Scheme 110.** Sodium borohydride reduction of the C13 methoxy analogue of chilenine.

If mild reduction is followed immediately by acetylation, elimination of the angular hydroxyl group is observed, and the product is acetoxyenamide **227**, which happens to be highly fluorescent (Scheme 111).<sup>61</sup>

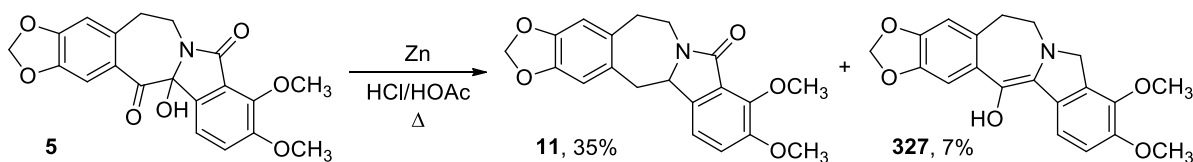


**Scheme 111.** Conversion of chilenine to an acetoxyenamide.

If the intermediate *trans* and *cis*-diols are first isolated and subjected separately to acetic anhydride in pyridine, the *cis*-diol **226** undergoes acetylation and elimination much more readily (i.e. without heating) due to the *trans* orientation of the angular hydroxyl group and the

neighboring hydrogen. The *trans*-diol **324** requires stronger conditions to undergo this transformation (i.e. heating at 60 °C for 18 h).<sup>1</sup>

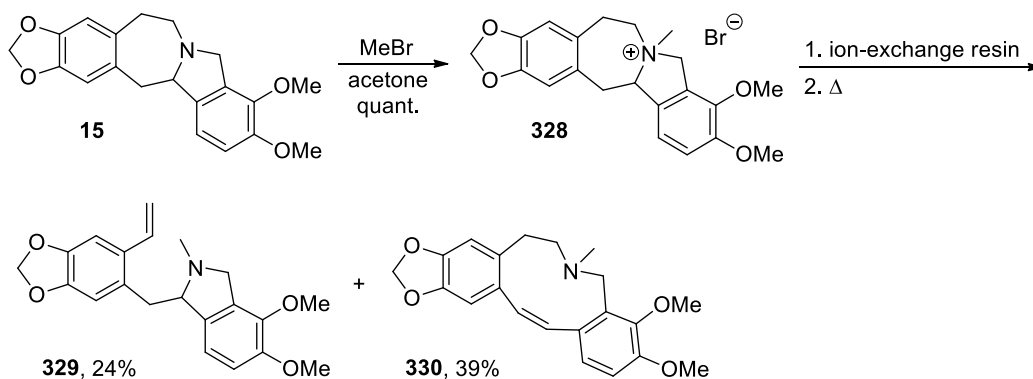
Dissolving metal reduction of chilenine (**5**) in strong acid results in the loss of the C13 and C14 oxygenation yielding lennoxamine (**11**) as the major product along with a small amount of enaminal **327** (Scheme 112).<sup>1,61</sup>



**Scheme 112.** Dissolving metal reduction of chilenine.

#### 5.4. Hofmann elimination

When chilenamine (**15**), also known as Schöpf's base VI, was quaternized with methyl bromide, the resultant methobromide (**328**) could be subjected to Hofmann elimination to yield a mixture of styrene **329** and the tetrahydrobenzazecine **330** (Scheme 113).<sup>79</sup>



**Scheme 113.** Hofmann degradation of chilenamine.

## 6. Conclusions

Over a period of nearly 50 years, the aporphoadanes have continually spurred advances in synthetic heterocyclic chemistry. Despite a relative lack of biological activity, these small, sometimes densely functionalized, alkaloids have prompted a myriad of strategically unique synthetic approaches. Given the close relationship of the aporphoadanes to a variety of other alkaloids, it is likely that these syntheses will continue to be useful, especially as new methods to interconvert these and other heterocycles are unveiled.

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## Author's Biography



**Michael Leonard** earned his B.A. in Chemistry from Goucher College (Baltimore, MD) in 1998 under the direction of Professor David E. Horn with whom he conducted research on the "Synthesis of symmetrically substituted 1,4-bis[(aminoalkyl)amino]-5,8-dimethylantracene-



9,10-diones” (published in this journal). Upon graduating from Goucher, he transitioned to the University of Pennsylvania for his doctoral studies in the laboratory of Professor Madeleine M. Joullié. His thesis focused on “I. Total Synthesis and Application of Fluorophore-Labeled Didemnin and Tamandarin Analogues; II. Synthetic Approaches to Pondaplin and Analogues; III. Yohimbanones: Formation and Reaction via Novel Rearrangements.” After obtaining his Ph.D. in 2003, he joined the faculty of Washington & Jefferson College, where is currently Associate Professor and Chair of Chemistry.