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Total Synthesis of (±)-Aspidophylline A

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Supporting Information

ABSTRACT: We report the total synthesis of (±)-aspidophylline A, one of many complex furoindoline-containing alkaloids that has not been synthesized previously. Our route features a number of key transformations, including a Heck cyclization to assemble the [3.3.1]-bicyclic scaffold as well as a late-stage interrupted Fischer indolization to install the furoindoline and construct the natural product's pentacyclic framework.

For decades, indole alkaloids isolated from natural sources have captivated the attention of synthetic chemists, leading to innovations in synthetic methodology and stunning achievements in total synthesis.[1] One particularly rich source of indole alkaloids is the *Apocynaceae* family of plants, found predominantly in Southeast Asia.[2] Natural products isolated from these plants are characterized by intricate polycyclic structures and a range of biological activity.[2,3] Alkaloids **1**−**3** (Figure 1) are representatives of more than 20 molecules in this family that possess a furoindoline motif, none of which have been synthesized previously.

With the ultimate goal of preparing alkaloids **1**−**3** and other family members, we selected aspidophylline A (**1**) as our initial synthetic target. **1** was isolated by Kam and co-workers in 2007 and was found to reverse drug resistance in resistant KB cells.[3a] The intricate pentacyclic framework of **1** presents many synthetic challenges, including the tricyclic furoindoline motif, a densely substituted cyclohexyl ring containing five contiguous stereogenic centers, and a bridged [3.3.1] bicycle. In this communication, we report the first total synthesis of (±)-aspidophylline A (**1**).

Our approach to **1** was inspired in part by our laboratory's previously described approach to fused indoline ring systems.[4] Specifically, we demonstrated that reactions between aryl hydrazines **4** and latent aldehydes **5** under acidic conditions provide basic furoindoline and pyrrolidinoindoline scaffolds **8** (Figure 2). The transformation, termed the "interrupted Fischer indolization", proceeds via a charge-accelerated rearrangement/cyclization cascade (see transition structures **6** and **7**).[4a] We envisioned that such a process could be used to access the pentacyclic framework of aspidophylline A if a late-stage diastereoselective variant[5] employing phenylhydrazine (**9**) and hemiketal **10** were to be deemed feasible. The implementation of this endgame strategy would not only serve to assemble the aspidophylline A scaffold but also validate our interrupted Fischer indolization methodology in a complex setting. It was anticipated that hemiketal **10** could be prepared from bicycle **11**, the product of Heck cyclization of cyclohexylamine **12**.[6,7] Finally, **12** would

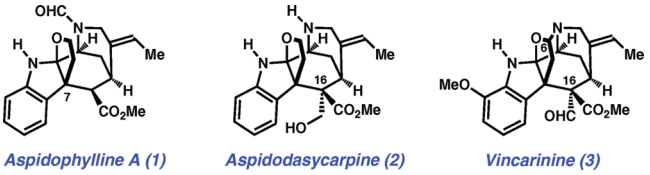

Figure 1. Furoindoline alkaloids **1**−**3** from the *Apocynaceae* plants.

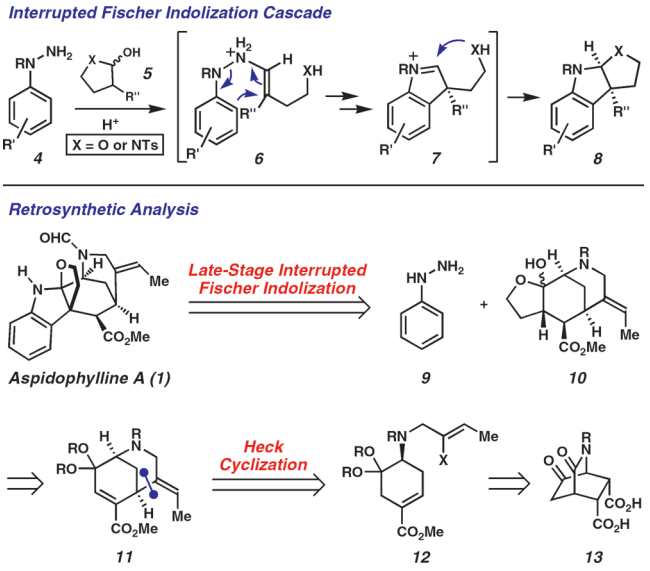

Figure 2. Interrupted Fischer indolization cascade and retrosynthetic analysis of aspidophylline A (**1**).

be derived from [2.2.2]-bicyclic lactam **13**, an intermediate believed to be accessible from readily available known compounds.[8]

Our synthesis commenced with the assembly of the [3.3.1]-bicyclic motif of aspidophylline A (Scheme 1). The thermal Diels−Alder reaction between pyridinone **14** and maleic anhydride furnished known bicycle **15**,[8] which was available in multigram quantities. Microwave irradiation of **15** with Cu_2O and bipyridyl in a quinoline/water mixture delivered alkene **17**. The transformation of **15** to **17** likely proceeds by enol ether and anhydride hydrolysis to furnish intermediate **16** followed by Cu(I)-promoted oxidative bis(decarboxylation).[9] Ketal protection and removal of the Bn protecting group provided lactam **18**, which in turn underwent *N*-tosylation and methanolysis to

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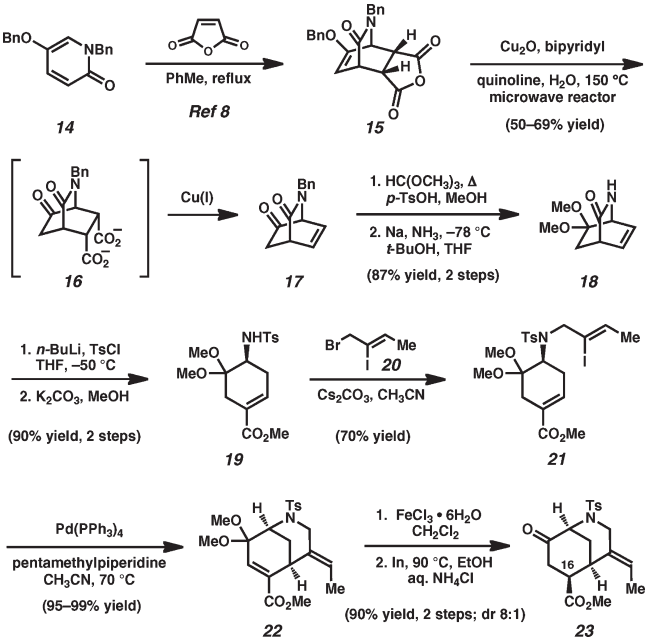
Scheme 1



provide α,β-unsaturated ester **19**. Subsequent alkylation with allylic bromide **20**[10] provided vinyl iodide **21**, the necessary substrate for Heck cyclization. Upon treatment of substrate **21** with Pd(0) under Vanderwal's conditions,[7c] bicycle **22** was obtained in quantitative yield. Ketal deprotection and olefin reduction furnished ketoester **23** as a mixture of C16 diastereomers (8:1 dr).

Having assembled the desired [3.3.1] bicycle, we turned our attention to introducing a C7 substituent en route to the desired interrupted Fischer indolization substrate. Although the lithium enolate of **23** was found to be unreactive toward various electrophiles, enolate alkylation proceeded smoothly with allyl iodide at −50 °C. The resulting product **24** was isolated as a single diastereomer and served as a versatile intermediate en route to the desired hemiketal **25**[11] and an alternate substrate, ketone **26**.[12] Unfortunately, the critical interrupted Fischer indolization proved challenging. In fact, both direct and stepwise variants of this key step (using substrates **25** and **26**, respectively) failed to deliver either of the desired products, pentacycle **27** or tetracycle **28** (Figure 3).[13,14]

Hypothesizing that the [3,3]-sigmatropic rearrangement of substrate **26** was sluggish,[14,15] we sought to prepare a more rigid substrate for use in the key step. The targeted substrate, lactone **31**, was prepared following the sequence shown in Scheme 2. Diastereoselective reduction of allyl ketone **24** provided alcohol **29**,[16] which underwent oxidative cleavage[17] and reduction to furnish diol **30**. Acid-promoted lactonization followed by Dess−Martin oxidation delivered ketoester **31**. Much to our delight, ketoester **31** proved to be an excellent substrate for Fischer indolization. Reaction with phenylhydrazine in the presence of trifluoroacetic acid (TFA) in dichloroethane at 40 °C generated intermediate **33**, presumably via transition structure **32**. Removal of solvent followed by addition of K_2CO_3 in MeOH with heating led to lactone methanolysis and cyclization (see transition structure **34**), affording pentacycle **27**. This one-pot sequence led to the introduction of three rings by assembly of one C−C bond and two C−heteroatom bonds,

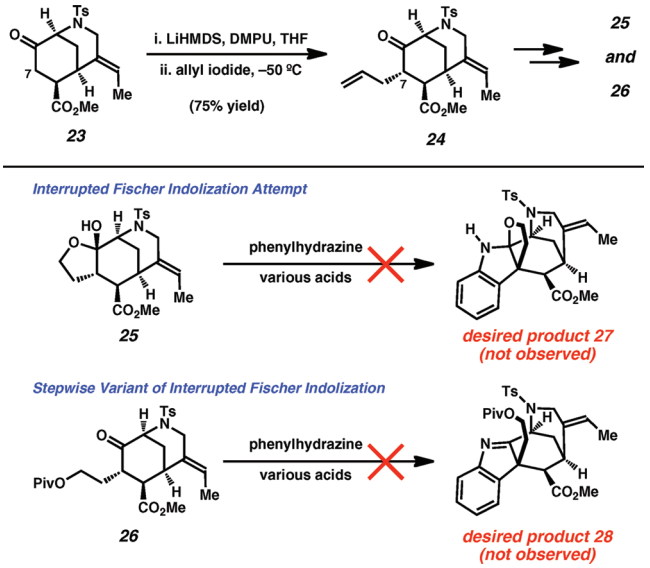
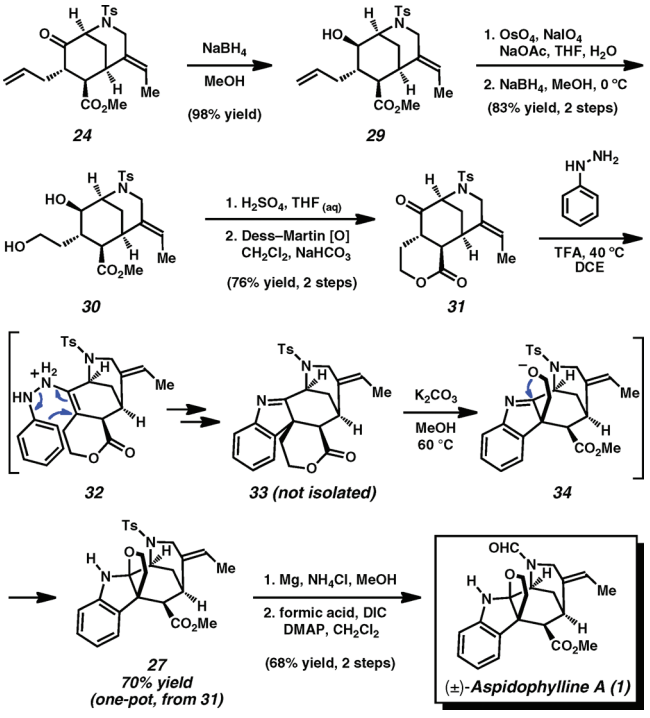


Figure 3. Interrupted Fischer indolization attempts employing substrates **25** and **26**.

Scheme 2



all with complete diastereoselectivity. Removal of the tosyl protecting group of **27** followed by formylation furnished aspidophylline A (**1**). Synthetic **1** was found to be indistinguishable from an authentic sample of the natural product by NMR, mass spectrometric, and chromatographic comparisons.[3a,18]

In summary, we have achieved the first total synthesis of (±)-aspidophylline A (**1**), one of many complex furoindoline-containing alkaloids that has not been synthesized previously. Our route to **1** proceeds in 18 steps from known Diels−Alder adduct **15** and features a number of key transformations, including (a)

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an oxidative bis(decarboxylation) to furnish [2.2.2]-bicyclic lactam **17**, (b) a Heck cyclization to assemble the natural product's [3.3.1]-bicyclic scaffold, and (c) a late-stage interrupted Fischer indolization to install the furoindoline and construct the full pentacyclic framework of **1**. Our synthesis of **1** validates the interrupted Fischer indolization approach to intricate indoline-containing natural products and sets the stage for future synthetic endeavors.

■ ASSOCIATED CONTENT

Supporting Information. Detailed experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) The conversion of **24** to **25** was achieved through a sequence involving (a) ketone protection as the cyclic ketal, (b) oxidative cleavage of the terminal olefin, (c) reduction of the corresponding aldehyde, and (d) acid-mediated ketal deprotection.

(12) The conversion of **24** to **26** was achieved through a sequence involving (a) ketone protection as the cyclic ketal, (b) oxidative cleavage of the terminal olefin, (c) reduction of the corresponding aldehyde, (d) Piv protection of the resulting alcohol, and (e) acid-mediated ketal deprotection.

(13) Under a variety of interrupted Fischer indolization conditions, substrate **25** underwent facile dehydration to the corresponding dihydrofuran.

(14) Although ketone **26** underwent condensation with phenylhydrazine under several interrupted Fischer indolization conditions, no evidence of [3,3]-sigmatropic rearrangement was detected.

(15) Ketone **23**, a substrate without the C7 side chain, readily underwent Fischer indolization upon treatment with phenylhydrazine and various acids. The factors that influence the likelihood of [3,3]-sigmatropic rearrangement in this series of compounds are currently under investigation.

(16) A more concise approach involving oxidative cleavage of the terminal olefin in **24** led to substantial decomposition.

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