

Unique structural topology and reactivities of the ABD tricycle in phomactin A†

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Stereoselective and transannular reactivities are described for the ABD tricyclic manifold of phomactin A that possesses a unique structural topology.

In recent years, we have been developing a formal *oxa*-[3 + 3] cycloaddition approach for the construction of natural products.^{1–9} Toward this effort, we embarked on a total synthesis of phomactin A [**1** in Fig. 1], which was isolated in 1991 from the culture filtrate of *Phoma* sp. [SANK 11486], a parasitic fungus found on the shell of *Chionoecetes opilio* off the coast of Fukui prefecture in Japan.¹⁰ Most of the phomactin family¹¹ display activity as PAF aggregation inhibitors [**1**: IC₅₀ = 10 μM].^{10,11} Their fascinating structural motif has attracted a number of synthetic efforts^{12,13} including Yamada's pioneering synthesis of a phomactin member [**D**]¹⁴ and elegant total syntheses of phomactin A reported by Pattenden¹⁵ and Halcomb.¹⁶

Our earlier efforts¹⁷ established an approach toward the ABD tricyclic core of phomactin A [**1**] [see **2**] via an intramolecular formal *oxa*-[3 + 3] cycloaddition reaction of diketone **3**. This represents a unique approach toward **1** in which the 12-membered D-ring, or the belt, is assembled at the very onset with the AB ring.^{12–16} Although this approach has not yet yielded a total synthesis, it has revealed an unusual structural topology in tricycle **2** that possesses some unique reactivities. We wish to communicate here these stereoselective and transannular reactivities as a result of this structural topology.

In our previous communication, we demonstrated that treatment of diketone **4** containing an enal motif [22 steps from (±)-2-methylcyclohexanone] with piperidinium acetate gave the desired ABD tricycle **6a** as a minor product via the desired successful intramolecular *oxa*-[3 + 3] formal cycloaddition pathway shown in **5a** [Scheme 1].¹⁷ The major products were a 4:1 inseparable mixture that was initially assigned as the regioisomer **6b** and what appeared to be the corresponding minor diastereomer [not shown]

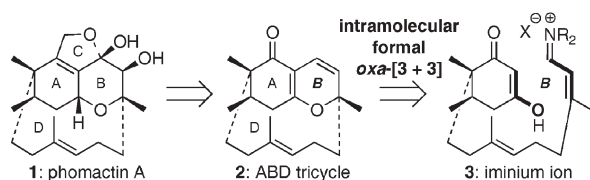


Fig. 1 A unique approach to phomactin A.

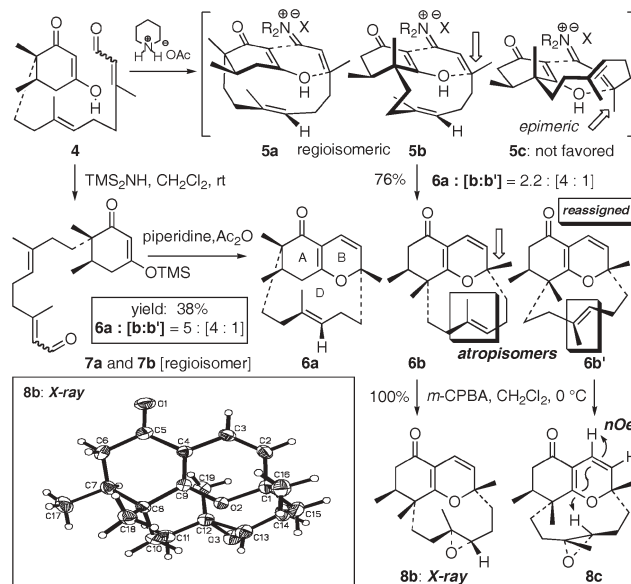
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that was proposed to be epimeric at the quaternary center alpha to the pyranyl oxygen atom [see the hollow arrow]. Both could be envisioned from transition states **5b** and **5c**, respectively, that are regioisomeric to **5a**. However, this minor diastereomer was ultimately reassigned as **6b'** [vide infra].

We have since attempted to improve this regioselectivity, most notably with using trimethylsilyl vinyllogous ester **7a** [and its regioisomer **7b** not shown] prepared from **4** and TMS₂NH. However, while the ratio of **6a**:[**6b**:**6b'**] was improved to 5:[4:1] from 2.2:[4:1], and while this represents the first example of this formal cycloaddition reaction employing a silyl enol ether,¹⁸ the overall yield dropped, presumably due to a slower *O*-1,4-addition to the vinyl iminium intermediate with the oxygen being silylated.²¹ However, it is noteworthy that this protocol is more consistent than that using piperidinium acetate. Collectively, these efforts provided a significant quantity of all three tricycles and allowed us to uncover the first two interesting findings.‡

First, *m*-CPBA epoxidation of the mixture containing **6b** and its initially assigned minor diastereomer [4:1 in ratio] led to two distinct and separable epoxides **8b** and **8c**¹⁹ in quantitative yield [Scheme 1]. The X-ray structure of the major epoxide **8b** unambiguously confirmed our original assignment of tricycle **6b**. However, key NOEs of the minor epoxide **8c** concisely revealed that the corresponding minor diastereomer is tricycle **6b'**, which interestingly is atropisomeric with **6b** at the trisubstituted olefin on the belt, and they do not equilibrate.²⁰



Scheme 1 Formal *oxa*-[3 + 3] cycloaddition and epoxidation.

Calculations using Spartan[®] 2002 [HF 6-31G*/B3LYP 6-31G* level] provided relative energies for all six possible atropisomers: **6a**, **6b**, and **6c**, the originally proposed minor diastereomer, at the top, with their allylic Me groups pointing inward and the respective atropisomers **6a'**–**c'**, with the allylic Me groups pointing outward, at the bottom [Fig. 2]. The three tricycles that we ultimately identified represent the most stable of the six. The originally assigned **6c** is higher in energy with its respective transition state **5c** [see Scheme 1] being quite strained upon re-examination.

The second finding is more relevant to our total synthesis effort. Tricycles **6b** and **6b'** were found to equilibrate efficiently under the same reaction conditions to give **6a** while reestablishing a ratio of 1.7:[4:1] for **6a**:[**6b**:**6b'**] [Scheme 2], which is likely the thermodynamic ratio.^{21–23} We believe the equilibration proceeds through pericyclic ring-opening²⁴ of **6b** and **6b'** to give 1-oxatriene **9**, and the overall isomerization from **9** to 1-oxatriene **12** would require a sequence of 1,4-addition of piperidine and β -elimination. It is also noteworthy that addition of an excess of Ac₂O led to a more efficient equilibration, a phenomenon that was also observed in the formal *oxa*-[3 + 3] cycloaddition. Ac₂O may play a role of siphoning off free amines to prevent products being tied up at the stage of **10** or **11**.

The success in equilibrating the two wrong tricycles to the desired **6a** rendered our approach to phomactin A [**1**] feasible but also led us to a series of unexpected reactivities. As shown in Scheme 3, all attempts to oxidize the endocyclic olefin of **6a** failed,

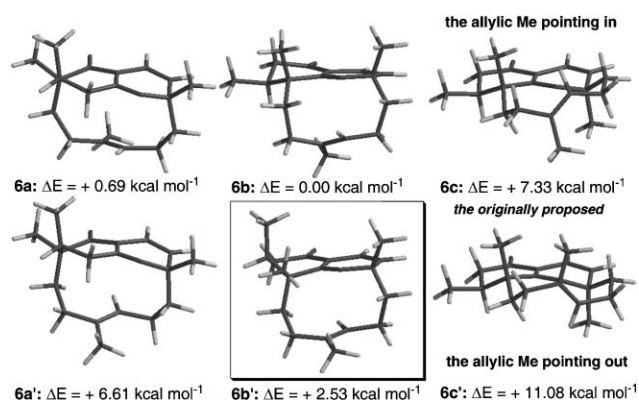
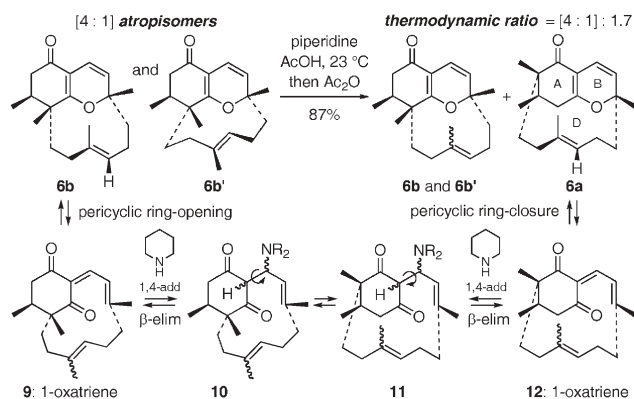


Fig. 2 Energy differences in all six possible atropisomers.



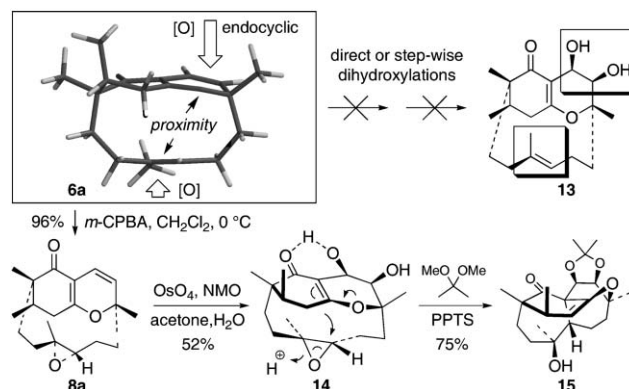
Scheme 2 Equilibrations of atropisomers **6b** and **6b'**.

with oxidation occurring preferentially at the belt olefin, although we had hoped the endocyclic olefin would be favored, especially under oxidative conditions that are electrophilic in nature.²⁵ It is however reasonable to suggest that the quaternary carbon adjacent to the endocyclic olefin may have hindered the approach of oxidative reagents.

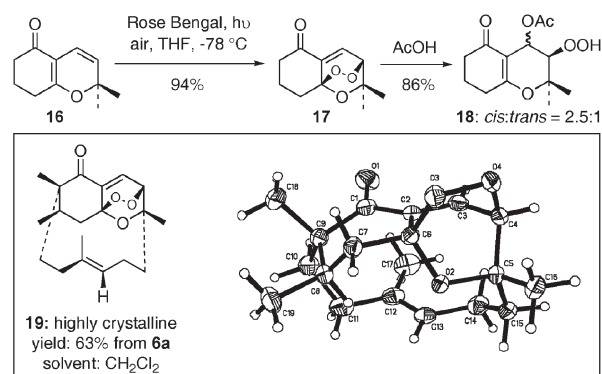
Specifically, only after the belt olefin was epoxidized with *m*-CPBA, could the endocyclic olefin in **8a** be efficiently dihydroxylated using OsO₄ and NMO to give diol **14** [Scheme 3]. However, subsequent attempts to protect the diol as an acetonide gave instead tetracycle **15**, which is likely the result of an acid-promoted transannular addition of the enol ether in **14** to the belt epoxide. This example represents a general phenomenon observed for numerous functionalization attempts using either **6a** or **8a** under acidic conditions. Such transannular reactivities could be rationalized given the close proximity of the belt olefin to the pyran ring [see the box].

Intriguingly, a singlet-oxygen Diels–Alder cycloaddition could be achieved selectively, leading to endoperoxides **17** and **19** from the model system **16** and **6a**, respectively, [Scheme 4] without a significant amount of competing [2 + 2] cycloaddition or ene reaction.²⁶ An X-ray structure of **19** was obtained to confirm every aspect of our assignment of **6a**.[‡] In addition, it reveals a structural conformation that closely matches phomactin A.¹⁰

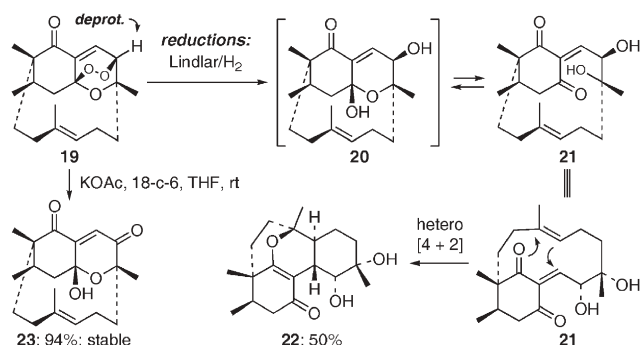
However, we quickly found that unlike the model system in which we were able to cleave the weak endoperoxide bridge in **17** using mild acidic conditions to give **18** [Scheme 4], breaking the endoperoxide bridge in **19** proved to be a challenge, and we



Scheme 3 Oxidations and transannular epoxide ring-opening.



Scheme 4 Singlet-O₂ Diels–Alder cycloaddition and endoperoxides.



Scheme 5 A transannular hetero-Diels-Alder cycloaddition.

observed another interesting transannular reaction involving the belt olefin [Scheme 5]. Specifically, reductive conditions such as Lindlar's hydrogenation efficiently led to a Tietze-type transannular hetero-Diels-Alder cycloaddition²⁷ through the ring-opened intermediate **21**, presumably from lactol **20**, to give tetracycle **22** in 50% yield as a single diastereomer.²⁸ The usage of thiourea or Ph₃P also led to a comparable outcome.

Ultimately, we found that under basic conditions, KOAc and 18-c-6 successfully cleaved the endoperoxide bridge *via* a deprotonation pathway [see arrow above **19**] to give enone **23** as a stable tricycle without any ring-opening that could have led to a similar transannular hetero-Diels-Alder cycloaddition pathway. This finding should help sustain our total synthesis endeavour.

We have described here interesting stereoselective and transannular reactivities associated with the ABD tricyclic manifold of phomactin A that has a unique structural topology.

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Notes and references

† Crystallographic data for: **8b**: [C₁₉H₂₆O₃], *M* = 302.40, orthorhombic, *P*₂₁₂₁₂, *a* = 8.8438(7) Å, *α* = 90°, *b* = 8.9335(7) Å, *β* = 90°, *c* = 20.8095(16) Å, *γ* = 90°, *V* = 1644.1(2) Å³, *T* = 173(2) K, *Z* = 4, *μ* = 0.081 mm⁻¹, 2177 [R(int) = 0.0216], final *R* indices [*I* > 2σ(*I*)] *R*₁ = 0.0314, *wR*₂ = 0.0804, *R* indices (all data), *R*₁ = 0.0332, *wR*₂ = 0.0814. **19**: [C₁₉H₂₆O₄], *M* = 318.40, monoclinic, *P*₂₁/*c*, *a* = 13.826(1) Å, *α* = 90°, *b* = 10.4515(9) Å, *β* = 106.751(2)°, *c* = 11.916(1) Å, *γ* = 90°, *V* = 1648.8(3) Å³, *T* = 173(2) K, *Z* = 4, *μ* = 0.088 mm⁻¹, 3784 [R(int) = 0.0481], final *R* indices [*I* > 2σ(*I*)] *R*₁ = 0.0425, *wR*₂ = 0.0910, *R* indices (all data), *R*₁ = 0.0744, *wR*₂ = 0.1010. CCDC 280698–280699. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b511338e

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