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Identification of an Unexpected 2-Oxonia[3,3]sigmatropic Rearrangement/Aldol Pathway in the Formation of Oxacyclic Rings. Total Synthesis of (+)-Aspergillin PZ

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Abstract

This paper reports the first unambiguous evidence that the cascade synthesis of tetrahydrofuran-containing oxacyclic molecules depicted in Scheme 12 can take place by a 2-oxonia[3,3]sigmatropic/aldol mechanism rather than by a Prins cyclization/pinacol rearrangement sequence. The 8-oxabicyclo[3.2.1]octyl aldehyde products of this reaction, **20** and **29**, were employed to complete the first total synthesis of the structurally remarkable isoindolone alkaloid (+)-aspergillin PZ (**1**). The lack of activity seen in two tumor cell lines for synthetic (+)-aspergillin PZ calls into question the suggestion that aspergillin PZ, like many aspochalasin diterpenes, might exhibit useful antitumor properties.

Keywords

total synthesis; Prins-pinacol rearrangement; 2-oxonia[3,3]sigmatropic rearrangement; mechanism; cascade reaction; natural products

1. Introduction

The isolation of aspergillin PZ (**1**, Figure 1) from a sample of the soil fungus *Aspergillus awamori* collected in Hebei province, China, was reported in 2002 by Pei and coworkers.¹ The constitution and relative configuration of aspergillin PZ was elucidated by 2D NMR studies and confirmed by single-crystal X-ray analysis. The pentacyclic structure of this isoindolone alkaloid contains ten contiguous stereocenters and an unusual 12-oxatricyclo[6.3.1.0^{2,7}]dodecane ring system (**2**). The isoindolone subunit found in aspergillin PZ is common among compounds isolated from *aspergillum* molds. Aspergillin PZ is closely related to the aspochalasin series of natural products, particularly aspochalasin

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Dedicated with admiration and friendship to Professor Gilbert Stork in honor of his 90th birthday.

Supplementary data.

Spectroscopic and analytical data as well as experimental procedures associated with this article can be found, in the online version, at doi: XXXXXXXX.

D (**3**),² and members of the cytochalasin family such as the actin polymerization inhibitor cytochalasin D (**4**).³ These previously reported natural products share the same carbon framework, but lack the structurally unique 12-oxatricyclo[6.3.1.0^{2,7}]dodecane core of aspergillin PZ.

Several members of the aspochalasin family have been shown to promote moderate deformation of *Pyricularia oryzae* conidia and have additionally shown cytotoxicity in lymphoma (MH60) and leukemia (ML60) cancer cell lines.⁴ In a phenotype assay,⁵ aspergillin PZ (**1**) was reported to induce morphological deformation of the conidia of *P. oryzae* at 0.089 μ M.¹ Natural analogues **5** and **6** of aspergillin PZ, whose three-dimensional structures have not been disclosed, are reported to exhibit cytotoxicity against the HL-60 cancer cell line: **5** = 29 μ g/mL, **6** = 22 μ g/mL.⁶ The correlation between the conidia deformation phenotype and cytotoxicity, as well as the cytotoxicity of related analogues, provided the implication that aspergillin PZ might display anticancer activity, although no such data has been reported to date.^{4,7}

We were attracted to develop a synthesis of aspergillin PZ on the basis of its novel structure, particularly the challenge in constructing its oxatricyclic ring system. In addition, synthetic access to this rare natural product would allow a preliminary examination of its therapeutic potential. We envisaged that the 12-oxatricyclo[6.3.1.0^{2,7}]dodecane moiety of aspergillin PZ might be assembled concisely by a Prins-pinacol cascade, a transformation that we have employed to construct various oxapolycyclic ring systems.^{8,9} In our earliest studies in this area, we utilized a Prins-pinacol cascade to assemble several 12-oxatricyclo[6.3.1.0^{2,7}]dodecane structures.¹⁰ However, further elaboration of these products toward aspergillin PZ appeared unattractive, leading us to redesign our synthetic strategy. At the heart of the revised synthetic strategy depicted in Scheme 1 are two multi-bond forming transformations: a Prins-pinacol cascade to forge the 8-oxabicyclo[3.2.1]octane ring system (**9**→**8**)¹¹ and an intramolecular Diels–Alder reaction to form the isoindolone subunit.¹²

Identification of (Z)-alkenyltetrahydropyranyl glycoside **9** as a potential precursor of 8-oxabicyclo[3.2.1]octyl aldehyde **8** was influenced by our previous demonstrations of the crucial role that an allylic stereocenter can play in organizing the first step of a Prins-pinacol cascade (Scheme 2).^{10b,13} As a 1,2-disubstituted double bond is a relatively weak nucleophile, we anticipated that the Prins cyclization step (**A**→**B**) would have a late transition state that resembles the hydropyranyl cation intermediate.^{12,14} This carbenium ion would be stabilized if the allylic hydrogen, rather than the C–O σ -bond, were aligned for hyperconjugative interaction with the vacant p-orbital. As a result, the oxocarbenium generated from **9** was expected to cyclize preferentially in a chair geometry to generate hydropyranyl cation **B**, which upon fast pinacol rearrangement would form oxabicyclic product **8**. In contrast, allylic epimer **10** would be expected to undergo Prins cyclization in a boat geometry (**C**→**D**) to generate ultimately the undesired oxabicyclic product **11**.^{10b,15}

The use of a late-stage intramolecular Diels–Alder cycloaddition in the synthesis of cytochalasin-type alkaloids was pioneered by Stork¹⁶ and developed extensively by the Thomas group¹² rendering its use in the total synthesis of aspergillin PZ appealing. As in cases studied earlier, we anticipated that intramolecular cycloaddition of a late-stage triene intermediate **7** (see Scheme 1) would take place by an *endo* transition state to generate the aspergillin PZ ring system.¹⁷

Herein we report that the cascade oxacyclic synthesis that typically proceeds by a Prins cyclization/pinacol rearrangement pathway can in certain circumstances proceed competitively through a 2-oxonia[3,3]sigmatropic rearrangement/aldol cyclization pathway.

We also describe the first total synthesis of (+)-aspergillin PZ (**1**) and preliminary evaluation of its antitumor activity.

2. Results and Discussion

2.1 A Prins-pinacol approach to the 8-oxabicyclo[3.2.1]octane fragment

Our initial studies were carried out with racemic substrates and began by elaboration of dihydropyran ester *rac*-**12**¹⁸ to aldehyde *rac*-**14** in three straightforward steps. Addition of the lithium acetylide generated from alkyne **15**¹⁹ to racemic aldehyde **14** provided propargylic alcohols *rac*-**16** and *rac*-**17** in a 1.3:1 ratio and 95% yield.²⁰ Separation of these products on silica gel, followed by their independent silylation and Lindlar reduction provided epimeric cyclization precursors *rac*-**18** and *rac*-**19** in good yield.

To evaluate experimentally our expectation that allylic precursors *rac*-**18** and *rac*-**19** would generate different Prins-pinacol products, these precursors were separately exposed to 0.5 equiv of SnCl₄ at 0 °C (Scheme 4). Indeed these epimers did lead with high selectivity to different oxabicyclo[3.2.1]octyl aldehyde products, *rac*-**20** and *rac*-**21**; however to our surprise, in each case ¹H NMR analysis showed that the siloxyethyl and formyl side chains of these products were trans, not cis as we had expected. To confirm that the siloxyethyl side chain was trans to the oxygen bridge in the product derived from precursor *rac*-**18**, Prins-pinacol product *rac*-**20** was transformed in three steps to crystalline *p*-bromobenzoate *rac*-**22** whose relative configuration was confirmed by single-crystal X-ray analysis.²¹

In an attempt to discern the origin of the unexpected trans aldehyde product, progress of the Prinspinacol reaction of *rac*-**18** was monitored by ¹H NMR. From this experiment, it appeared that two aldehyde products were formed initially, which slowly converged to a single product as the reaction progressed. This finding suggested that *rac*-**20** was the result of epimerization that occurred after the loss of the *tert*butyldimethylsilyl group. Screening a number of Lewis and Brønsted acids (BF₃·OEt₂, TiCl₄, SnBr₄, TMSOTf, TfOH) for the Prins-pinacol reaction of *rac*-**18**, as well as various quench conditions (Et₃N, *N,N*-dimethylaniline, DMSO), did not lead to the isolation of any of the formyl epimer of *rac*-**20**.

We reasoned that generation of the initial oxocarbenium ion from a precursor having a better leaving group would allow the cascade reaction to be carried out at a lower temperature, hopefully facilitating isolation of the desired cis aldehyde epimer. Acetate was chosen as the leaving group to facilitate ionization and in the hope that its bidentate character might sequester the Lewis acid and minimize epimerization. Glycosyl acetate *rac*-**28** was synthesized from dihydropyran ester *rac*-**12** as summarized in Scheme 5. Epoxidation of dihydropyran *rac*-**12** with dimethyldioxirane (DMDO) at –78 °C, followed by opening of the epoxide with ethanethiol and catalytic trifluoroacetic anhydride (TFAA) provided *O,S*-acetal *rac*-**23** in 69% yield. This intermediate was elaborated to propargylic alcohol *rac*-**25** by silyl protection, reduction to the aldehyde, and addition of the lithium salt of alkyne **15**. The initially produced 1.3:1 mixture of propargylic alcohol epimers could be increased to 10:1 by Swern oxidation²² of the epimer mixture, followed by reduction of the ketone product with diisobutylaluminum hydride (DIBALH) in hexanes at –78 °C.²³ By this sequence, *rac*-**25** (10:1 dr) was obtained in 31% overall yield from *rac*-**12**. Semi-hydrogenation of *rac*-**25** (Pd/CaCO₃, H₂, quinoline) and silyl protection of the alcohol provided *rac*-**27** in 84% yield over 2 steps. The thio acetal was then selectively hydrolyzed by reaction with MeI and Ag₂CO₃ in MeCN/H₂O at 80 °C, and the resulting hemiacetal acetylated to provide acetate *rac*-**28**.²⁴

As we had hoped, the transformation of glycosyl acetate *rac*-**28** to an 8-oxabicyclo[3.2.1]octane product could be accomplished at low temperature. For example,

exposure of *rac*-**28** to 0.5 equiv of SnCl₄ in CH₂Cl₂ at –78 °C, followed by quenching with Et₃N at –78 °C, provided a 1.3:1 inseparable mixture of epimeric aldehyde products *rac*-**20** and *rac*-**29** in 42% yield (Scheme 6). In situ monitoring of this reaction by ¹H NMR at –78 °C indicated that these two aldehydes were formed initially in a ~1:1 ratio. Screening a variety of Lewis acids (BF₃·OEt₂, TMSOTf, SnCl₄, Sn(OTf)₄, Sn(OTf)₂, TiCl₄, AlBr₃), Brønsted acids (TfOH, HN(Tf)₂, TFA), solvents (CH₂Cl₂, pentane, EtCN), and lower reaction temperatures (–95 °C) were unsuccessful in improving either the diastereomeric ratio or the yield of the Prins-pinacol products.²⁵

2.2 Identification of a competitive 2-oxonia-[3,3]-sigmatropic/aldol pathway

The apparent invariance of the ratio of 8-oxabicyclo[3.2.1]octyl aldehydes *rac*-**20** and *rac*-**29** produced at low temperature from glycosyl acetate precursor *rac*-**28** suggested the possibility that both were produced in kinetically controlled processes. Although our earliest investigations of the Prins-pinacol reaction provided compelling evidence that an alternative 2-oxonia[3,3]sigmatropic rearrangement/aldol mechanism was not involved in the transformations studied at the time,²⁶ it appeared possible that such a process might be operative in the present case.²⁷ As outlined in Scheme 7, trans aldehyde *rac*-**20** would be a potential direct product of a 2-oxonia[3,3]sigmatropic rearrangement/aldol cyclization mechanism as long as intramolecular aldol cyclization of the initially produced sigmatropic isomer **F** is not more rapid than single-bond rotation of this intermediate to generate intermediate **G**.^{28,29}

To probe the possibility of the 2-oxonia[3,3]sigmatropic pathway, *d*₂-*rac*-**28** was prepared by partial reduction of *rac*-**25** with D₂, and subsequently elaborated to *d*₂-*rac*-**28** to evaluate if H/D exchange occurred over the course of the reaction. Subjecting *d*₂-*rac*-**28** to 0.5 equiv of SnCl₄ in CH₂Cl₂ at –78 °C provided *rac*-**20**/*rac*-**29** with no observed loss of deuterium by mass spectrometric analysis (Scheme 8). Conversely, exposure of *rac*-**28** to 2.1 equiv of SnCl₄ in the presence of 1.5 equiv of *d*₄-CD₃OD produced at –78 °C the *rac*-**20**/*rac*-**29** mixture without incorporation of deuterium. The absence of H/D exchange in these experiments strongly suggests that under the reaction conditions at –78 °C the trans aldehyde product *rac*-**20** is directly produced in the cascade sequence and is not formed by epimerization of its aldehyde epimer.

More insight into the origin of trans 8-oxabicyclo[3.2.1]octyl aldehyde *rac*-**20** was obtained from studies of cis epimer *rac*-**29**. Although this isomer could not be obtained in pure form from the mixture of aldehyde epimers generated from glycosyl acetate *rac*-**28**, it could be prepared from trans epimer *rac*-**20** by a multi-step sequence (*vide infra*). Exposure of cis aldehyde *rac*-**29** to DBU at room temperature for 12 h provided exclusively trans epimer *rac*-**20** (Table 1, entry 1). Subjecting the cis aldehyde *rac*-**29** to SnCl₄ or HN(Tf)₂ at –78 °C in CH₂Cl₂ (entries 3 and 5) did not result in observable epimerization. Likewise, epimerization did not occur under the conditions used to quench the reaction of acetate *rac*-**28** (entry 2). However, when cis aldehyde *rac*-**29** was subjected to HN(Tf)₂ or SnCl₄ at 0 °C, epimerization was quickly observed (entries 4 and 6). Thus we conclude that the substantial formation of the trans aldehyde product, *rac*-**20**, from glycosyl acetate precursor at –78 °C is the result of a 2-oxonia[3,3]sigmatropic/aldol pathway and not from epimerization of its cis stereoisomer *rac*-**29**. Upon warming the reaction mixture to 0 °C, *rac*-**29** epimerizes such that trans aldehyde *rac*-**20** becomes the exclusive product. Whether the substantial amount of the cis epimer *rac*-**29** produced at –78 °C is the result of competitive reaction by Prins cyclization/pinacol rearrangement and 2-oxonia[3,3]sigmatropic rearrangement/aldol pathways, or exclusively the result of the latter pathway is unknown.

2.3 Total Synthesis of (+)-Aspergillin PZ

The intervention of a 2-oxonia[3,3]sigmatropic/aldol pathway in the critical assembly of the 8-oxabicyclo[3.2.1]octane unit of aspergillin PZ showed that a concise synthesis of this structurally unusual isoindolone alkaloid could not be realized by the synthetic strategy outlined in Scheme 1. However, to establish whether developing a more concise approach was warranted, we decided to use the chemistry established in this investigation to prepare (+)-aspergillin PZ in order to confirm or raise in question the suggestion of its antitumor properties. This synthesis began with enantioenriched dihydropyran **12** (92% ee), which was converted in 3 steps to aldehyde **14** (Scheme 9). By the use of Carreira's method,³⁰ alkyne **15**¹⁹ was added with high diastereoselectivity to provide enantioenriched propargylic alcohol **16** in 92% yield. Protection of the alcohol, followed by Lindlar reduction gave cyclization precursor **18** in 80% yield. Exposure of alkenyl glycoside **18** to 0.5 equiv of SnCl₄ at 0 °C delivered 8-oxabicyclo[3.2.1]octyl aldehyde **20** in 49% yield.

After several potentially short sequences for inverting the C6 stereocenter of aldehyde **20** proved unworkable, a multi-step sequence was developed (Scheme 10). Cleavage of the silyl group of **20**, followed by Pinnick oxidation³¹ and lactonization provided trans lactone **31**, which upon reaction with DBU in refluxing benzene was converted in high yield to cis lactone **32**. Reduction of this intermediate with LiAlH₄, followed by selective silylation with TBDPSCI/DMAP and oxidation of the resulting alcohol **33** delivered aldehyde **29** in 27% overall yield from its trans epimer **20**.

The elaboration of aldehyde **29** to (+)-aspergillin PZ is summarized in Scheme 11. After failing to elaborate the diene side chain by a Wittig–Horner approach,³² intermediate **36** was obtained in 41% yield by sequential Takai olefination^{33,34} and Suzuki cross-coupling of vinyl iodide **34** with boronic acid **35**.³⁵ After elaborating diene **36** to dienyl aldehyde **37** in a conventional fashion, the lithium enolate of lactam **38** was added to provide aldol adduct **39** in 77% yield for the 3 steps. Oxidation of this intermediate with either Dess–Martin periodinane³⁶ or Swern conditions²¹ provided the corresponding β-keto lactam in disappointing low to moderate, and variable yields (36–57%).³⁷ Selenation of keto lactam **40** gave selenide **41**, which upon oxidation with *m*-chloroperbenzoic acid (*m*-CPBA) and heating at 100 °C provided a single tetracyclic product **42** in 56% overall yield.¹¹ Removal of the benzoyl and silyl groups from **42** unveiled synthetic (+)-aspergillin PZ (**1**), [α]_D +115, whose ¹H and ¹³C NMR data matched closely those reported for the natural product.^{1,38}

With access to a synthetic sample of (+)-aspergillin PZ (**1**), its activity against two highly invasive tumor lines (A2058 melanoma and DU145 prostate cancer) was determined. No useful activity (IC₅₀ >10 μM) was found in either cell line.³⁹

3 Conclusion

The present study provides the first definitive evidence that the cascade transformation depicted in Scheme 12 can take place by a 2-oxonia[3,3]sigmatropic/aldol pathway as well as by the more common Prins-pinacol mechanism. As the stereochemical outcome of these two sequences can differ in some situations, as in the case reported here, gaining additional insight into structural features that favor a specific mechanistic pathway is important.²⁸ In the transformations reported here, the fact that the product of [3,3]-sigmatropic rearrangement **F** (Scheme 7) is a highly stabilized, disubstituted α-alkoxy carbenium ion, whereas the product **E** (Scheme 7) of Prins cyclization is a secondary carbenium ion favors the 2-oxonia-[3,3]-sigmatropic/aldol pathway.

Because the stereoselective construction of 8-oxabicyclo[3.2.1]octyl aldehyde **29** was undermined by the intervention of 2-oxonia[3,3]sigmatropic/aldol pathway, the first

synthesis of (+)-aspergillin PZ (**1**) reported here does not represent a satisfactory solution to the synthetic challenges presented by this novel structure. Nonetheless, this synthesis did allow a preliminary evaluation of the biological properties of (+)-aspergillin PZ to be carried out. The lack of activity seen in two tumor cell lines for synthetic (+)-aspergillin PZ, calls into question the suggestion^{1,7} that aspergillin PZ, like many aspochalasin diterpenes, might exhibit useful antitumor properties.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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32. A Wittig–Horner olefination was utilized by Thomas and co-workers for the synthesis of related cytochalasins see refs. 12b,d,e, but was not suitable for base-sensitive, epimerizable substrates such as **29**.
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34. The methyl ketone is the major byproduct produced from an α -elimination and carbene insertion, see: Hodgson DM, Comina PJ. Synlett. 1994:663–664.
35. Gamsey S, DeLaTorre K, Singaram B. Tetrahedron: Asymmetry. 2005; 16:711–715.
36. Dess DB, Martin JC. J. Org. Chem. 1983; 48:4155–4156.
37. Alternative methods to couple lactam **38** with the 8-oxobicyclo[3.2.1]octane fragment by addition of the lithium enolate of **38** to an acyl imidazole intermediate, or by a Baylis–Hillman reaction, were found to be low yielding, see ref 15.
38. (a) Unfortunately, a sample of natural (+)-aspergillin PZ was not available for direct comparison. (b) The optical rotation of natural aspergillin PZ was not reported.¹
39. Data kindly provided by Dr. Sangkil Nam, Beckman Research Institute, City of Hope, Duarte, California

Figure 1.
Aspergillin PZ, its 12-Oxatricyclo[6.3.1.0^{2,7}]dodecane Core, and Related Natural Products.

Scheme 1.
Retrosynthetic Analysis of Aspergillin PZ.

Scheme 2.
Stereochemical Analysis of the Prins-pinacol Reaction.

Scheme 3.
 Synthesis of the Prins-Pinacol Precursors *rac-18* and *rac-19*.

Scheme 4.
Unexpected Formation of the trans Aldehydes *rac*-**20** and *rac*-**21**.

Scheme 5.
Synthesis of Glycosyl Acetate *rac-28*.

Scheme 6. Initiation of the Prins-Pinacol Cascade at Low Temperature From Glycosyl Acetate *rac-28*.

Scheme 7.
Potential Prins-Pinacol and 2-Oxonial[3,3]sigmatropic/Aldol Pathways.

Scheme 8.
Deuterium Labeling Experiments.

Scheme 9.
Synthesis of Enantioenriched 8-oxabicyclooctyl aldehyde **20**.

Scheme 10.
Preparation of cis Aldehyde **29**.

Scheme 11.
Completion of the Total Synthesis of (+)-Aspergillin PZ.

Scheme 12.

Prins-pinacol and [3,3]-Sigmatropic Rearrangement/Aldol Pathways.

Table 1 Stability and epimerization of cis aldehyde epimer *rac*-**29** under various reaction conditions.

Entry	Conditions	cis:trans ^a
1	DBU, PhH, rt, 12 h	100% trans
2	5 equiv Et ₃ N, CD ₂ Cl ₂ -78 °C → rt, 12 h	100% cis
3	0.5 equiv SnCl ₄ , CH ₂ Cl ₂ , -78 °C, 30 min	100% cis
4	0.5 equiv SnCl ₄ , CH ₂ Cl ₂ , 0 °C, 15 min	1:1.9
5	15 mol% HN(Tf) ₂ , CH ₂ Cl ₂ , -78 → -40 °C, 30 min	100% cis
6	15 mol% HN(Tf) ₃ , CH ₂ Cl ₂ , 0 °C, 30 min	1:4

^a Ratio of *rac*-**29**:*rac*-**20** determined by integration of ¹H NMR spectra