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

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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.

1. Introduction

The isolation of aspergillin PZ (**1**, Fig. 1) from a sample of the soil fungus *Aspergillus awamori* collected in Heibei province, China, was reported in 2002 by Pei and co-workers.[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 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 μM.[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 μg/mL, **6**=22 μg/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 have 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

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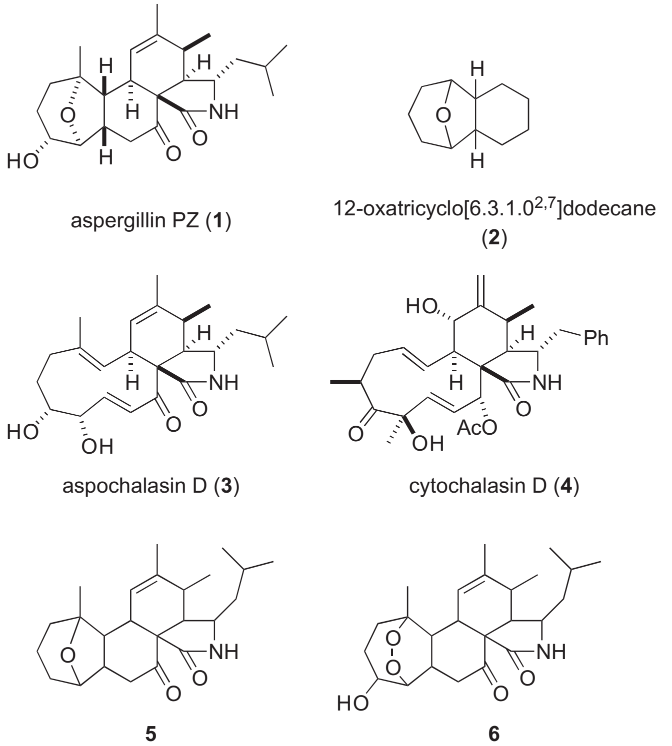


aspergillin PZ (**1**)

12-oxatricyclo[6.3.1.0^{2,7}]dodecane (**2**)

aspochalasin D (**3**)

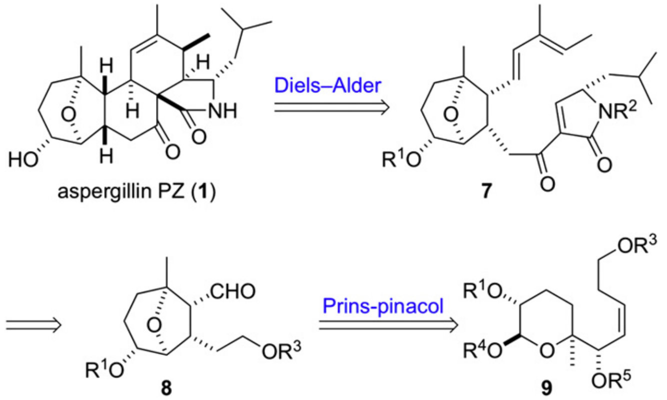
cytochalasin D (**4**)

5

6

Fig. 1. Aspergillin PZ, its 12-oxatricyclo[6.3.1.0^{2,7}]dodecane core, and related natural products.

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]



aspergillin PZ (**1**)

7

8

9

Scheme 1. Retrosynthetic analysis of aspergillin PZ.

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 Stork[16] and developed extensively by the Thomas group[12] 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

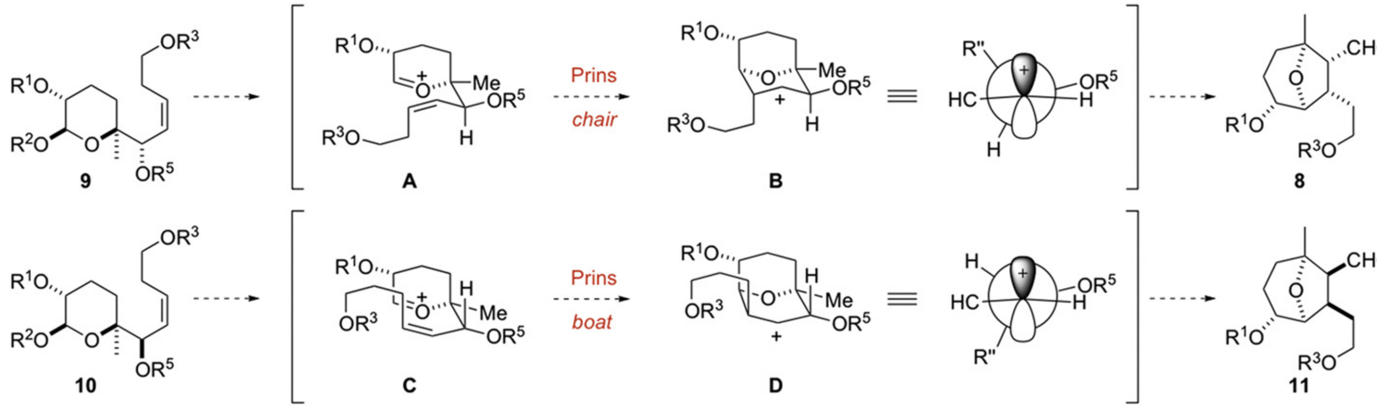
2.1. A Prins-pinacol approach to the 8-oxabicyclo[3.2.1]octane fragment

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 (Scheme 3).

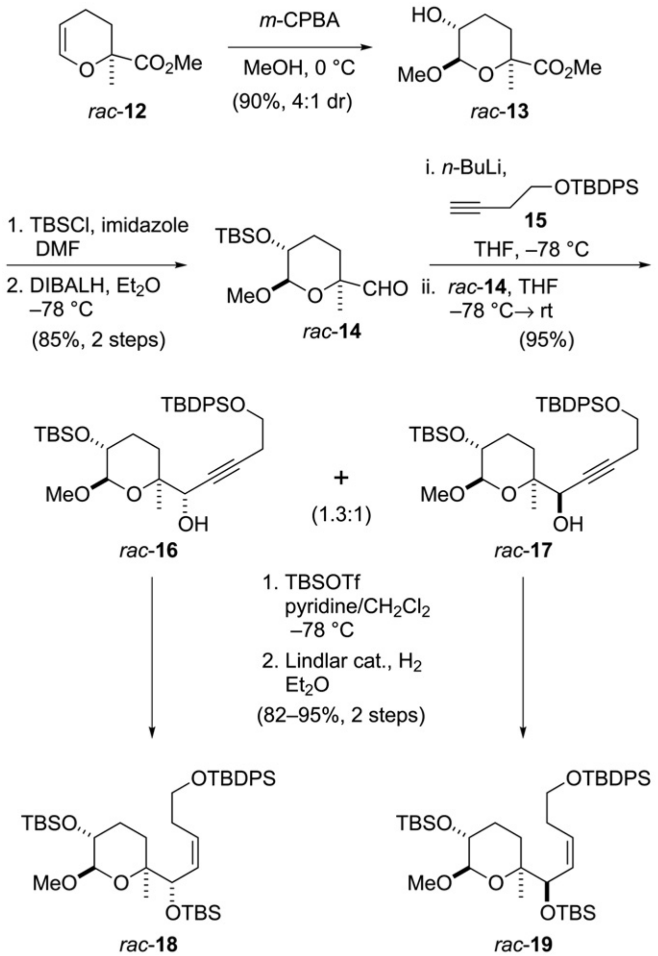
To evaluate experimentally our expectation that allylic precursors *rac*-**18** and *rac*-**19** would generate different Prins-pinacol products, these precursors were separately exposed to 0.5 equiv of $SnCl_4$ at 0 °C (Scheme 4). Indeed these epimers did lead with high selectivity to different oxabicyclo[3.2.1]octyl aldehyde products, *rac*-**20** and *rac*-**21**; however to our surprise, in each case ^{1}H 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 Prins-pinacol reaction of *rac*-**18** was monitored by ^{1}H 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 ($BF_3 \cdot OEt_2$, $TiCl_4$, $SnBr_4$, TMSOTf, TfOH) for the Prins-pinacol reaction of *rac*-**18**, as well as various quench conditions (Et_3N, *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

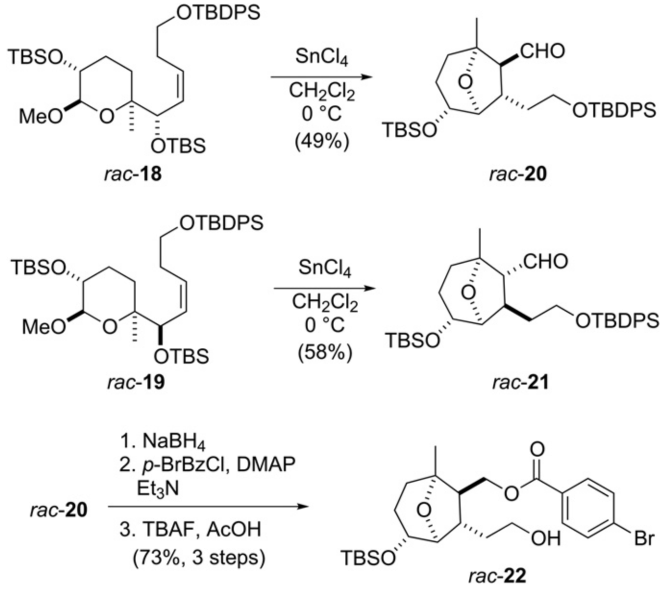


Scheme 2. Stereochemical analysis of the Prins-pinacol reaction.



Scheme 3. Synthesis of the Prins-pinacol precursors *rac*-**18** and *rac*-**19**.

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 oxidation[22] 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/$CaCO_3$, H_2, 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 Ag_2CO_3 in MeCN/H_2O at 80 °C, and the resulting hemiacetal acetylated to provide acetate *rac*-**28**.[24]

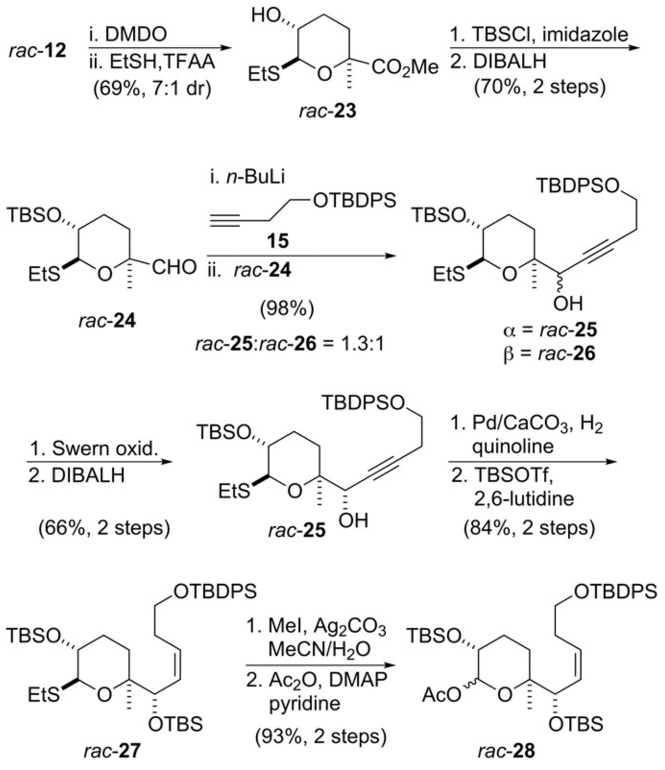


Scheme 4. Unexpected formation of the *trans* aldehydes *rac*-**20** and *rac*-**21**.

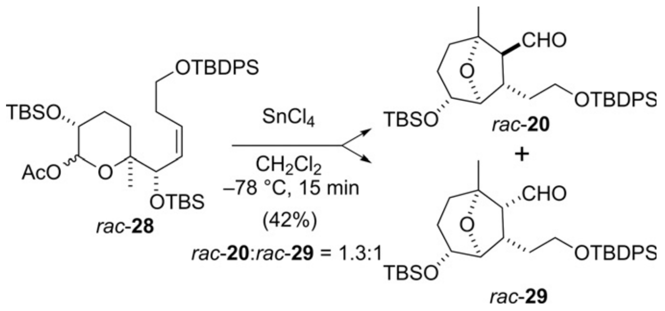
As we had hoped, the transformation of glycosyl acetate *rac*-**28** to an 8-oxabicyclo[3.2.1]octane product could be accomplished at low temperature. For example, exposure of *rac*-**28** to 0.5 equiv of $SnCl_4$ in CH_2Cl_2 at −78 °C, followed by quenching with Et_3N at −78 °C, provided a 1.3:1 inseparable mixture of epimeric aldehyde products *rac*-**20** and *rac*-**29** in 42% yield (Scheme 6). In situ monitoring of this reaction by ^{1}H NMR at −78 °C indicated that these two aldehydes were formed initially in a ∼1:1 ratio. Screening a variety of Lewis acids ($BF_3\cdot OEt_2$, TMSOTf, $SnCl_4$, $Sn(OTf)_4$, $Sn(OTf)_2$, $TiCl_4$, $AlBr_3$), Brønsted acids (TfOH, $HN(Tf)_2$, TFA), solvents (CH_2Cl_2, 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



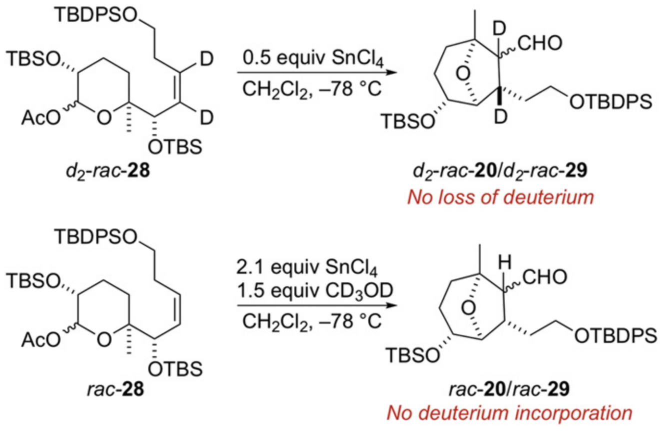
Scheme 5. Synthesis of glycosyl acetate *rac*-**28**.



Scheme 6. Initiation of the Prins-pinacol cascade at low temperature from glycosyl acetate *rac*-**28**.

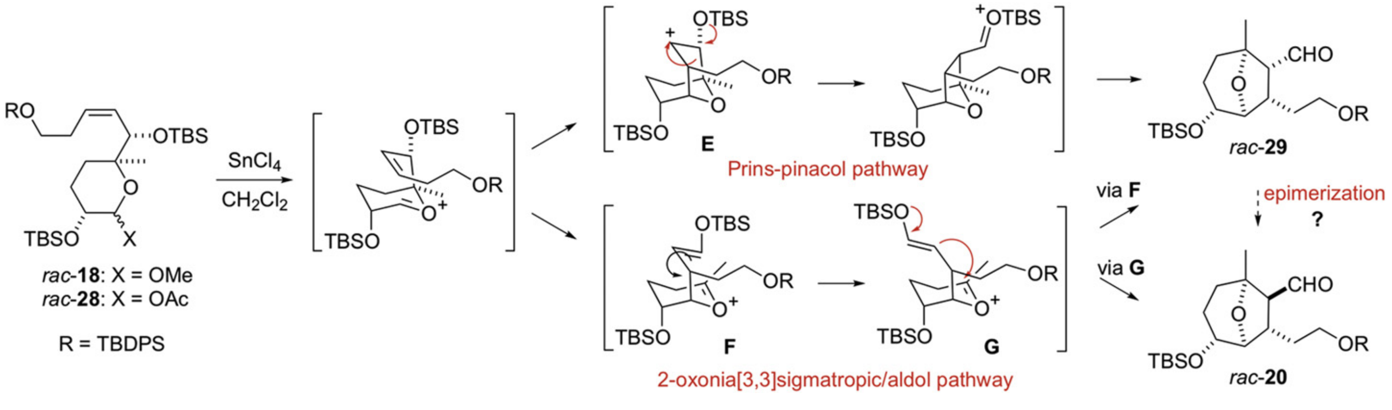
a process might be operative in the present case.[27] As outlined in Scheme 7, *trans* aldehyde *rac*-**20** would be a potential direct product of a 2-oxonia[3,3]sigmatropic rearrangement/aldol cyclization mechanism as long as intramolecular aldol cyclization of the initially produced sigmatropic isomer **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 D_2, 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 $SnCl_4$ in CH_2Cl_2 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 $SnCl_4$ in the presence of 1.5 equiv of d_4-CD_3OD 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.



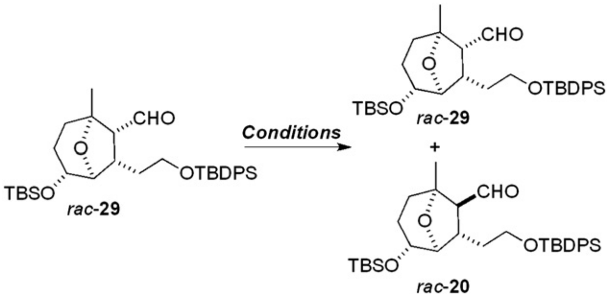
Scheme 8. Deuterium labeling experiments.

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 $SnCl_4$ or $HN(Tf)_2$ at −78 °C in CH_2Cl_2 (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 $SnCl_4$ at 0 °C, epimerization was quickly observed



Scheme 7. Potential Prins-pinacol and 2-oxonia[3,3]sigmatropic/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_3N, CD_2Cl_2, −78 °C→rt, 12 h	100% cis
3	0.5 equiv $SnCl_4$, CH_2Cl_2, −78 °C, 30 min	100% cis
4	0.5 equiv $SnCl_4$, CH_2Cl_2, 0 °C, 15 min	1:1.9
5	15 mol % $HN(Tf)_2$, CH_2Cl_2, −78→−40 °C, 30 min	100% cis
6	15 mol % $HN(Tf)_2$, CH_2Cl_2, 0 °C, 30 min	1:4

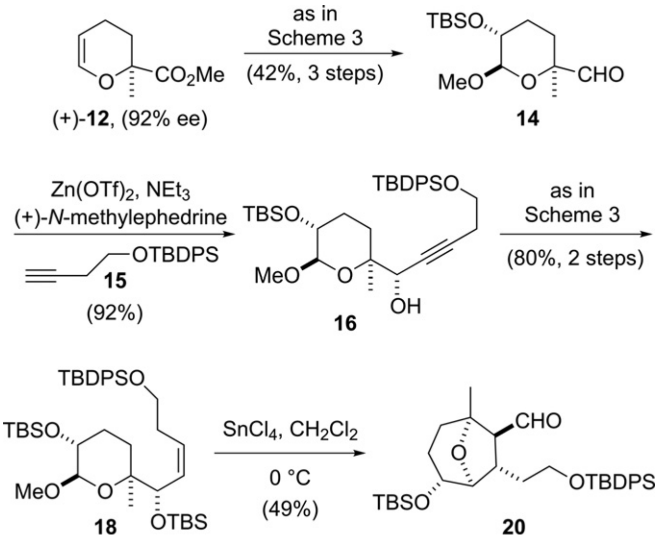
[a] Ratio of *rac*-**29**:*rac*-**20** determined by integration of ^{1}H NMR spectra.

(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.

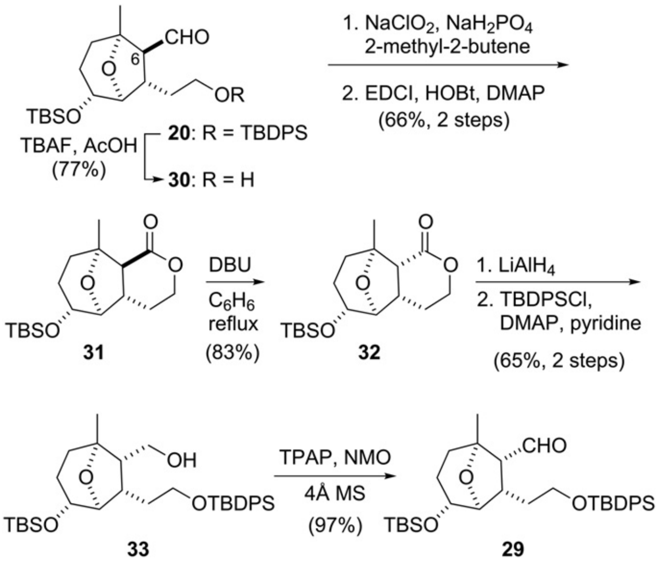
2.3. Total synthesis of (+)-aspergillin PZ

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 $SnCl_4$ 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 oxidation[31] 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 $LiAlH_4$, followed by selective silylation with TBDPSCl/DMAP and oxidation of the resulting alcohol **33** delivered aldehyde **29** in 27% overall yield from its *trans* epimer **20**.



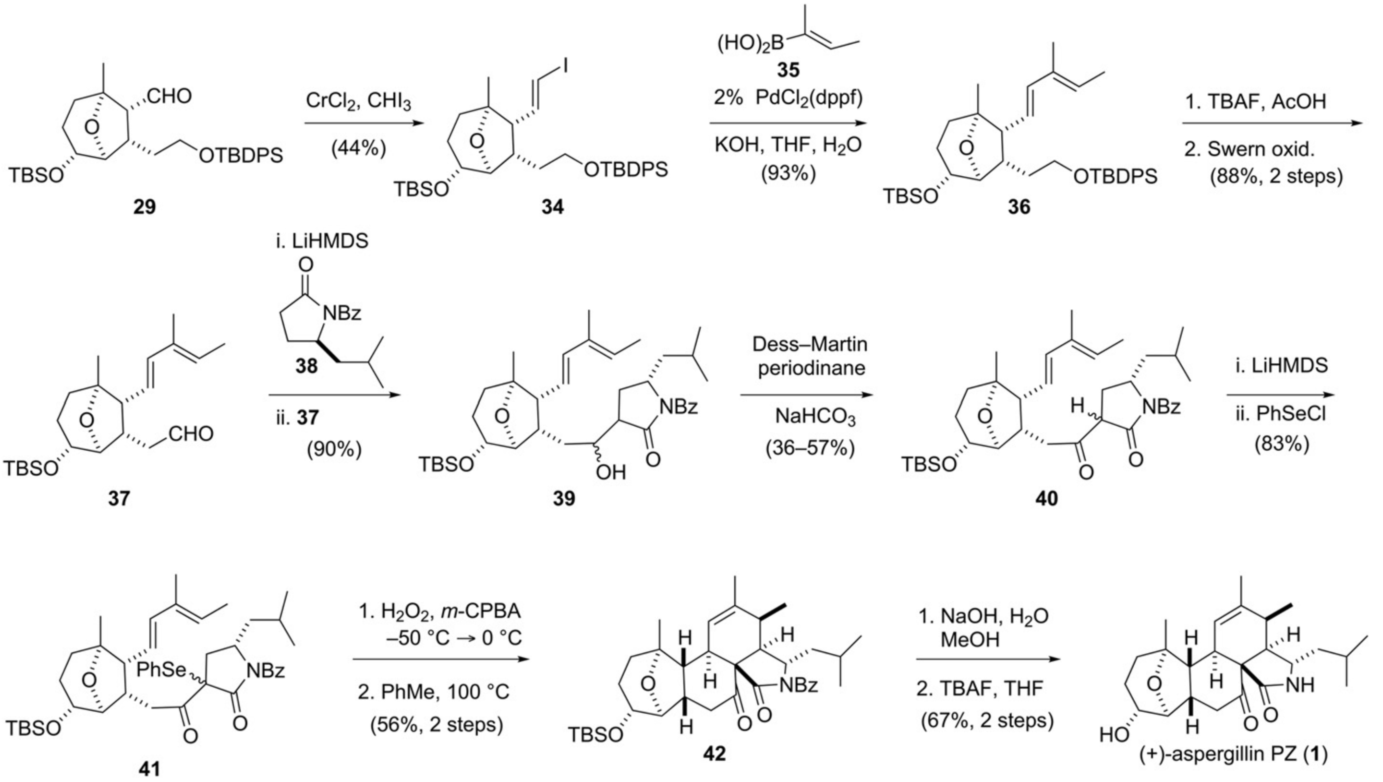
Scheme 9. Synthesis of enantioenriched 8-oxabicyclooctyl aldehyde **20**.



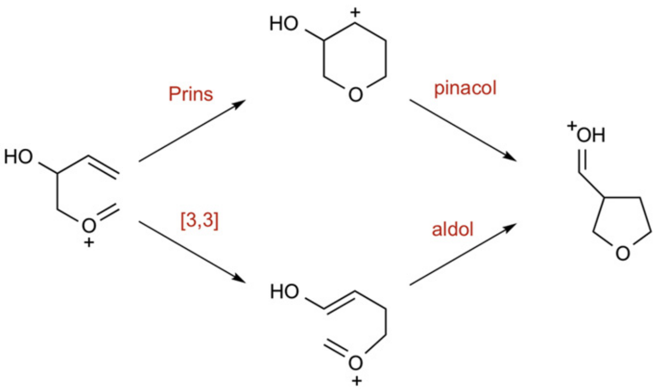
Scheme 10. Preparation of *cis* aldehyde **29**.

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 periodinane[36] or Swern conditions[21] provided the corresponding β-keto lactam in disappointingly 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**), $[\alpha]_D$ +115, whose ^{1}H and ^{13}C 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 (IC_{50}>10 μM) was found in either cell line.[39]



Scheme 11. Completion of the total synthesis of (+)-aspergillin PZ.



Scheme 12. Prins-pinacol and [3,3]-sigmatropic rearrangement/aldol pathways.

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.[29] 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.

Acknowledgements

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Supplementary data

Full experimental procedures and spectroscopic data for all new compounds are available as supplementary data. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.09.079.

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39. Data kindly provided by Dr. Sangkil Nam, Beckman Research Institute, City of Hope, Duarte, California.