

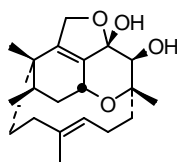
Synthetic Approaches to Phomactin A

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ABSTRACT



Phomactin A

Phomactin A is a biologically active marine natural product containing a unique bridged-heterocyclic core. The unusual ring system, along with the six stereocenters contained in phomactin A, provide the synthetic chemist with interesting and difficult challenges. Several approaches to the synthesis of phomactin A, including two recent total syntheses, are highlighted here.

Phomactin A (**1**) was isolated from the culture filtrate of *Phoma* sp. (SANK 11486), a parasitic marine fungus found on the shell of a crab, *Chionoecetes opilio*, by Sugano *et al.* in 1991 (Figure 1).¹ To date, a total of seven phomactins have been isolated, all of which contain, in some form, an unusual bicyclo[9.3.1] pentadecane core.² The phomactins possess novel biological activity as they are platelet activating factor (PAF) antagonists. Platelet activating factor is a phospholipid mediator released in the body by several cell types³ that may have a role in causing asthma and other inflammatory diseases.⁴ Phomactin A inhibits PAF-induced platelet aggregation at a modest level ($IC_{50} = 10 \mu M$), but has no effect on adenosine diphosphate, arachidonic acid, or collagen-induced platelet aggregation. This suggests that **1** represents a new class of PAF antagonist. Phomactin D (**2**) is the most potent phomactin inhibitor of PAF ($IC_{50} =$

$0.8 \mu M$) and has been the subject of some medicinal studies.⁵

Phomactin A is the most stereochemically complex of the phomactins, and has attracted the most attention from the synthetic community. Although (+)-phomactin D was synthesized in 1996,⁶ the total synthesis of **1** was only recently reported.

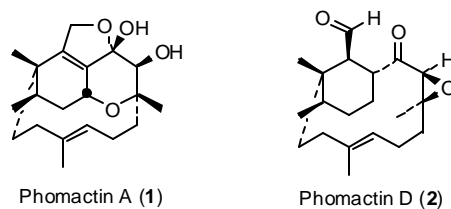


Figure 1. Structures of phomactins A and D.

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.; 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.; Kuwano, H.; Hata, T. *J. Antibiot.* **1995**, *48*, 1188-1190.

³ Koltai, M.; Braquet, P. G. *Clin. Rev. Allergy* **1994**, *12*, 361-380.

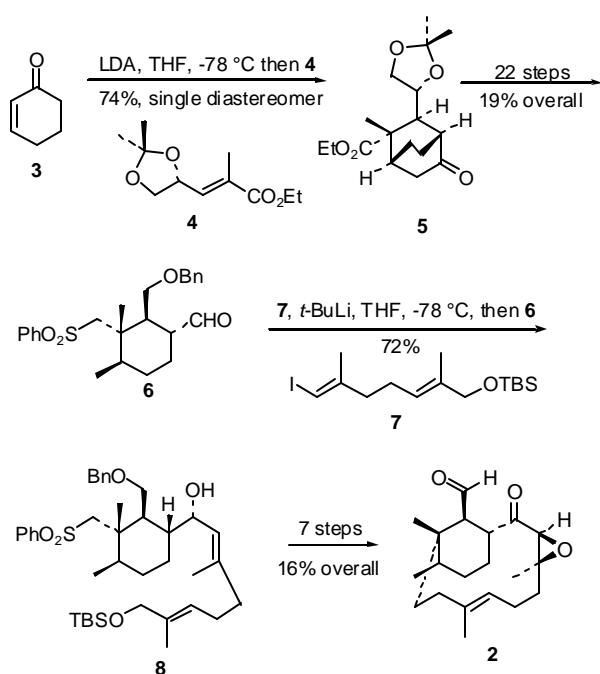
⁴ Xhu, X.; Muñoz, N. M.; Kim, K. P.; Sano, H.; Cho, W.; Leff, A. R. *J. Immunol.* **1999**, *163*, 3423-3429.

⁵ Sugano, M.; Sato, A.; Saito, K.; Takaishi, S.; Matsushita, Y.; Iijima, Y. *J. Med. Chem.* **1996**, *39*, 5281-5284.

⁶ Miyaoka, H.; Saka, Y.; Miura, S.; Yamada, Y. *Tetrahedron Lett.* **1996**, *37*, 7107-7110.

phomactin D total synthesis. The two existing total syntheses of **1** share much in common with the aforementioned synthesis of **2** which is highlighted in Scheme 1. A conjugate addition/trapping using chiral ester **4** set the stereochemistry at the crucial quaternary center. A high yielding series of transformations lead to the key aldehyde **6**. Addition of the alkenyl-lithium derived from iodide **7** provided alcohol **8** as a single diastereomer. The free alcohol was protected and the allylic chloride was formed. The key macrocyclization proceeded in modest yield to provide the core of **2**. Global deprotection/desulfurization was followed by a directed epoxidation and double oxidation to give the natural product.

Scheme 1

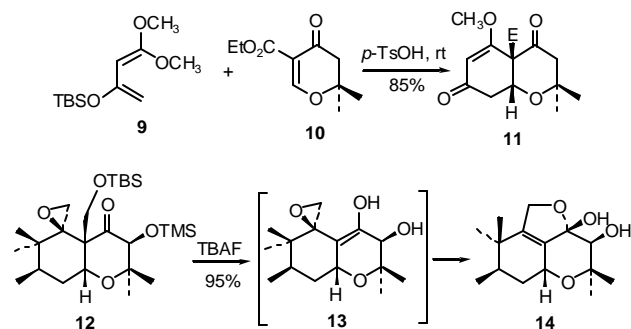


Totah published a clever [4 + 2] route to the furanochroman core of phomactin A (Scheme 2).⁷ Model system **14** was efficiently synthesized and elaborated to the phomactin A core. The initial Diels-Alder reaction was followed by several protections, alkylations, and numerous oxidation state transforms. Finally, the model system was completed in the most noteworthy operation in this strategy. An elegant TBAF-induced retro-aldol-elimination cascade served not only to expel formaldehyde and to open the epoxide moiety present in **12**, but closed the highly sensitive and easily aromatized hydrated furan in one step and in excellent yield to afford the phomactin core **14**. Plans for the further elaboration of the Diels-Alder reaction to a more complex system were not discussed, and no plan for addressing the 12-membered ring was disclosed.

⁷ Seth, P. P.; Totah, N. I. *Org. Lett.* **2000**, *2*, 2507-2509.

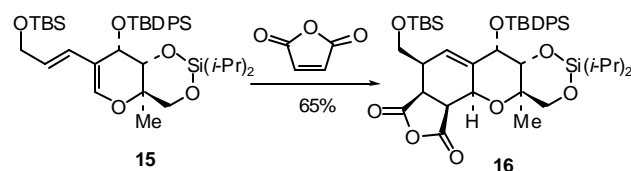
Danishefsky also published a [4 + 2] route (shown in Scheme 3) that, like Totah's strategy, generates the cyclohexane moiety subsequent to pyran formation.⁸ Conformationally rigid dihydropyran **15** was formed *via* a catalytic, enantioselective hetero-Diels-Alder reaction.⁹ The reaction of **15** with maleic anhydride at ambient temperature lead to the highly functionalized *endo*-tetracycle **16**. While this is an elegant model system which could potentially lead to *ent*-**1**, no information was provided as to how the 12-membered macrocycle would be formed, or how the synthesis would be completed.

Scheme 2



In 2001, Maleczka published a route to **1** which is similar to the phomactin D synthesis.¹⁰ The authors expressed the desire to access several phomactins by employing a divergent strategy. The synthesis, shown in Scheme 4, was centered around the Nozaki-Hiyama-Kishi (NHK) coupling of racemic vinyl iodide **17** which was prepared *via* Julia olefination. Unfortunately, the Julia reaction gave an inseparable 1.3:1 mixture of *E/Z* isomers. The key cyclization proceeded as anticipated, and after separation of olefin isomers, **18** was obtained in modest yield. Interestingly, the undesired *Z* isomer reacted faster than the *E* isomer. The authors expressed interest in obtaining a *Z*-phomactin analog in order to perform an SAR study. The model system was completed by the opening of the epoxide in **19** which was

Scheme 3

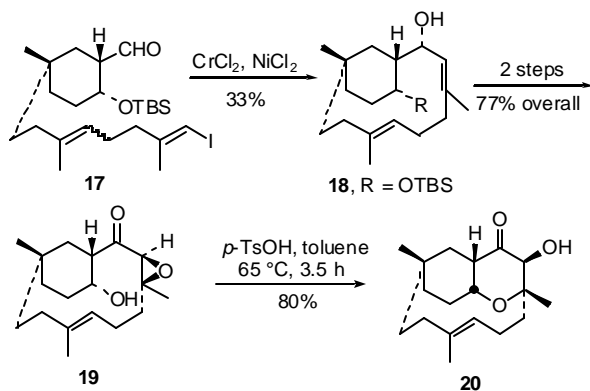


⁸ Chemler, S. R.; Iserloh, U.; Danishefsky, S. J. *Org. Lett.* **2001**, *3*, 2949-2951.

⁹ Yao, S.; Johannsen, M.; Audrain, H.; Jørgensen, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 8599-8605.

¹⁰ Mi, B.; Maleczka, R. E. *Org. Lett.* **2001**, *3*, 1491-1494.

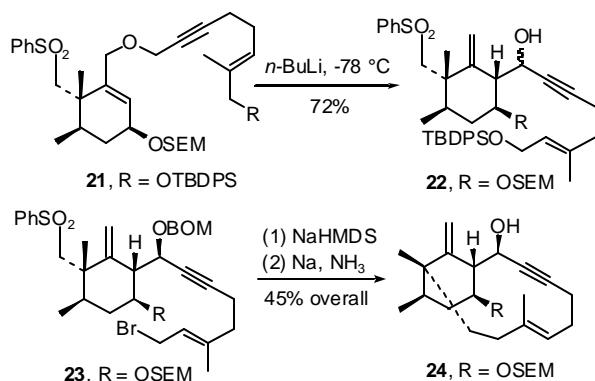
Scheme 4



accomplished by heating with an acid catalyst to afford pyran **20**.

Thomas *et al.* recently disclosed the creative 2,3-Wittig rearrangement (Scheme 5) of sulfone **21** to afford alcohol **22** as an inconsequential mixture of epimers.¹¹ In a fashion similar to the phomactin D synthesis, the macrocycle was closed *via* the relatively efficient intramolecular displacement of allylic bromide **23**. Although seemingly conventional, this appears to be the most successful method of ring closure discovered thus far. However, several operations must be conducted to complete the total synthesis of (\pm)-**1**; the alkyne must be appropriately functionalized and the pyran will presumably be formed from the epoxide after the SEM protected alcohol is inverted to the proper configuration.

Scheme 5

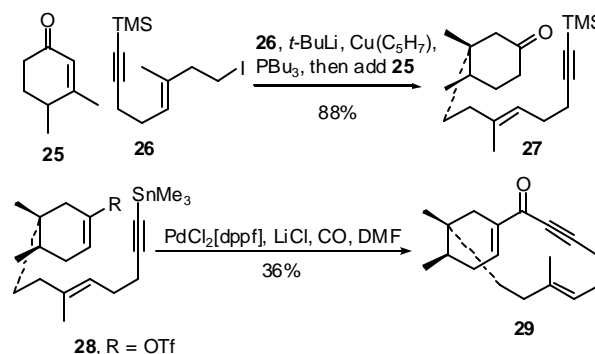


The Rawal publication is concerned with the approach to phomactins C and D, but is noteworthy due to the rapidity with which the phomactin core was converged

¹¹ Balnaves, A. S.; McGowan, G.; Shapland, P. D. P.; Thomas, E. *J. Tetrahedron Lett.* **2003**, *44*, 2713-2716.

upon.¹² Iodide **26** (Scheme 6) was readily generated in six steps and the derived mixed cuprate's conjugate addition to enone **25** occurred in remarkable yield and high (13:1 ratio) diastereoselectivity. The efficient use of the mixed alkynyl cuprate represents an excellent method for formation of the important quaternary stereocenter. The model was completed by formation of the kinetic triflate followed by a palladium catalyzed homologation/coupling to afford ketone **29** in an unoptimized 36%. Alternatively, the triflate could be formylated and upon desilylation, the resultant aldehyde cyclized (NaHMDS) and then oxidized to afford **29**. Unfortunately, this modification served only to increase the synthetic path length (four additional operations), and did not increase overall yield (also 36% over the five steps).

Scheme 6



Pattenden published an early model system for phomactin A in 1996.¹³ The work showed that the furanochroman core **14** could be obtained (although tediously) from a 1,3-cyclohexanedione derivative. Later work unveiled the more advanced NHK approach¹⁴ that eventually lead to the first total synthesis of (\pm)-**1**.¹⁵ In addition, a complimentary intramolecular RCM approach to the macrocycle was also discussed. The eventual NHK approach is similar to the phomactin D synthesis in that the 12-membered belt is "stitched" on to an existing cyclohexane framework and a series of oxidations and deprotections complete the synthesis.

Pattenden's groundbreaking synthesis is highlighted in Scheme 7. The key coupling substrate **33** was efficiently synthesized, and the NHK reaction proceeded in modest yield to afford alcohol **34**. Disappointingly, the VO(acac)₂ catalyzed epoxidation of **35** lead primarily (5:1 ratio) to the bis-epoxide where the indicated olefinic residue was also epoxidized from the β -face, along with the desired mono-epoxide. The total

¹² Houghton, T. J.; Choi, S.; Rawal, V. H. *Org Lett.* **2001**, *3*, 3615-3617.

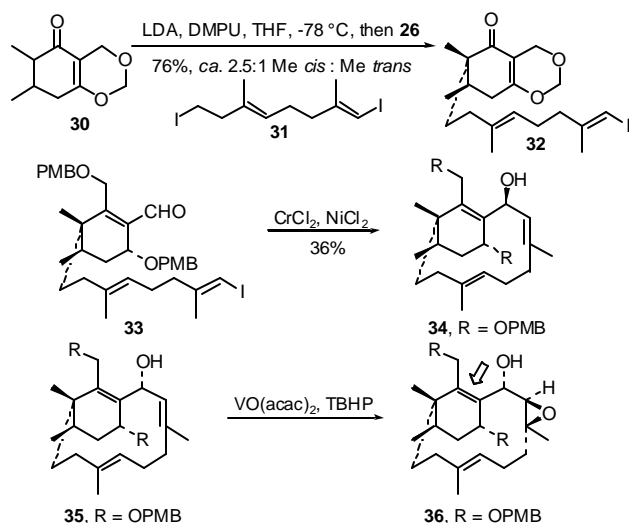
¹³ Foote, K. M.; Hayes, C. J.; Pattenden, G. *Tetrahedron Lett.* **1996**, *37*, 275-278.

¹⁴ Foote, K. M.; John, M.; Pattenden, G. *Synlett* **2001**, 365-368.

¹⁵ Goldring, W. P. D.; Pattenden, G. *Chem. Commun.* **2002**, 1736-1737.

synthesis was completed by oxidation of the free alcohol and removal of both PMB ethers which induced spontaneous cyclization to (\pm)-**1**.

Scheme 7

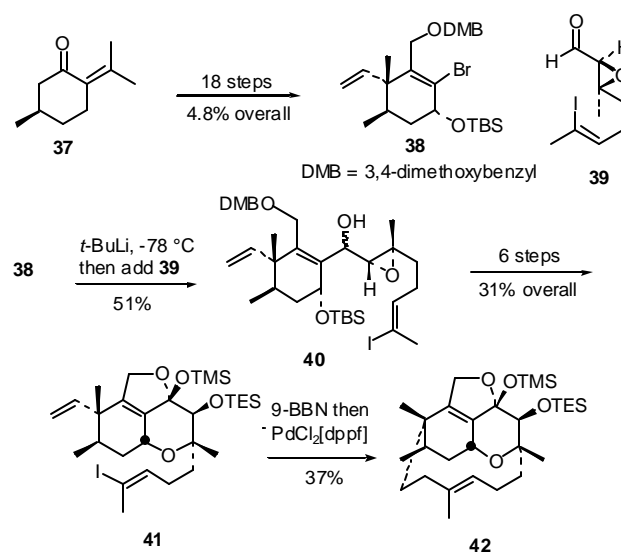


Several months later, Halcomb reported a 26 step total synthesis of (+)-**1**.¹⁶ The route followed closely the previously published model system,¹⁷ but is again similar in style to the phomactin D synthesis. The enantioselective route (Scheme 8) began with commercial (*R*)-(+)-pulegone (**37**) which was laboriously transformed using classical steps, into bromide **38**. Lithiation of the bromide and addition to aldehyde **39** afforded alcohol **40** in 51% yield as an inconsequential mixture of epimers. The key macrocyclization protocol involved the intramolecular *B*-alkyl Suzuki coupling of iodide **41**. As is the case for several other approaches, coupling efficiency was not optimal; the crowded environment of the vinyl moiety in **41** may inhibit the hydroboration step. The inability of several groups' efforts to smoothly form the macrocycle may indicate the fundamental inability of current synthetic methods to achieve such a transformation and thus, the opportunity exists for new methodological development. The synthesis was completed by simple TBAF deprotection of **42** which gave (+)-**1**.

There exists in the framework of phomactin A several areas which hold the opportunity for improvement over the previous endeavors: (i) A more efficient strategy for formation of the 12-membered ring is needed; both total syntheses have faltered at this stage. (ii) Approaches to the highly-substituted pyran by methods other than epoxide opening should lead to vastly different retrosyntheses and possibly, markedly more efficient

routes. (iii) The overall number of oxidations contained in the synthesis, especially in the later stages, should be minimized. Oxidations, in general, do not increase complexity, and often invoke further complications such as cumbersome protecting group strategies. (iv) Finally, the highly substituted cyclohexane ring appears to be difficult (requiring a large number of steps) to form in an enantioselective fashion. Here lies an opportunity for a new application or improvement in asymmetric catalysis.

Scheme 8



In summary, various approaches to the phomactin A core, two of which have resulted in total syntheses, were highlighted. The difficult nature of structures such as **1** will continue to be the driving force for the development of new and better methodologies in organic synthesis.

¹⁶ Mohr, P. J.; Halcomb, R. L. *J. Am. Chem. Soc.* **2003**, *125*, 1712-1713.

¹⁷ Mohr, P. J.; Halcomb, R. L. *Org. Lett.* **2002**, *4*, 2413-2416.