

Intramolecular Formal *oxa*-[3 + 3] Cycloaddition Approach to the ABD System of Phomactin A

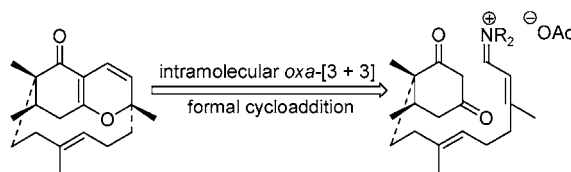
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ABSTRACT



The ABD-ring of phomactin A was synthesized using an intramolecular formal *oxa*-[3 + 3] cycloaddition of an α,β -unsaturated iminium salt tethered to a 1,3-diketone. This represents the first time that the 12-membered ring has been formed simultaneously with the 1-oxadecalins and should afford a facile route to the challenging structure of phomactin A.

Phomactin A (**1a**) was isolated in 1991 by Sugano and co-workers from the culture filtrate of *Phoma* sp. (SANK 11486), a parasitic fungus harvested off the coast of Japan.¹ The phomactins display novel biological activity as platelet activating factor (PAF) aggregation inhibitors (**1a**: IC₅₀ = 10 μ M). PAF is a phospholipid mediator that is alleged to have a role in asthma and other inflammatory diseases.² The phomactins are of current interest due to their novel mode of action on PAF, as well as their interesting and challenging molecular architecture.

A number of phomactins have since been isolated,³ but the first total synthesis of a phomactin (phomactin D, **1b**) was not achieved until 1996.⁴ Despite the efforts of a number of groups toward the phomactin core,⁵ phomactin A did not succumb to total synthesis until 2002 when Pattenden ((\pm)-

1a), and then Halcomb ((+)-**1a**) in 2003, reported their successes.⁶

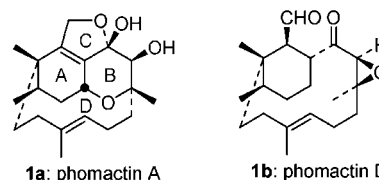


Figure 1. Phomactins A and D.

We have developed a formal *oxa*-[3 + 3] cycloaddition method for constructing 1-oxadecalins.^{7–9} Reactions of

(1) Sugano, M.; Sato, A.; Iijima, Y.; Oshima, T.; Furuya, K.; Kuwano, H.; Hata, T.; Hanzawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 5463–5464.

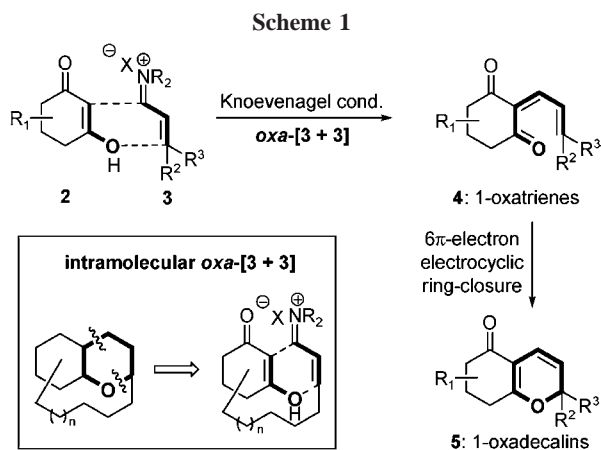
(2) (a) Sugano, M.; Sato, A.; Saito, K.; Takaishi, S.; Matsushita, Y.; Iijima, Y. *J. Med. Chem.* **1996**, *39*, 5281–5284. (b) Xhu, X.; Muñoz, N. M.; Kim, K. P.; Sano, H.; Cho, W.; Leff, A. R. *J. Immunol.* **1999**, *163*, 3423–3429.

(3) (a) Sugano, M.; Sato, A.; Iijima, Y.; Furuya, K.; Haruyama, H.; Yoda, K.; Hata, T. *J. Org. Chem.* **1994**, *59*, 564–569. (b) Sugano, M.; Sato, A.; Iijima, Y.; Furuya, K.; Hata, T.; Kuwano, H. *J. Antibiot.* **1995**, *48*, 1188–1190.

(4) Miyaoka, H.; Saka, Y.; Miura, S.; Yamada, Y. *Tetrahedron Lett.* **1996**, *37*, 7107–7110.

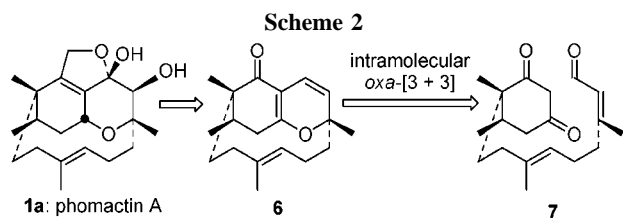
(5) (a) Foote, K. M.; Hayes, C. J.; Pattenden, G. *Tetrahedron Lett.* **1996**, *37*, 275–278. Foote, K. M.; John, M.; Pattenden, G. *Synlett* **2001**, 365–368. (b) Kallan, N. C.; Halcomb, R. L. *Org. Lett.* **2000**, *2*, 2687–2690. Mohr, P. J.; Halcomb, R. L. *Org. Lett.* **2002**, *4*, 2413–2416. (c) Seth, P. P.; Totah, N. I. *Org. Lett.* **2000**, *2*, 2507–2509. (d) Mi, B.; Maleczka, R. E. *Org. Lett.* **2001**, *3*, 1491–1494. (e) Chemler, S. R.; Iserloh, U.; Danishefsky, S. J. *Org. Lett.* **2001**, *3*, 2949–2951. (f) Houghton, T. J.; Choi, S.; Rawal, V. H. *Org. Lett.* **2001**, *3*, 3615–3617. (g) Balnaves, A. S.; McGowan, G.; Shapland, D. P.; Thomas, E. J. *Tetrahedron Lett.* **2003**, *44*, 2713–2716.

diketones **2** with α,β -unsaturated iminium salts **3** proceed through a Knoevenagel condensation followed by a 6π -electron electrocyclic ring closure of 1-oxatrienes **4** to give 1-oxadecalins **5** (Scheme 1). Despite our efforts and those



of others,¹⁰ this formal *oxa*-[3 + 3] cycloaddition reaction has never been employed in an intramolecular manner. We wish to communicate here our preliminary success in developing an intramolecular formal *oxa*-[3 + 3] cycloaddition approach toward the synthesis of the ABD portion of phomactin A.

Our basic approach to the synthesis of phomactin A is shown in Scheme 2. We were initially uncertain as to the



feasibility of applying the *oxa*-[3 + 3] to **1a** given the possibility that cyclization could potentially occur onto either oxygen of the diketone. Upon evaluation of the system, it became evident that there can be three products of intra-

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(8) For recent applications of the formal *oxa*-[3 + 3] cycloaddition in natural product synthesis, see: (a) Kurdyumov, A. V.; Hsung, R. P.; Ihlen, K.; Wang, J. *Org. Lett.* **2003**, *5*, 3935–3938. (b) Hsung, R. P.; Cole, K. P.; Zehnder, L. R.; Wang, J.; Wei, L.-L.; Yang, X.-F.; Coverdale, H. A. *Tetrahedron* **2003**, *59*, 311–324.

(9) For a review on stepwise *hetero*-[3 + 3] formal cycloadditions, see: Hsung, R. P.; Wei, L.-L.; Sklenicka, H. M.; Shen, H. C.; McLaughlin, M. J.; Zehnder, L. R. In *Trends in Heterocyclic Chemistry*; Research Trends: Trivandrum, India, 2001; Vol. 7, pp 1–24.

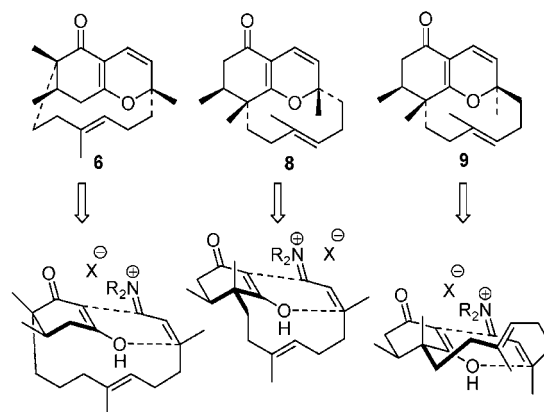
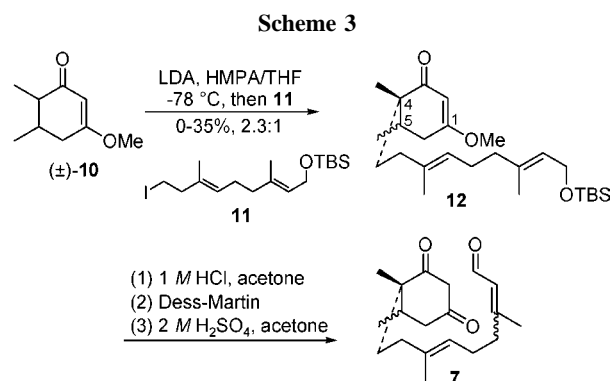


Figure 2. Possible regioisomers of cyclization.

molecular cyclization (see Figure 2). The desired mode of cyclization involves formation of the 12-membered D-ring, while the undesired modes create 10-membered rings. The success of this reaction would provide a novel approach toward phomactin in which the 12-membered D-ring is assembled at the onset, instead of being constructed near the end.^{4–6} We decided to test the possibility experimentally.

Our first approach to enal **7** is shown in Scheme 3. Attempting to take advantage of oxygenation built into the



system, vinyllogous ester (±)-**10**^{6a} was an attractive retron, provided that it could be alkylated with an electrophile such as iodide **11** (prepared in eight steps). Unfortunately, in our hands this alkylation proved to be problematic in two important aspects: (1) the yield was unreproducible and low and (2) the diastereoselectivity was a disappointing 2.3:1, favoring the desired *cis* isomer with respect to the C4- and C5-methyl substituents. Furthermore, these diastereomers were extremely difficult to separate chromatographically.

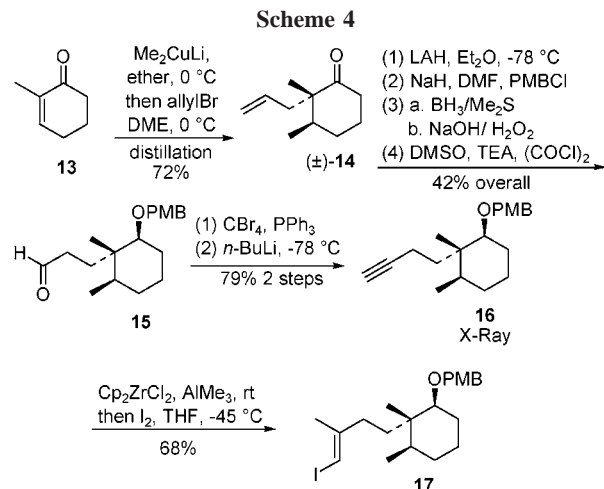
The mixture was elaborated over three steps to the enals **7**. The cyclization of enals **7** (olefin geometry scrambled

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upon treatment with H₂SO₄) was found to occur under very mild conditions, affording a complex mixture of products. Several of the reaction products could be attributed to dimerization/oligomerization of the starting material (as evidenced by the crude LC/MS), and there appeared to be peaks in the ¹H NMR assignable to desired product. However, the mixture contained signals resulting from C5-methyl diastereomers as well.

In short, this experiment encouraged us in that the key cyclization appeared to be feasible, but absolute certainty as to the identity of the products could only be obtained if a single diastereomer was subjected to the reaction conditions. Additionally, the paramount cyclization should be performed under conditions of high dilution to ensure that only the intramolecular reaction occurs.

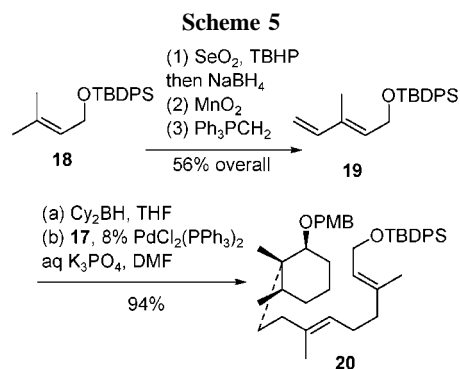
We decided to sacrifice brevity and chose a route that would allow for isolation of a single isomer of **7** using chemistry that could potentially produce large quantities of material. As shown in Scheme 4, conjugate addition/



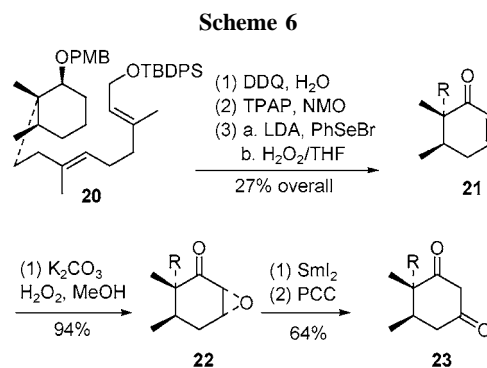
trapping¹¹ of enone **13**¹² afforded, after distillation, ketone (±)-**14** as an 11:1 mixture of diastereomers. Due to the incompatibility of an ethylene ketal with AlMe₃, the ketone was reduced and protected as its PMB ether. The alkene was subjected to hydroboration/oxidation followed by Swern oxidation to afford aldehyde **15**. Corey–Fuchs homologation¹³ proceeded smoothly to afford alkyne **16**, the structure of which was unambiguously assigned via single-crystal X-ray analysis. Last, Negishi carboalumination followed by an iodine quench¹⁴ provided vinyl iodide **17**.

The terpene side chain was completed using a *B*-alkyl Suzuki coupling^{6b,15} of iodide **17** with the borane derived from diene **19**, which was rapidly assembled from prenyl

alcohol (Scheme 5). In this case, the use of Cy₂BH was preferable, as 9-BBN seemed to promote an undesired side reduction.



With **20** in hand, the necessary oxygenation was installed through a six-step procedure (Scheme 6). Removal of the PMB ether under standard DDQ conditions occurred readily; TPAP oxidation then afforded the ketone in good yield. Oxidation to enone **21**, however, proved to be problematic; unidentified byproducts were isolated after the initial selenation step, the olefins of which appeared to have suffered electrophilic attack. Nucleophilic epoxidation of **21** proceeded smoothly and with high selectivity to afford the α-epoxide **22** (assigned by ¹H NOE experiments) as the only observed diastereomer. To open the epoxide, SmI₂ reduction at low temperature was the only protocol surveyed that reliably opened the epoxy-ketone in a completely regioselective manner.¹⁶

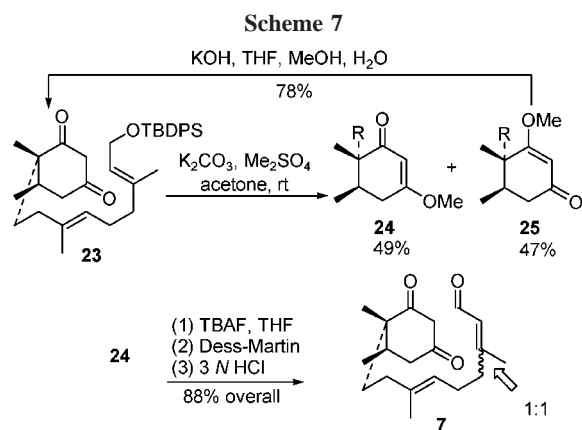


We had hoped to use the Noyori method to simply isomerize the α,β-epoxy ketone directly to the 1,3-diketone.¹⁷ Unfortunately, under numerous conditions, the reaction was complicated by both poor conversion and competing reduction, which afforded mixtures of **23** and the same β-hydroxy ketone produced from SmI₂ reduction.

(11) Coelho, F.; Diaz, G. *Tetrahedron* **2002**, *58*, 1647–1656.
 (12) Warnhoff, E. W.; Martin, D. G.; Johnson, W. S. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 162–166.
 (13) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769–3792.
 (14) Negishi, E.; Horn, D. E.; Yoshida, T. *J. Am. Chem. Soc.* **1985**, *107*, 6639–6647.
 (15) Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513.

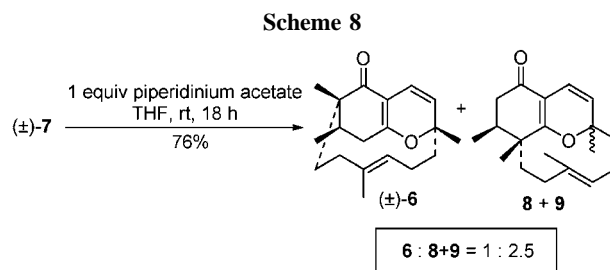
(16) Molander, G.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 2596–2599.
 (17) Suzuki, M.; Watanabe, A.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 2095–2096.

The sensitive 1,3-diketone in **23** was protected as its vinylogous methyl ester (Scheme 7). The two possible



regioisomers of the esterification were observed in a 1:1 ratio and were easily separated. Subsequent reactions showed that regioisomer **25** was much more resistant to hydrolysis than **24**; thus, only **24** was carried forward, while its isomer was recycled (KOH, THF/MeOH/H₂O, 78%). Deprotection of the silyl ether and periodinane oxidation led to a single isomer of the enal. Hydrolysis of the methyl ester again scrambled the olefin geometry but proceeded in high yield, providing the desired diketone **7**.

At last, with pure enal **7** in hand, we attempted the key *oxa*-[3 + 3] cycloaddition (Scheme 8). Using conditions of high dilution (5 mL/mg), we were pleased to discover all three potential intramolecular products (**6**:(**8** + **9**) = 1:2.5). While isomers **8** and **9** existed as an unassignable and inseparable 4:1 mixture, the desired cycloadduct (\pm)-**6** was easily separated and its structure confirmed using ¹H NOE, ¹H–¹H COSY, and ¹H–¹³C HMBC experiments.



In summary, we have described here an approach to the ABD-ring of phomactin A, featuring an intramolecular formal *oxa*-[3 + 3] cycloaddition as the key step to simultaneously form the 12-membered D-ring with the 1-oxadecalin. Further optimization of the synthetic route to enal **7**, including an enantioselective approach, as well as studies directed toward the completion of the total synthesis of phomactin A, are underway.

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Supporting Information Available: Spectroscopic data for all new compounds along with detailed experimental procedures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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