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Biomimetic Synthesis of (+)-Aspergillin PZ

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Abstract

The cytochalasans are a large family of polyketide natural products with potent bioactivities. Amongst them, the aspochalasins show particularly intricate and fascinating structures. To gain insight into their structural diversity and innate reactivity, we have developed a rapid synthesis of aspochalasin D, the central member of the family. It proceeded in 13 steps starting from divinyl carbinol and utilized a high pressure Diels-Alder reaction that features high regio- and stereoselectivity. So far, our work has culminated in a biomimetic synthesis of aspergillin PZ, an intricate pentacyclic aspochalasan.

Graphical Abstract

Delivering under pressure: The cytochalasans are a large family of polyketide natural products with fascinating structures and potent bioactivities. We have developed a rapid synthesis of aspochalasin D, the central member of this family. It proceeds in 13 steps starting from divinyl carbinol and utilized a high pressure Diels-Alder reaction. So far, our work has culminated in a biomimetic synthesis of aspergillin PZ, an intricate pentacyclic aspochalasan.

Keywords

Diels-Alder Cycloaddition; High Pressure; Total Synthesis; Biomimetic Synthesis; Cytochalasans

The cytochalasans comprise an important and ever growing chapter of natural product chemistry.^[1] Since the discovery of cytochalasins A and B in the 1960s with their eponymous function (*cytos* = cell and *chalis* = relaxation) targeting the actin cytoskeleton, ^[2] the structural diversity of this family has grown to include members that incorporate a variety of amino acids, macrocycle sizes and types, and various substitution and oxygenation

patterns. Many members offer an array of bioactivities that sustain their relevance to both chemists as synthetic targets and biologists as valuable tools.^[3]

Derived from leucine, the antibiotic aspochalasin B (**1**) and its co-isolates aspochalasins A, C, and D (**2**) were elucidated by Keller-Schierlein and Kupfer in 1979.^[4a-b] Notably, they differ from other members of the cytochalasans by the incorporation of an extra methyl substituent at C14, resulting in a trisubstituted (*E*)-configured double bond (Scheme 1a). Together with the conformational restriction enforced by the 11-membered ring, this methyl substitution plays an important role in broadening the skeletal diversity available to this cytochalasan subclass. For example, the polycyclic structures of spicochalasin A (**4**),^[4c] aspergillin PZ (**5**),^[4d] and flavichalasin C (**6**)^[4e] suggest their origin from **1**, **2**, and **3**, respectively, via the intermediacy of a carbonium ion at C14. This complexity has recently been further heightened by the discovery of the heterodimeric, trimeric, and tetrameric structures of the merocytochalasans (*e.g.*, **7–9**).^[4f-k] These compounds were suggested to arise from a combination of aspochalasin B (**1**) or D (**2**) with the pyrogallol epicoccine (**10**).

Given our longstanding interest in the chemistry of pyrogallols and our recent synthesis of epicoccine (**10**) and its complex derivatives,^[5] the tantalizing prospect of obtaining such intricate structures from **10** and **1** or **2** through an oxidative cascade prompted us to develop a robust, scalable synthesis of the aspochalasans. This program would also give us an opportunity to explore the interconnections of the tricyclic aspochalasins with the pentacyclic ones, in particular with aspergillin PZ (**5**).

Aspergillin PZ (**5**) was first isolated in 2002 from *Aspergillus awamori* following a screen for antitumor and antifungal leads, and has since been re-isolated from several species of *Aspergillus* as well as from *Trichoderma gamsii*.^[4d-e,6] Its intricate pentacyclic skeleton features one quaternary carbon and ten contiguous stereocenters, five of which reside on an oxabicyclo[3.2.1]octane subunit. To date, the synthetic challenge posed by this molecule has been answered only once. In Overman's landmark synthesis, **5** was obtained in 28 steps from methyl pyruvate. The evaluation of the synthetic material called into question the bioactivity of the natural product with respect to tumor cells.^[7] We hypothesized that aspochalasin D (**2**) is the likely biogenetic precursor to aspergillin PZ (**5**) via a "vinylogous Prins reaction" (Scheme 1b).^[8] We reasoned that **5** is formed from **2** via transannular attack of the nucleophilic trisubstituted alkene^[9] onto an activated enone, followed by interception of the resultant tertiary carbocation by one of the hydroxy groups. Herein, we describe a 13-step synthesis of aspergillin PZ utilizing such a strategy.

In considering such a solution to the aspochalasans, we were attracted to the use of 1,3,5-trienes as 4 π -components in a Diels-Alder construction of the isoindolone core, as pioneered by Stork and used to great effect by Vedejs.^[10,11] Following numerous efforts on a variety of substrates to forge the 11-membered ring by a ring-closing metathesis at 19,20,^[12] we arrived at the strategy shown in Scheme 2a utilizing a Horner-Wadsworth-Emmons (HWE) macrocyclization (*i.e.*, **13**). The HWE reaction was first explored in cytochalasan synthesis by Tamm^[13] and notably applied in a difficult intramolecular setting by Myers,^[14] albeit with appreciable epimerization of the stereocenter adjacent to the aldehyde. Oxygenated polyolefin **15** was envisioned to be prepared in a convergent manner by a Pd-catalyzed

cross-coupling of a 1,3-dienylboronate derived from tiglic aldehyde and a vinyl iodide derived from divinyl carbinol via Sharpless asymmetric epoxidation and subsequent kinetic resolution.^[15] A selective oxidation of the C18 hydroxyl of aspochalasin D (**2**) would then allow access to aspochalasin B (**1**) and its relatives.^[16]

Our synthesis commenced with the ring-opening of enantioenriched epoxy alcohol **22** with propargyl magnesium bromide to provide diol **23** in excellent yield (Scheme 3). Among the propargyl anions and derivatives of epoxide **22** explored to establish the 1,2-*anti* diol of **2**, organometallic addition by this method onto this unprotected epoxy alcohol was the only reproducible and scalable combination. Diol **23** was then subjected to a one-pot ozonolysis-reduction sequence and threefold TBS protection to provide alkyne **24** in excellent yield over two steps. Formal addition of iodomethane across this alkyne to yield vinyl iodide **25** was reliably achieved by a two-step sequence involving silylcupration, alkylative quenching of the *in situ* generated vinyl cuprate, and treatment of the resulting vinyl silane with NIS.^[17] Unfortunately, extensive efforts to achieve this transformation by the method of Negishi (ZrCp₂Cl₂/AlMe₃) proved to be highly substrate dependent and was found to work solely on free diol **23** and only in moderate yields (< 60%).^[18,19]

In preparation for the Suzuki-Miyaura cross-coupling to triene **15**, tiglic aldehyde was elaborated to 1,3-dienylboronate **17** as shown in Scheme 2b. Due to volatility and storage considerations, the lithium acetylide derived from Corey-Fuchs alkynylation was trapped with TMSCl to provide enyne **16** in good yield over 2 steps.^[20] Following TMS-deprotection, the crude solution of free enyne was subjected to Cy₂BH-accelerated hydroboration using catecholborane to furnish catechol ester **17**, which was additionally used without purification.^[21] Dienophile precursor **19** was readily prepared from lactam **18** by *C*-carbomethoxylation and selenation in excellent yield.^[22] Treatment of selenide **19** with H₂O₂ then provided **14**, which was used immediately in Diels-Alder studies.

Model studies of this [4+2] cycloaddition indicated that the combination of an ester group at C9 of the dienophile and a methyl group at C6 was deleterious (Scheme 2b). In stark contrast to Vedejs' studies which contain chloroacetyl and (trimethylsilyl)methyl at these respective positions,^[11b,23] productive cycloaddition could only be achieved under high pressure conditions.^[24] Model triene **20** proved to be moderately unstable to acid, and pressurizing a solution of **14** and **20** to 9 kbar over 2 hours provided cycloadduct **21** on gram-scale in 52% yield with an isomeric ratio of 6:1. With this result in hand, we proceeded on toward the aspochalasans. Although the union of iodide **25** with **17** indeed provided desired triene **15**, this polyene was found to be not only more acid-sensitive, but also less reactive toward cycloaddition with **14**. Simple filtration of the Suzuki-Miyaura reaction mixture through a short plug of silica gel, however, was found to suffice, and upon pressurization with **14** to 10 kbar over prolonged exposure (16.5 hours), desired isoindolone **26** could be obtained in 41% yield with an isomeric ratio of 13:1. NOESY analyses confirmed that these [4+2] cycloadditions had indeed taken place with the correct regioselectivity and in an *endo* manner with respect to the *N*-benzoyl imide.

Addition of lithio dimethyl methylphosphonate then effected *N*-debenzoylation and concomitant β-keto phosphonate formation to yield **27**. Whereas the use of HF/MeCN

effected rapid threefold TBS deprotection, selective deprotection of the primary TBS could be achieved using a large excess of $\text{Et}_3\text{N}\cdot 3\text{HF}$. Dess-Martin oxidation then provided aldehyde **13** which was immediately used without purification. Macrocyclization under Masamune-Roush conditions (LiCl , $i\text{-Pr}_2\text{NEt}$) then provided enone **28** with virtually no epimerization in 46% yield over 3 steps requiring a single chromatographic purification.^[25] The structure of **28** was secured by single-crystal X-ray analysis, showing that the C17 and C18 siloxy groups adopt *pseudo*-equatorial and *pseudo*-axial positions, respectively (see Scheme 4).^[26]

Having forged the aspochalasan framework, double desilylation of **28** with excess TBAF completed the total synthesis of aspochalasin D (**2**), albeit in moderate yield. Previously we had established that the bis-TES analog of **28** could be desilylated at 0 °C with near stoichiometric amounts of TBAF within 10 minutes. In contrast, **28** could not be desilylated at 0 °C and was slow to react at ambient temperature using a large excess of TBAF. In congruence with Keller-Schierlein and Kupfer's structural studies, treatment of **2** with MnO_2 did indeed provide aspochalasin B, but with accompanying 1,2-diol cleavage to the corresponding dialdehyde.^[4a] We subsequently discovered that the selective oxidation of the C18 hydroxyl could be achieved without C-C bond cleavage using DDQ. The spectral data of aspochalasin D (**2**) matched closely with that obtained by Hayakawa,^[4b] and the spectral data of aspochalasin B (**1**) matched closely with the limited ^1H data and incomplete list of ^{13}C resonances available for aspochalasin B (**1**) (see Supporting Information).^[4a]

With aspochalasins B and D in hand, we set out to explore the pentacyclic aspochalasans. Given the sensitivity of the substrate, we assumed that access to **5** would require a careful screen of a variety of Lewis acids and Brønsted acids. We quickly found, however, that deprotection of TBS-silyl ether **28** using HF/MeCN rather than TBAF effected a clean and fast conversion to aspergillin PZ (**5**), the spectral data of which were in excellent agreement with that of natural **5** and Overman's synthetic material. This cascade proceeded not only with exquisite stereoselectivity but also in excellent yield (Scheme 4).

Upon closer consideration of the mechanism of this transformation, we recognized that a direct vinylogous Prins-type cyclization of **2** or **28** could not account for **5**. Given the lowest energy conformation of the 11-membered macrocycle, which was elucidated by NOESY measurements and our X-ray structure of **28** (Scheme 4, Supporting Information), cyclization would be expected to yield a *trans*-fused tetracyclic or pentacyclic aspochalasan similar to flavichalasin C (**6**). As such, the selective formation of aspergillin PZ under acidic conditions may reflect a Curtin-Hammett scenario. We propose that under the influence of Brønsted acid an equilibrium is established between conformers **29** and **30**, obtained by bond rotation about C18-C19. The subsequent ring closure of rotamer **30** is faster than the cyclization of **29**, leading to *cis*-fused aspergillin PZ (**5**). Rotamer **29**, by contrast, would afford a *trans*-fused diastereomer of aspergillin PZ, compound **31**. Density functional theory calculations at the DSD-PBEP86/def2-QZVPP level show that **5** is more stable than **31** by 35 kJ/mol (see Supporting Information).

While we were preparing our manuscript for publication Deng and Tang each reported a biomimetic synthesis of asperchalasin A (**7**) and the related heterodimers.^[27] Their elegant

work proved the validity of our proposal on the biomimetic synthesis of the merocytochalasans via isobenzofuran Diels-Alder addition.^[28] Their approach also relied on an efficient total synthesis of **1** and/or **2**, which in Deng's case is strategically remarkably similar to ours. In our case, however, the intermolecular Diels-Alder reaction of triene **15** proceeded with a high degree of stereoselectivity and the triene was not obtained from the chiral pool but via catalytic asymmetric synthesis. With a robust synthetic entry to the family at hand, we will further explore the fascinating chemistry of the aspochalasans and the merocytochalasans and investigate their biological activities, in particular with respect to the actin cytoskeleton.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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(a) Selected aspochalasans, merocytochalasans, and epicoccine.

(b) Proposed biomimetic cascade to aspergillin PZ and flavichalasin C.

Scheme 1.

Selected Aspochalasans and Biosynthetic Relationships.

(a) Retrosynthetic analysis of the aspochalasans.

(b) Fragment assembly and model high-pressure Diels-Alder system.

Scheme 2.

(a) Fragment Assembly and (b) Model [4+2] Cycloaddition.

Scheme 3.

Total Synthesis of (-)-Aspochalasin D and (-)-Aspochalasin B.

Scheme 4.
Biomimetic Synthesis of (+)-Aspergillin PZ.