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 family[11] display activity as PAF aggregation inhibitors [**1**: IC_{50} = 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 Pattenden[15] and Halcomb.[16]

Our earlier efforts[17] 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] 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*].

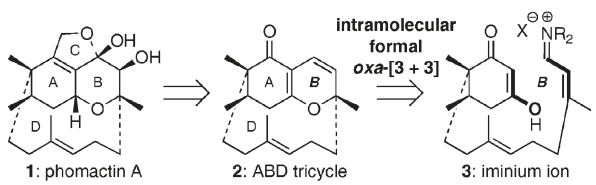
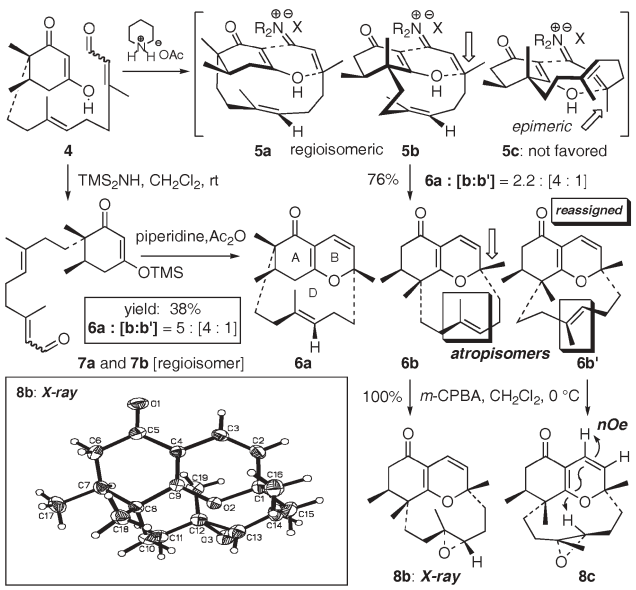


Fig. 1 A unique approach to phomactin A.

We have since attempted to improve this regioselectivity, most notably with using trimethylsilyl vinylogous ester **7a** [and its regioisomer **7b** not shown] prepared from **4** and TMS_2NH. 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.

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† Electronic supplementary information (ESI) available: Experimental procedures, full characterization and NMR spectra for all new compounds, and X-ray structural data. See DOI: 10.1039/b511338e

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-opening[24] 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 Ac_2O led to a more efficient equilibration, a phenomenon that was also observed in the formal *oxa*-[3 + 3] cycloaddition. Ac_2O 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, 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 OsO_4 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

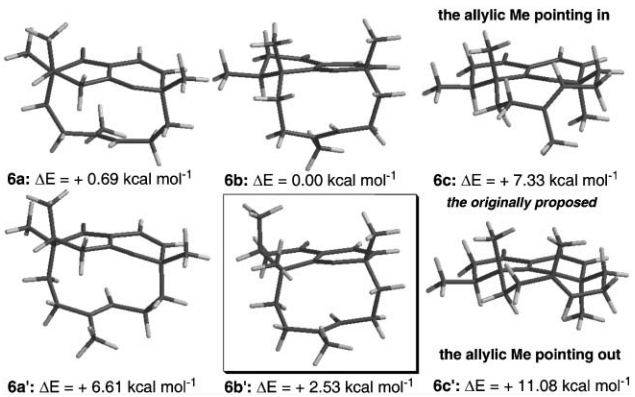
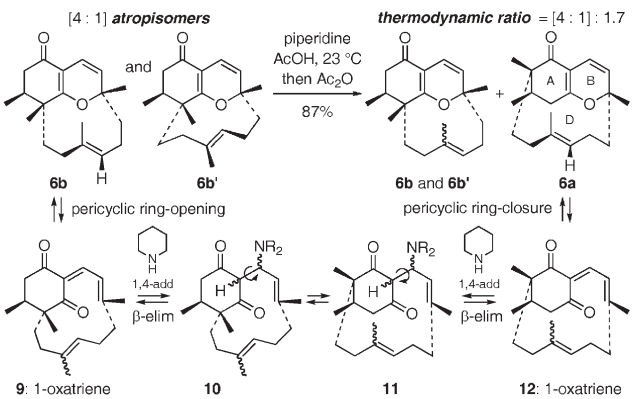
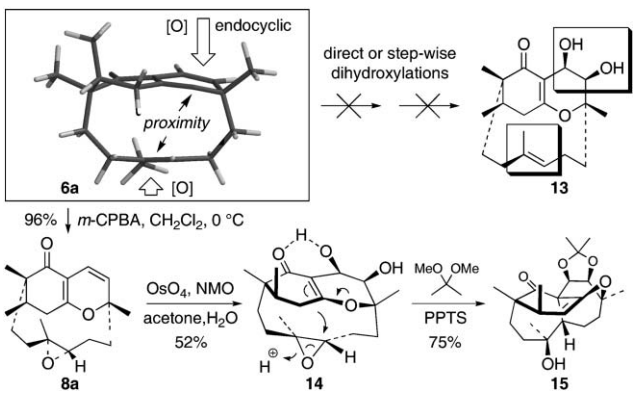


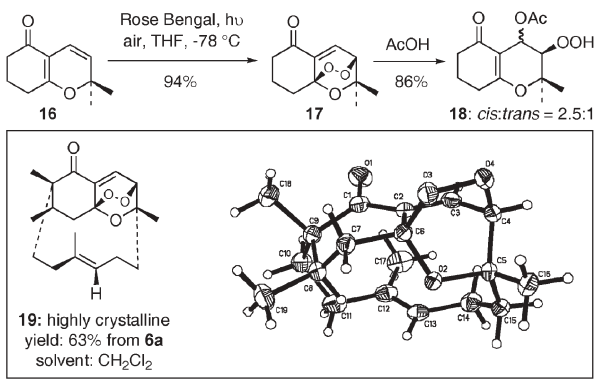
Fig. 2 Energy differences in all six possible atropisomers.



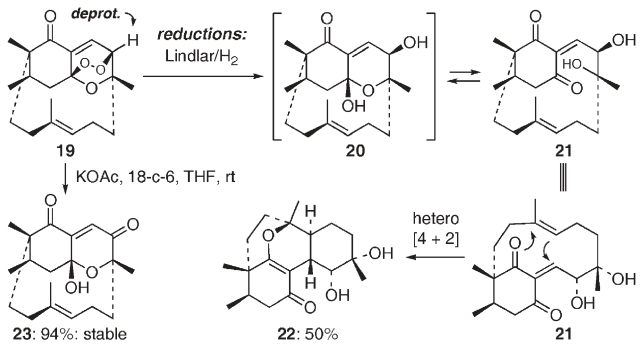
Scheme 2 Equilibrations of atropisomers **6b** and **6b′**.



Scheme 3 Oxidations and transannular epoxide ring-opening.



Scheme 4 Singlet-O_2 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 cycloaddition[27] 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 Ph_3P 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**: $[C_{19}H_{26}O_3]$, M = 302.40, orthorhombic, $P2_12_12_1$, 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) Å^3, T =173(2) K, Z = 4, μ = 0.081 mm^{-1}, 2177 [R(int) = 0.0216], final R indices [$I > 2\sigma(I)$], R_1 = 0.0314, wR_2 = 0.0804, R indices (all data), R_1 = 0.0332, wR_2 = 0.0814. **19**: $[C_{19}H_{26}O_4]$, M = 318.40, monoclinic, $P2_1/c$, 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) Å^3, T =173(2) K, Z = 4, μ = 0.088 mm^{-1}, 3784 [R(int) = 0.0481], final R indices [$I > 2\sigma(I)$] , 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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