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Total Synthesis of Aspeverin via an Iodine(III)-Mediated Oxidative Cyclization

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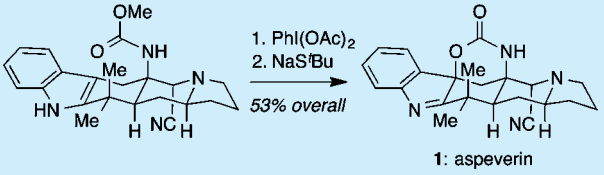
Supporting Information

ABSTRACT: The first total synthesis of aspeverin, a prenylated indole alkaloid isolated from *Aspergillus versicolor* in 2013, is described. Key steps utilized to assemble the core structure of the target include a highly diastereoselective Diels–Alder reaction, a Curtius rearrangement, and a unique strategy for installation of the geminal dimethyl group. A novel iodine(III)-initiated cyclization was then used to install the bicyclic urethane linkage distinctive to the natural product.



Prenylated indole alkaloids derived from fungi constitute a broad class of secondary metabolites containing a diverse array of molecular structures. Many of these alkaloids display important biological activities ranging from antibiotic and antihelmintic properties to potent cytotoxicity.[1] This diversity in both structure and function has rendered various prenylated indoles attractive targets in total synthesis studies.[2] Reported by Ji and co-workers and isolated from *Aspergillus versicolor*, aspeverin (**1**) has a number of structural features that prompted our attention from a synthetic perspective (Figure 1). Most striking is the unprecedented cyclic urethane linkage, joining the angular nitrogen atom in the C:D ring junction and the C-3 carbon of the indole ring. Additionally, **1** contains a rarely observed α-cyanoamine linkage.[3]

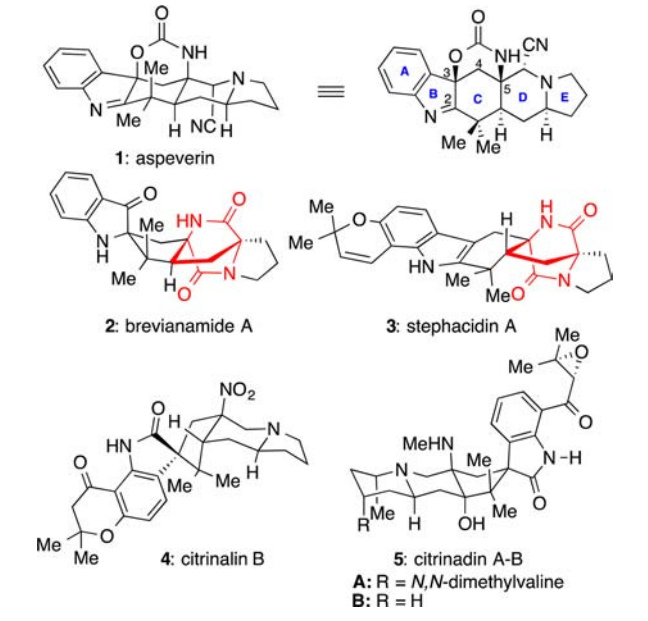


Figure 1. Representative prenylated indole alkaloids and structure of aspeverin (**1**).

A number of prenylated indole alkaloids with unusual scaffolds, including citrinalin B (**4**) and citrinadins A and B (**5**) among others, have received much synthetic attention in recent years.[4,5] It is hypothesized that these molecules are biosynthetically derived from indole alkaloids containing a bicyclo[2.2.2]-diazaoctane core structure, highlighted in red in the cases of **2** and **3**.[4b,1b] The total syntheses of citrinadins A and B (**5**) were completed in 2013 by the Martin and Wood groups, respectively.[6,7] During the course of our studies, elegant syntheses of *ent*-citrinalin B (***ent*-4**) and cyclopiamine B (not shown) and related biosynthetic studies were also completed in a collaborative venture between the Sarpong, Berlinck, Miller, Tantillo, and Andersen groups.[8] Aspeverin appears to share structural similarities with this small group of natural products and may well share similar origins.

Retrosynthetically, we envisioned the synthesis of **1** as occurring through a late-stage oxidative cyclization of **6** to install the bicyclic urethane linkage. In this fashion, the normally nucleophilic indole would be serving as the electrophilic component in the cyclization event (Figure 2). Although oxidatively mediated addition of carbamates to 2,3-dialkyl-substituted indoles has not been previously explored, we hoped that suitable electrophilic activation of the indole would set the stage for cyclization of a pendant carbamate.[9] Indeed, addition of other nucleophiles to the C-3 carbon of indoles mediated by hypervalent iodine reagents as well as other oxidants are known.[10,11] Alternatively, the corresponding *N*-hydroxyindole might also serve to enable nucleophilic attack of a carbamate at the C-3 position of the indole.[11b,12] We anticipated that our proposed route could well be preferable to an alternate approach involving discrete oxidation of the indole to a 3-hydroxyindo-

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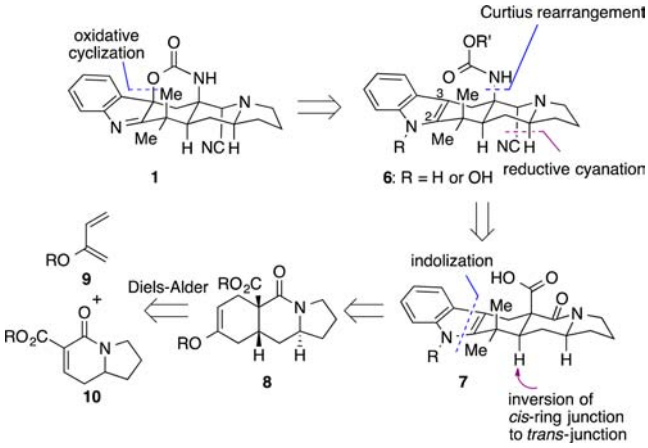


Figure 2. Retrosynthetic analysis.

lenine. Thus, in our proposed route, there is no need to control the stereochemical relationship between C3 and C5 (as shown in Figure 1). Moreover, 3-hydroxyindolenines are prone to undergo rearrangements to yield either pseudoindoxyl or spiro-oxindole rings.[13] An oxidative cyclization approach would circumvent both of these potential issues.

The α-cyanoamine functionality in **6** was traced back via a reductive cyanation of the corresponding lactam, culminating in axial attack of cyanide onto an intermediate iminium ion to control diastereoselectivity.[14] The angular nitrogen atom could, in turn, arise from a Curtius-type rearrangement, thus leading back to carboxylic acid **7**. This disconnection then prompted the possibility of using the ester precursor of the acid as a dienophilic activating group to build the CDE ring system of the molecule via a Diels–Alder reaction between **9** and **10**, with facial selectivity guided by the distal stereocenter in indolizidine **10**.[15]

This route would require manipulation of Diels–Alder adduct **8** to convert the initial *cis*-ring fusion into the required *trans*-junction found in the natural product. We anticipated two potential synthetic sequences toward this end (Figure 3). It was previously shown that enol ethers within *cis*-decalin ring systems can undergo olefin isomerization, an effect we have capitalized upon to synthesize "iso-Robinson annulation" products such as **11**.[16] We were also interested in using known indole reactivity to form the *trans*-ring junction through a benzylic oxidation of indole **12**.[17] Thus, a ketone (cf. **13**) would be used to achieve epimerization (cf. **14**). The ketone would then serve as a functional handle for installation of the geminal dimethyl group.

In the forward direction, we started with known indolizidine **15** (Scheme 1).[18] Iodination of **15** using modified conditions

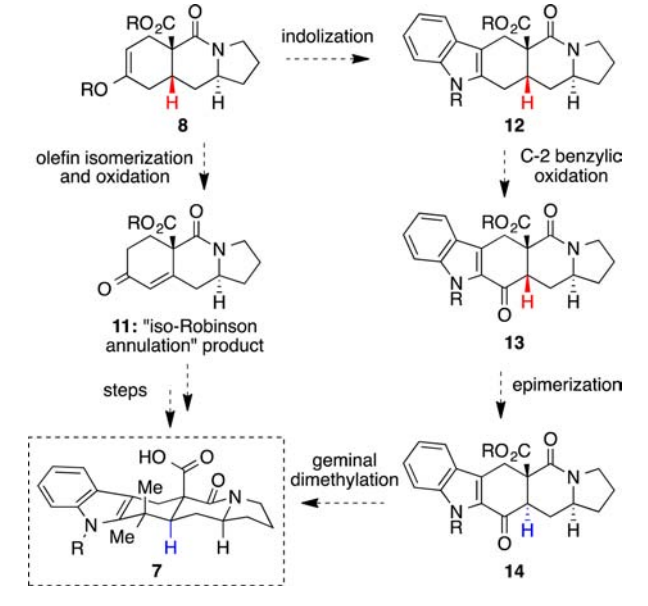
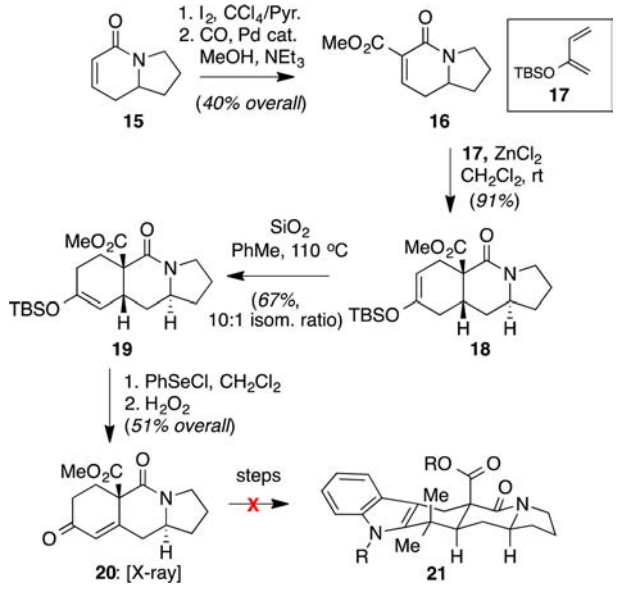


Figure 3. Alternate strategies for conversion of **8** to **7**.

Scheme 1. Diels–Alder Reaction and Olefin Isomerization–Oxidation Sequence



reported by Johnson and co-workers, followed by a Pd-catalyzed carbonylation of the resulting iodide, gave **16**.[19] As expected, **16** smoothly underwent a Diels–Alder reaction with **17** in the presence of $ZnCl_2$ at room temperature to furnish **18** as a single diastereomer in 91% yield. We then explored both strategies discussed above to access key intermediate **21**. Indeed, we found that the silyl enol ether double bond of **18** could be isomerized under previously described conditions to furnish **19**.[16a] Subsequent oxidation of **19** via formation of the corresponding phenylselenide followed by elimination of the *in situ* generated selenoxide furnished enone **20**. It is interesting to note that this intermediate contains the stereochemical configuration *opposite* to that expected to arise using a Robinson annulation strategy.[20] Unfortunately, preliminary efforts to efficiently elaborate enone **20** (and related systems) to furnish the *trans*-ring junction with the requisite geminal dimethyl group in place were not successful. Ultimately, we pursued the second strategy discussed in Figure 3.

In this approach, we hoped to install the indole ring prior to inversion of the C:D ring junction and use the inherent reactivity of indoles to functionalize at the C-2 benzylic position. Reaction of **22** with phenylhydrazine produced only the undesired Fischer indole regioisomer **23**. This regioselectivity was not unexpected, given the established regiochemical preference for Fischer indole syntheses within *cis*-fused ring systems.[21] Accordingly, a two-step approach was taken. Regioselective arylation of **18** with *o*-nitrophenyliodonium fluoride (NPIF) **24** furnished a nitroaryl ketone, which underwent reductive cyclization, as precedented, to afford benzylated *N*-hydroxyindole **25** in excellent yield (Scheme 2).[22,23]

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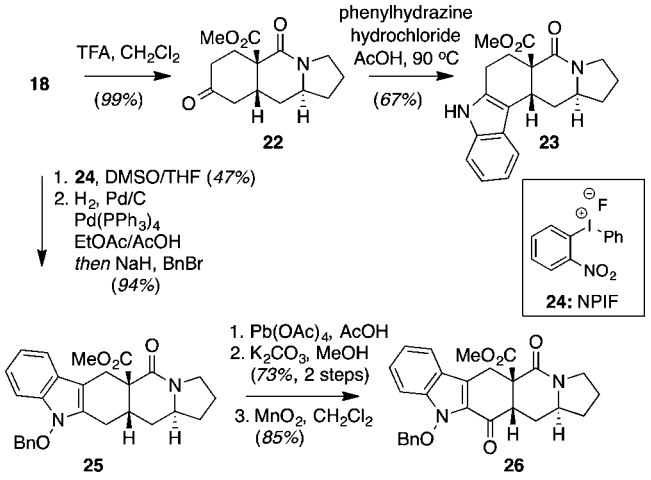
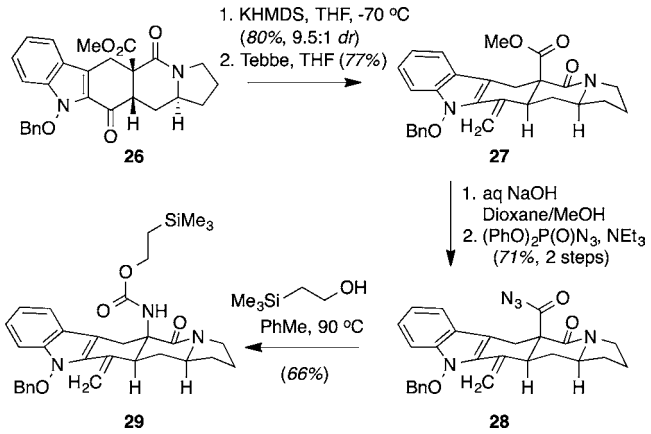
Scheme 2. Attempted Fischer Indole Synthesis and Regioselective Indolization Followed by Benzylic Oxidation



With the pentacylic ring system in place, we focused our attention toward inverting the *cis*-ring fusion. Using a stepwise oxidation approach, **25** efficiently reacted with $Pb(OAc)_4$ in AcOH to install an acetate functionality benzylic to the C-2 carbon of the indole.[17c] Subsequent hydrolysis and oxidation of the resulting alcohol using MnO_2 afforded the desired ketone **26** in good overall yield. Pleasingly, following treatment with KHMDS at low temperature, the enolate of **26** underwent kinetic protonation to yield the desired *trans*-ring junction in 9.5:1 dr (separable) and 80% isolated yield (Scheme 3). Although

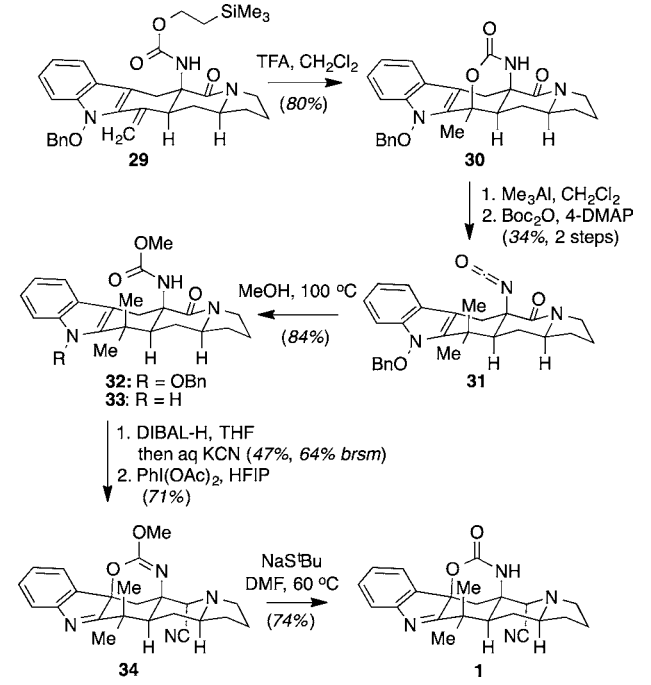
Scheme 3. Epimerization and Curtius Rearrangement



attempts at functionalizing this electron-rich ketone proved to be quite challenging, methylenation could be accomplished using the Tebbe reagent, giving **27** in 77% yield.[24] Before turning our attention to installation of the requisite geminal dimethyl group, we first subjected the carboxylic acid of **27** to Curtius rearrangement conditions.[25] Formation of acyl azide **28** followed by thermolysis in the presence of 2-(trimethylsilyl)ethanol yielded the desired carbamate **29**.

Faced with the challenge of converting the exocyclic methylene into a geminal dimethyl group, an unexpected cyclization product ultimately proved to be useful. Treatment of **29** with TFA cleanly afforded bicycle **30** in 80% yield (Scheme 4). Reaction of **30** with Me_3Al successfully reopened the cyclic carbamate to install the desired geminal dimethyl group, with formation of the corresponding primary amine. Attempts to

Scheme 4. Completion of the Synthesis of Aspeverin



reprotect the free amine with a *tert*-butoxycarbonyl group instead resulted in formation of stable isocyanate **31** in 34% yield over two steps.[26] Upon heating **31** in MeOH, **32** is rapidly formed (not isolated). Extended heating of **32**, however, led entirely to **33** (and benzaldehyde) via disproportionation of the *N*-benzyloxy indole. Partial reduction of **33** with DIBAL-H followed by workup with a concentrated KCN solution afforded the corresponding α-cyanoamine as a single diastereomer in 47% yield along with recovered starting material.[27] Gratifyingly, upon treatment with a slight excess of $PhI(OAc)_2$ in HFIP, this carbamate underwent the desired oxidative cyclization to form **34** in 71% yield as the only substantially observed product. Subsequent demethylation using sodium *tert*-butylthiolate in DMF cleanly afforded **1** in 74% yield, which was in spectroscopic agreement with reported data for the natural product.

In summary, we have completed the first total synthesis of aspeverin (**1**) in 20 steps from known indolizidine **15**. Moreover, **15** is known in enantiopure form, lending this synthetic route to an asymmetric synthesis if desired.[18,28] Key steps in our overall route include (1) a highly diastereoselective Diels–Alder reaction to build up the CDE ring system of the molecule, which can be efficiently epimerized to yield the desired *trans*-ring fusion; (2) an unconventional approach to the installation of a geminal dimethyl group via a Me_3Al-mediated ring opening of **30**; and (3) a novel oxidative cyclization of an angular carbamate promoted by $PhI(OAc)_2$ to yield the cyclic urethane linkage observed in the natural product. To the best of our knowledge, this represents the first example of an intramolecular cyclization of a carbamate functionality onto an indole mediated by a hypervalent iodine reagent, a strategy that may have further implications for substrate-controlled oxidations of indoles.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, characterization data (including spectra for new compounds), X-ray crystal structures, and CIF

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data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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