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The Phomactins. A Novel Group of Terpenoid Platelet Activating Factor Antagonists Related Biogenetically to the Taxanes

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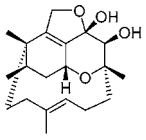
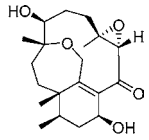
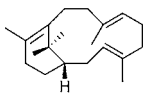
ABSTRACT
A description of the structurally unusual "phomactin" family of platelet activating factor antagonists recently found in the marine fungus *Phoma* sp. is presented. The phomactins show an interesting structural and biosynthetic relationship with the more familiar taxane group of antitumor compounds isolated from yew trees. The Account highlights and discusses this unique relationship and also presents a cogent picture of plausible biogenetic interrelationships within the family of phomactins. Complementary synthetic endeavors with the phomactins are interwoven in the discussions, alongside contemporaneous biosynthetic studies with both the phomactins and the taxanes.

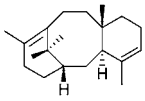
Introduction

The phomactins are an intriguing family of platelet activating factor antagonists found in the marine fungus *Phoma* sp. The first member to be isolated and characterized was phomactin A (**1**) in 1991.[1] Since then, several


phomactin A (**1**)


phomactin H (**2**)


verticillene (**3**)

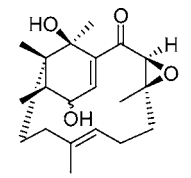

taxadiene (**4**)

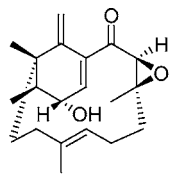
other phomactins have been described, which are clearly connected biogenetically to one another and to phomactin A.[2] The last member to be described, in 2004, was phomactin H (**2**).[3] The phomactins are diterpenes with a core bicyclo[9.3.1]pentadecane ring system. This ring system has close congruence with the "verticillene" carbon framework, namely, **3**, which for many years has been considered to be the biogenetic precursor to the tricyclic 6,8,6-ring system **4** present in the taxane family of anticancer natural products.[4]

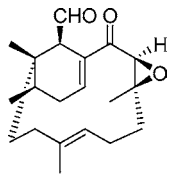
In this Account, we provide a description of the phomactin diterpenes, drawing attention to their structural and biogenetic interrelationships, their biological properties, and their unique interface with the taxanes. We also give a brief overview of synthetic studies that have been carried out within the phomactins, particularly as they relate to unravelling some of the biogenetic interconnections between members of this interesting family of secondary metabolites.

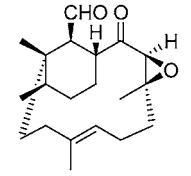
Discovery of the Phomactins and their Platelet Activating Factor Activity

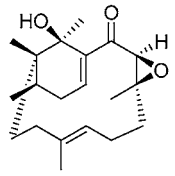
Phomactin A (**1**) was isolated from the lipophilic extracts of the fungus *Phoma* sp. (SANK 11486) by Sato and co-workers following a screening study of marine organisms that inhibit platelet activating factor (PAF)-induced platelet aggregation and binding of PAF to its receptors.[1] This particular strain of *Phoma* was found on the shell of the crab *Chionoecetes opilio*, which inhabits the waters of Fukui Prefecture, Japan.

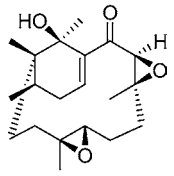

5a, α-OH; phomactin B
5b, β-OH; phomactin B1

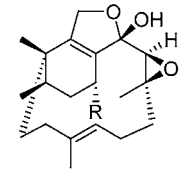

phomactin B2 (**6**)

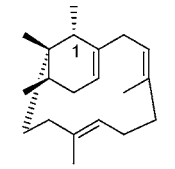

phomactin C (**7**)
(Sch 47918)

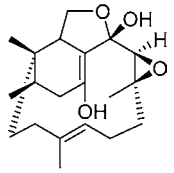

phomactin D (**8**)


phomactin E (**9**)


phomactin F (**10**)


11a, R = H; phomactin G
11b, R = OH; Sch 49028


Sch 49026 (**12**)


Sch 49027 (**13**)

Over a number of years, Sato and co-workers, together with researchers from Schering Plough in the U.S.A., independently isolated 11 additional phomactins to phomactin A from *Phoma* sp., that is, phomactins B (**5a**),

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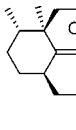
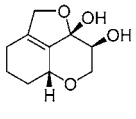
B1 (**5b**), B2 (**6**), C (**7**), D (**8**), E (**9**), F (**10**), and G (**11a**),[2c,d] and the compounds designated Sch 49028 (**11b**), Sch 49026 (**12**), and Sch 49027 (**13**).[2a,b] Nearly a decade later, in 2004, a new member, phomactin H (**2**), was isolated from an unrelated marine fungus whose structure reveals an interesting biogenetic connection and structural relationship with the other phomactins.[3]

Cleomeolide (**14**), a diterpene found in the herb *Cleome viscose*, is the only other natural product closely related to the phomactins.[5] A common structural feature accommodated in the hydrocarbon core, namely, **12**, of several phomactins is an epoxyketone, namely, phomactins B, C, D, E, F, and H, and enzymatic oxidation of **12** provides a clear biosynthetic link to other phomactins. Indeed, in our publications we have proposed key biogenetic connections within most of the earlier isolated phomactins,[6] and later in this Account, we show a possible connection between phomactin H (**2**), the most recently isolated member of this family, and phomactin A (**1**).


cleomeolide (**14**)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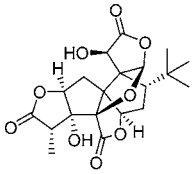
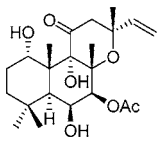
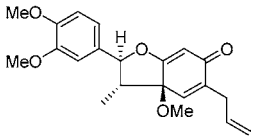

ginkgolide A (**16**)


forskolin (**17**)


kadsurenone (**18**)

The full structure of phomactin A (**1**) was first determined in part using NMR spectroscopy, but the stereostructure followed only after X-ray analysis of a suitable crystalline derivative.[1] The stereostructures of phomactins C and E were also determined using X-ray crystal structure analysis, but all the other phomactins were characterized using NMR spectroscopy. Phomactin A contains an interesting and unusual tricyclic furanochroman ring system, namely, **15**, embedded within its bicyclic core, that is **12**, making it the most structurally complex and, therefore, the most synthetically demanding of the phomactins.

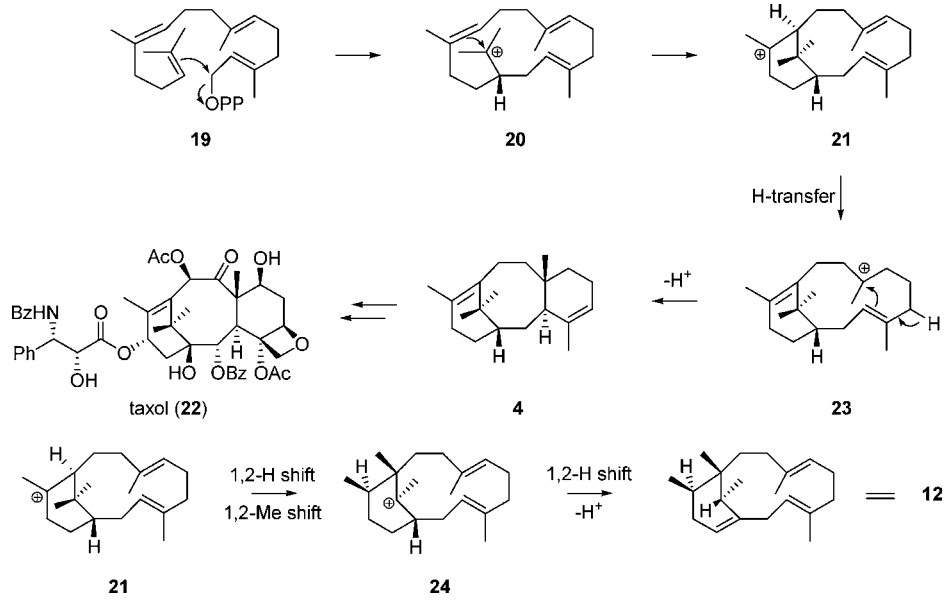
PAF is a naturally occurring ether phospholipid (1-*O*-alkyl-2*R*-acetylglycerol-3-phosphorylcholine) that induces the release of histamine from platelets.[7] It regulates important biological functions, including platelet aggregation, vascular permeability, smooth muscle contraction, and hypotension,[8] and is implicated in a number of debilitating conditions. Inhibition of the binding of PAF to its receptor or inhibition of its production offers a potential treatment for a number of inflammatory and respiratory diseases (e.g., asthma) and scope in organ transplant rejection.

Among the known phomactins, phomactin D (**8**) has been found to exhibit the highest level of PAF antagonism.[2c] Several other interesting natural products show PAF antagonist activity, including the diterpenes ginkgolide A (**16**), isolated from the Chinese tree *Ginkgo biloba* L.,[9] and forskolin (**17**), isolated from the roots of *Coleus forskholii*,[10] as well as several lignans, for example, kadsurenone (**18**) isolated from the plant *Piper futokadsurae*.[11]

Biosynthetic Interrelationships among the Phomactins and with the Taxanes

The phomactins share an interesting structural homology, and thus biosynthesis, with the taxane family of natural products, compare taxadiene, **4**. In fact, it has been established that both families of natural products are derived biosynthetically from geranylgeranyl diphosphate (GGDP, **19**) via a common biosynthetic intermediate, the verticillenyl carbocation **21** (Scheme 1).[4,12] Thus, macrocyclization of GGDP **19** first leads to the macrocyclic ("cembrane") carbocation **20**, which then suffers transan-

Scheme 1. Structural Homology and Biogenetic Connection between the Phomactins and the Taxanes



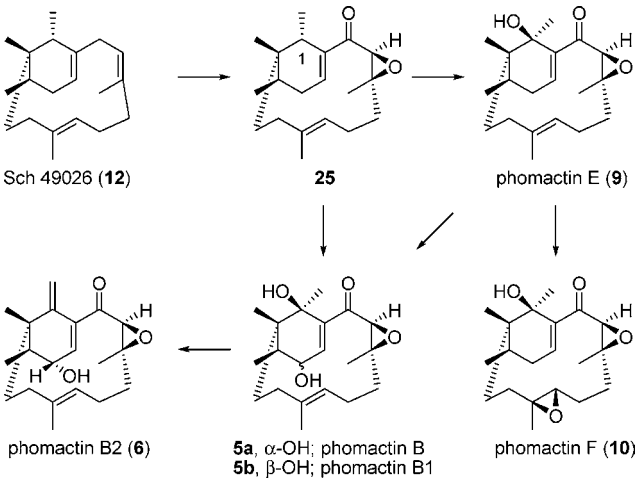
nulation leading to the verticillenyl carbocation **21**. The carbocation **21** then undergoes one of two possible modes of reaction, leading ultimately to either the phomactins or the taxanes. Thus, an intramolecular proton transfer in **21**, followed by a transannulation of the newly formed carbocation **23** leads to taxadiene **4**. A series of controlled enzymatic oxidations and substitution steps then ultimately leads to Taxol (**22**). In an alternative pathway (Scheme 1), a sequence of 1,2-hydride and 1,2-methyl shifts in the verticillenyl cation **21** first leads to the carbocation intermediate **24**, which then undergoes 1,2-hydride shift followed by elimination of a proton, leading to the phomactatriene **12** (Sch 49026).

The relative stereochemistries of the three contiguous methyl groups in Sch 49026 (**12**) were originally assigned the syn,syn stereochemistry.[2b] However, Oikawa and coworkers later noted that the β-stereochemistry originally assigned to the C-1 methyl group in **12** was not consistent with that found in phomactin E (**9**).[12] Hydroxylations of secondary metabolites in vivo, by cytochrome P450 or flavin monooxygenases, usually proceed with retention of configuration,[13] which suggested that the stereochemistry shown in **9** could not be derived from the stereostructure originally assigned to **12**. Subsequently, Oikawa and coworkers carried out biosynthetic incorporation experiments using ^{13}C-labeled precursors, which led them to propose a cyclization mechanism for the conversion of GGDP **19** into **12**, via **21**. They also re-isolated the hydrocarbon **12** and assigned its configuration at C-1 following NOE experiments. Based on these experiments, the three contiguous methyl groups in **12** were therefore assigned the revised syn,anti stereochemical relationship (see Scheme 1).

The connection between the phomactins and the taxanes extends beyond their structural and biosynthetic relationship. The phomactins inhibit the PAF receptor, which, for example, causes the formation of F-actin,[14] a filamentous structure that gives cells their characteristic shape. Taxol on the other hand stabilizes microtubules,[15] a filamentous structure important for cell division. Both families of natural products therefore have an effect on the cell cytoskeleton leading to changes in the shape and structure of the cell, as well as its ability to divide.

The phomactatriene **12** (Sch 49026) is the first logical and identifiable biosynthetic precursor to other oxygenated phomactins. Thus, it is likely that a sequence of enzymatic oxidations of the phomactatriene **12** first leads to the hypothetical intermediate **25** or to phomactin C (**7**) (Scheme 2). A stereoselective hydroxylation at C-1 in **25** would next lead to phomactin E (**9**), which could then act as a common biosynthetic intermediate to several other phomactins. For example, allylic hydroxylation of **9**, on the cyclohexene ring, would lead to the phomactins B (**5a**) or B1 (**5b**). Alternatively, the phomactins B and B1 could be formed directly from the epoxyketone **25** via selective and sequential hydroxylations. Regioselective dehydration of phomactin B (**5a**) would then lead to phomactin B2 (**6**). It is likely that phomactin F (**10**) is formed from phomactin E (**9**) by selective epoxidation of

Scheme 2. Plausible Biogenetic Connections between the Phomactins 5, 6, 9, 10, and 12



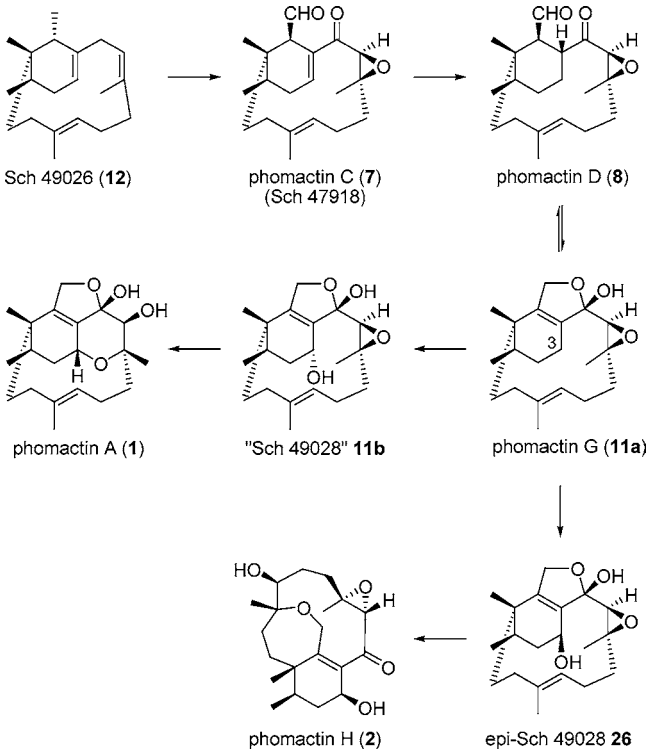
the more electron-rich carbon−carbon double bond. In fact, treatment of phomactin E with *m*-CPBA in vitro has been found to produce phomactin F directly.[2d] This observation suggests that the stereoselectivity of the β-epoxidation is directed by the preferred conformation of the substrate.

The remaining phomactins, that is, phomactins A, G, and H, most likely arise via an alternative pathway, starting with the selective oxidation of the phomactatriene **12** leading to phomactin C (**7**), also known as Sch 47918. A stereoselective 1,4-reduction of the enone in **7** would next lead to phomactin D (**8**), which we have proposed in an earlier publication to exist in an equilibrium with phomactin G (**11a**) (Scheme 3).[6d] Stereoselective allylic oxidation of **11a** at C-3 would then lead to the alcohol **11b**, which is also a natural product known as Sch 49028. The epoxy alcohol **11b** would then be expected to undergo pyran ring formation with simultaneous opening of the epoxide leading to phomactin A (**1**). Our own total synthesis of phomactin A, which is described later, uses a similar protocol lending credence to this proposed biosynthetic pathway.[6a,c]

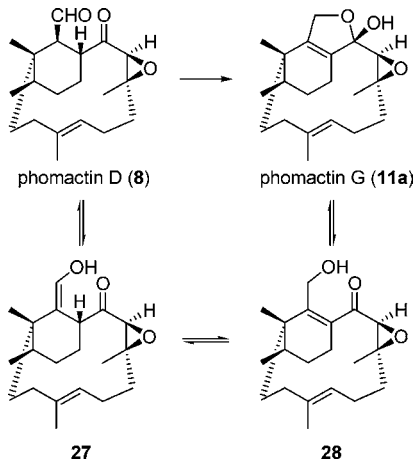
The structural homology between phomactins D (**8**) and G (**11a**), and their possible interconversion, merits some further discussion. Both structures are at the same oxidation level, and tautomerization of phomactin D (**8**) to the enol **27**, followed by an, albeit demanding, isomerization to the allylic alcohol **28**, and then cyclic hemiketal formation ultimately produces phomactin G (**11a**) (Scheme 4). The phomactins D and G have been the targets of successful total syntheses,[6d,16] but the connection between them has not been proven experimentally. In Scheme 3, we have proposed that phomactin G (**11a**) is the likely biosynthetic precursor to phomactin A via the α-allyl alcohol **11b** (Sch 49028).

Phomactin H (**2**) was isolated from an unidentified marine fungus (MPUC 046) living in a symbiotic relationship with the marine algae *Ishige okamurae* collected at Tateishi, Kanagawa Prefecture, Japan.[3] What is intriguing about phomactin H is that MPUC 046 is not closely related on a molecular phylogenetic tree to *Phoma* sp., the fungus

Scheme 3. Plausible Biogenetic Connections between the Phomactins 2, 7, 8, 11, and 12



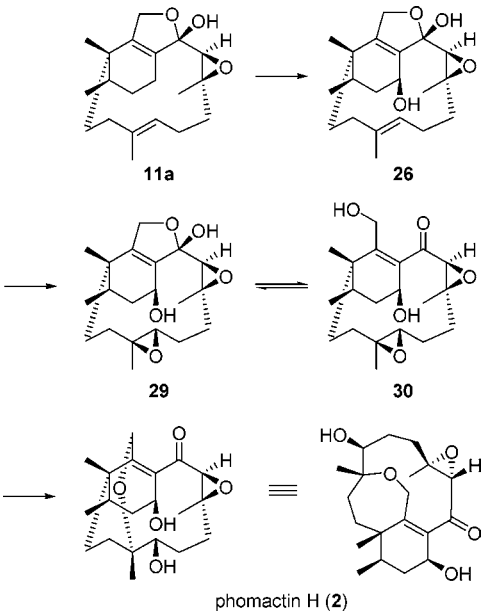
Scheme 4. Interconversion of Phomactins D and G



from which all other phomactins have been isolated. The novel structure of **2**, which contains an oxepane moiety and the unique phomactin skeleton, was determined by single-crystal X-ray diffraction analysis.

It is possible that phomactin H (**2**), similar to phomactin A (**1**), also has its origins in phomactin G (**11a**). Thus, enzymatic oxidation of phomactin G to the allyl alcohol **26**, compare the epimeric allyl alcohol **11b**, followed by a stereoselective epoxidation of the trisubstituted double bond, would lead to the bis-epoxide **29** (Scheme 5). The stereochemical outcome of the epoxidation step leading to **29** is similar to the conversion of phomactin E (**9**) into F (**10**)[2d] and is predicted based on the preferred conformation of **26**. The cyclic hemiketal **29** is in tautomeric equilibrium with the hydroxy ketone **30**. At this time, we suggest that the oxepane moiety in **2** is formed by

Scheme 5. Plausible Biosynthetic Pathway to Phomactin H (2) from Phomactin G (11a)



cyclization from the primary alcohol in **30** into the more substituted carbon of the proximate epoxide. A different order of events, that is, the oxidation to **26** and the epoxidation to **29**, could also apply. With this perspective, it is reasonable to assume therefore that phomactin G (**11a**) is a common intermediate in the biosynthesis of both phomactin A (**1**) and phomactin H (**2**). Interestingly, our research group synthesized the β-allylic alcohol **26** as part of an investigation into the structure of Sch 49028 (**11b**).[6b] It is conceivable therefore that structure **26** is a natural product waiting to be isolated.

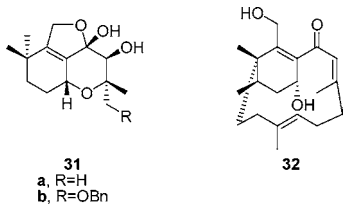
Some of the aforementioned structural and biogenetic interrelationships within the phomactin family of natural products have been suggested as a result of our investigations directed toward their total synthesis. These investigations, alongside those of others, are briefly summarized below.

Total Synthesis of Phomactin A (1) and other Phomactins

Phomactin A (**1**) was the first member of the phomactins to be characterized and remains the most structurally complex and synthetically demanding of this intriguing family of secondary metabolites. Nevertheless, despite considerable efforts over more than a decade, only two total syntheses of this demanding target have so far been described.[6a,c,17] A synthesis of phomactin D (**8**) was published by Yamada and co-workers in 1996,[16] and more recently our own group presented a synthesis of phomactin G (**11a**),[6d] which, as mentioned earlier, is related structurally to phomactin D by way of tautomerism and isomerization (see Scheme 4).

Any synthetic approach toward phomactin A (**1**) has needed to establish methodology for forming the macrocyclic portion of the oxygenated bicyclo[9.3.1]pentadecane

ring system **32**, together with elaboration of the unusual



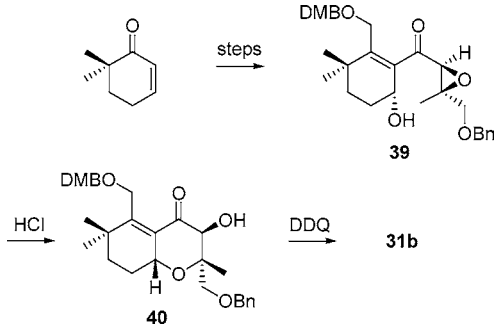
31
a, R=H
b, R=OBn

32

tricyclic furanochroman core **31** (cf. **15**) within this structure.

In some of our own early studies, we developed a synthesis of the furanochroman core **31a** in phomactin A, which we based on rudimentary biogenetic considerations.[18] Thus, the allylic alcohol intermediate **35** was first elaborated in six straightforward steps from the vinylogous ester **33**, proceeding via the derivative **34** (Scheme 6). Deprotection of the methoxymethyl (MOM) ether **35** with camphor sulfonic acid next gave the dihydrofuran **36**, which was then reduced using DIBAL-H at −78 °C leading to the alcohol **37**. The furanochroman **38** was now produced from **37**, after treatment with phenylselenyl chloride, followed by oxidation and base-catalyzed elimination of the resulting phenylselenide. Finally, treatment of the enol ether **38** with dimethyldioxirane gave a mixture of *syn*- and *anti*-vicinal diols, from which the *syn*-(*β*,*β*)-diol **31a** could be separated by chromatography. Much later, Mohr and Halcomb described a similar approach to the furanochroman core **31b** in phomactin A,[19] whereby the epoxide intermediate **39**, produced from 6,6-dimethylcyclohex-2-enone, was first cyclized to the corresponding pyrone **40** in the presence of dilute HCl, which, on deprotection of the 3,4-dimethoxybenzyl (DMB) ether, gave spontaneously the dihydrofuran diol **31b** (Scheme 7).[20]

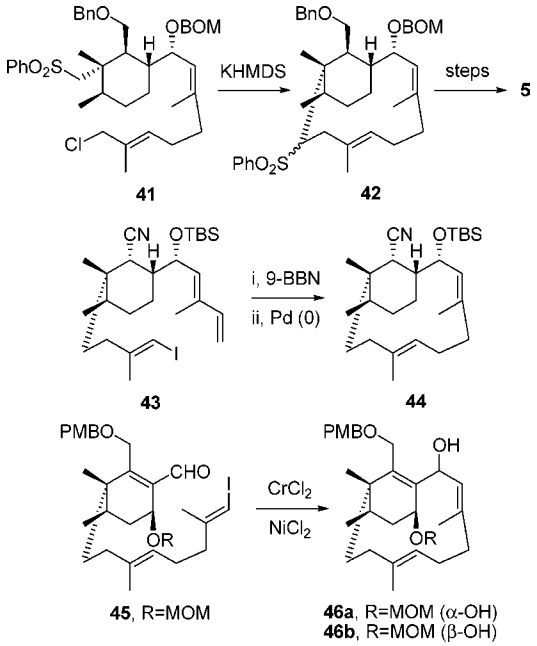
Scheme 7. Assembly of the Furanochroman 31b (from ref 19)



39

40

Scheme 8. Assembly of the Bicyclo[9.3.1]pentadecane Ring System 46 (from refs 16, 24, and 26)



41

42

43

44

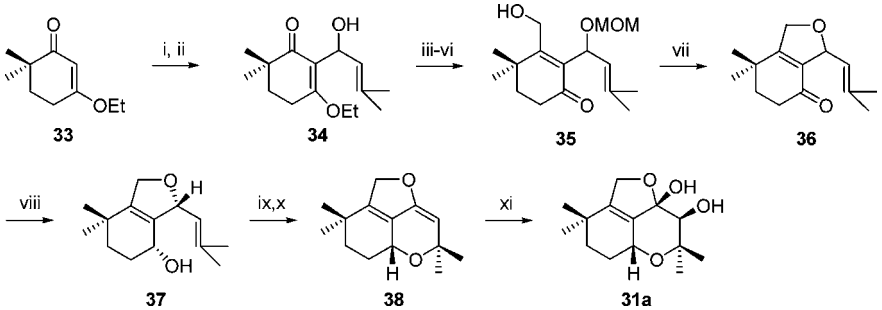
45, R=MOM

46a, R=MOM (α-OH)
46b, R=MOM (β-OH)

A wide variety of synthetic designs have been explored to elaborate the macrocyclic portion of the bicyclo[9.3.1]-pentadecane unit **32**. For example, in their synthesis of phomactin D (**8**), Yamada and co-workers[16] prepared the phenyl sulfone intermediate **41** and showed that it underwent macrocyclization in the presence of potassium hexamethyldisilazane (KHMDS) at room temperature producing **42** which, in three further steps, could be converted into the natural product (Scheme 8). A similar intramolecular sulfone alkylation strategy has also been used by Thomas and co-workers in their approach to the phomactins.[21]

Both intramolecular Pd-catalyzed Suzuki[22] and chromium(II)-mediated Nozaki−Hiyama−Kishi (NHK)[23] coupling reactions have featured prominently in the recent literature, including studies among the phomactins. Thus, in contemporaneous synthetic studies Halcomb[24] and Danishefsky[25] and their respective colleagues have described the use of the intramolecular *β*-alkyl Suzuki

Scheme 6[a]



33

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37

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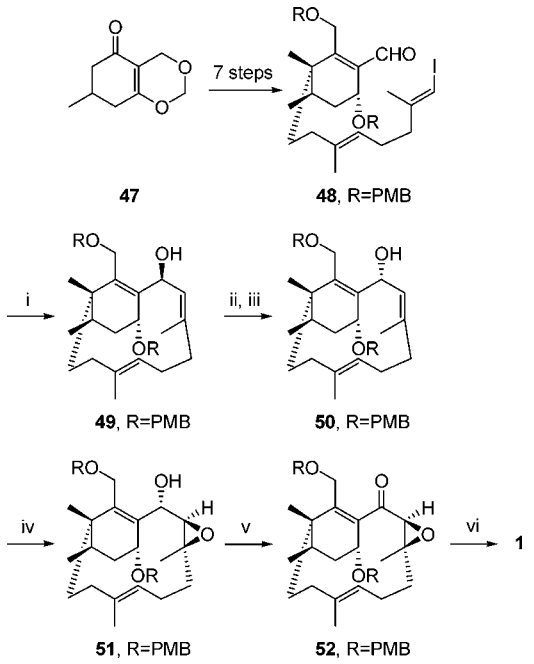
31a

[a] Reagents and conditions: (i) NBS, CCl_4, rt, 70%; (ii) *t*-BuLi, THF, −78 °C; then 3-methylbutenal, −78 °C, 56%; (iii) MOMCl, *i*-Pr_2EtN, CH_2Cl_2, 40 °C, 90%; (iv) $TMSCH_2Li$, Et_2O, 0 °C; (v) KH, THF, rt, 89% (two steps); (vi) *m*-CPBA, EtOH, rt, 31%; (vii) CSA, CH_2Cl_2, rt, 91%; (viii) *i*-Bu_2AlH, PhMe, −78 °C, 46%; (ix) PhSeCl, K_2CO_3, CH_2Cl_2, −78 °C, 79%; (x) *m*-CPBA, CH_2Cl_2, 0 °C; then THF, KOH, 65 °C; (xi) DMDO, Me_2CO, H_2O, 22% (two steps) (from ref 18).

Scheme 9. Pattenden's Total Synthesis of (±)-Phomactin A (1)[a]

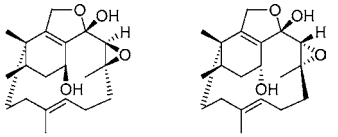


[a] Reagents and conditions: (i) $CrCl_2$ (6 equiv), $NiCl_2$ (1 equiv), DMSO, THF, rt, 58%; (ii) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 0 °C to rt, 97%; (iii) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH, CH_2Cl_2, −78 °C to 0 °C, 96%; (iv) $VO(acac)_2$, *t*-BuOOH, PhH, rt, 86%, ca. 1:1 (**51** and bis-epoxide); (v) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 0 °C to rt, 80%; (vi) DDQ, CH_2Cl_2–H_2O (18:1), 0 °C to room temperature, 83% (from refs 6a and 6c).

reaction from an appropriate terminal alkene–terminal vinyl iodide precursor to synthesize the macrocyclic ring in the phomactins, for example, **43** → **44**. In other contemporaneous investigations, our own research group was the first to report the scope for the intramolecular NHK reaction in elaboration of the oxygenated bicyclo-[9.3.1]pentadecane ring system in phomactin A,[26] namely, **45** → **46**, and the same strategy was also used by Mi and Maleczka to synthesize precursors for elaboration to phomactin C and D analogues.[27] Other synthetic approaches that have been described toward the macrocyclic portion of **32** include a Pd-catalyzed carbonylative alkyne enol triflate coupling,[28] ring-closure metathesis,[26] and an interesting intramolecular oxa-[3 + 3] cycloaddition involving an α,β-unsaturated iminium salt tethered to a 1,3-diketone.[29]

In 2002, our research group published the first total synthesis of phomactin A (**1**),[6a] capitalizing on the earlier model work we had developed toward the two main structural units **31** and **32** embedded in its structure.[18,26] Thus, the pivotal aldehyde vinyl iodide intermediate **48** was first elaborated in seven straightforward steps from the easily available dioxin **47** (Scheme 9). Treatment of **48** under NHK coupling conditions, that is, Cr(II)/Ni(II), next led to the oxygenated bicyclo[9.3.1]pentadecane **49** ("phomactin") with, unfortunately, the incorrect β-OH stereochemistry at the newly introduced stereogenic center. Following inversion of this center to the corresponding α-OH stereochemistry, that is **50**, epoxidation using $VO(acac)_2$-*t*-BuOOH then led to the required β-epoxide **51**, which was smoothly oxidized to the corresponding epoxyketone intermediate **52**. Finally, treatment of **52** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in CH_2Cl_2 resulted in simultaneous deprotection of the two PMB groups and spontaneous pyran cyclic hemiketal formation leading to phomactin A (**1**) in a single step.[6a,c] Significantly, we were not able to obtain any evidence for either the formation or intermediacy of the structure **11b**, known as Sch 49028 and purported to be a natural phomactin, during the conversion of **52** into phomactin A in our studies. By chance, however, when we recorded the ^1H NMR spectrum of our synthetic (±)-phomactin A in $CDCl_3$ instead of CD_3OD, the chemical shift data were found to be identical with those reported for the mystery natural Sch 49028 whose ^1H NMR data were also recorded in $CDCl_3$.[2b] We concluded therefore that the phomactin Sch 49028 has no independent existence in nature and that it was incorrectly assigned in the literature. Indeed it is identical with phomactin A which, shows small differences in the chemical shift data when its ^1H NMR spectrum is measured in $CDCl_3$ rather than in CD_3OD.

As a corollary to our studies with phomactin A (**1**), we carried out further synthetic studies in pursuit of the "mystery Sch 49028" structure **11b** and prepared the isomeric structures **26** and **53**.[6b] Perhaps not too much



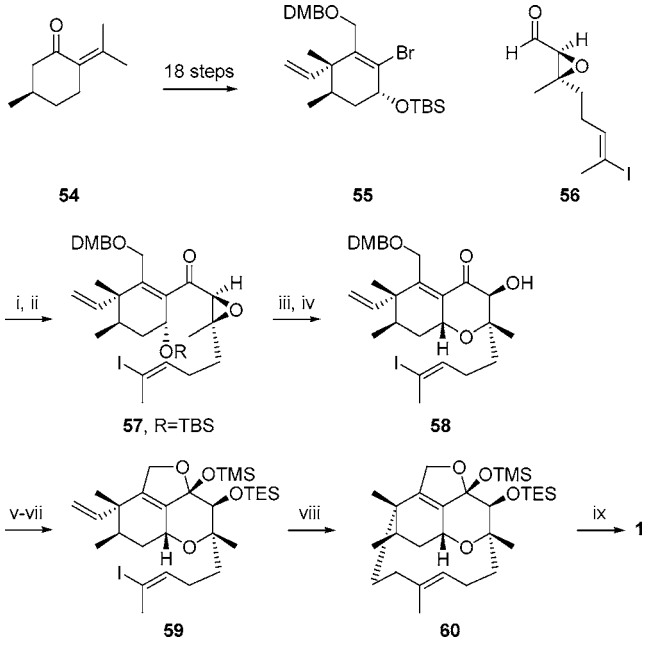
to our surprise, neither of these structures showed spectroscopic data consistent with those reported for the purported Sch 49028 natural product, and neither could be induced to undergo pyran and other oxygen ring formation leading to phomactin structures analogous to phomactin A.

In contemporaneous work, Mohr and Halcomb built on their model studies, which led to synthesis of the furanochroman **31b**[19] and the macrocyclic ring system **44**,[24] and developed a total synthesis of nonracemic phomactin A (**1**), which they published in preliminary form in 2003.[17] Thus, in 18 steps, starting from commercial *R*-(+)-pugelone **54**, the vinyl bromide **55** was first prepared, which was then coupled to the epoxy-aldehyde **56** produced from geraniol, ultimately leading to the ketone **57** following oxidation of the newly formed secondary alcohol (Scheme 10). Deprotection of the silyl ether group in **57** followed by acid-catalyzed cyclization next produced the hydroxy-pyranone **58**. Manipulation of protecting groups in **58**, with concomitant cyclic hemiketal ring formation ultimately gave the key intermediate **59**. Regioselective hydroboration of **59**, using 9-borabicyclo[3.3.1]-nonane (9-BBN), followed by Suzuki coupling then gave the phomactin core **60**, which on removal of the silyl ether protecting groups produced (+)-phomactin A (**1**).

PAF Activity of the Phomactins

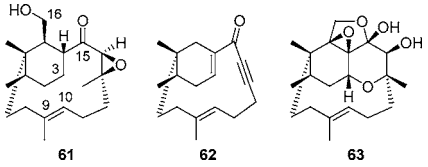
Following the isolation of the phomactins, a small number of biological activity studies of related phomactin struc-

Scheme 10. Halcomb's Total Synthesis of (+)-Phomactin A (1)[a]



[a] Reagents and conditions: (i) *t*-BuLi, −78 °C; then **56**; (ii) Dess−Martin periodinane, 45% (over two steps); (iii) TBAF, 91%; (iv) 1% HCl, *tert*-amyl alcohol, 65%; (v) TES−Cl, 83%; (vi) DDQ, 87%; (vii) TMS−OTf, py, 0 °C, 81%; (viii) 9-BBN, THF, 40 °C; then H_2O; $Pd(dppf)Cl_2$, $AsPh_3$, Tl_2CO_3, 6:3:1 THF/DMF/H_2O, rt, 37%; (ix) TBAF, 78% (from ref 17).

tures were reported. Thus, Sato and co-workers synthesized a number of analogues of phomactin C (**7**), for example, **61**, and observed an interesting pattern in the



structure−activity relationship for the binding of PAF to its receptors.[30] In general, higher levels of activity were observed when (a) the lipophilicity of the C-9/C-10 carbon−carbon double bond was preserved, (b) the carbonyl group at C-15 was reduced to a secondary alcohol with the β-stereochemistry, and (c) oxygen atom at C-16 was substituted. Rawal and co-workers also conducted some PAF binding studies with synthetic intermediates related to phomactins C and D.[31] They found that the presence of a carbon−carbon double bond in the six-membered ring marginally increased the PAF activity. Furthermore, the presence of a carbon−carbon triple bond in the larger ring, as in structure **62**, led to an increase in the PAF activity relative to the analogous compounds with either a single or double bond at the same position. Our group in Nottingham also examined a range of phomactin structures, such as **26**, **53**, and **63**, relative to phomactins A and G for their ability to inhibit the binding of PAF to its receptors.[32] Interestingly, we found that the activities of the analogues were very similar to those of the natural phomactins, indicating that changes to the stereochemistry of, for example, the epoxide and the C-3 secondary alcohol groups within the compounds examined made little difference to the magnitude of their biological activity.

Conclusions and Perspective

The PAF antagonism properties associated with the phomactins, together with their structural complexity and structural homology with the taxanes, have prompted a number of research groups around the globe to study the biosynthesis, the total synthesis, and the biological activity of this important family of natural products. At the present time, the only members of this family to yield to total synthesis are phomactins A (**1**), D (**8**), and G (**11a**). These synthetic studies have provided insight into many of the structural and biogenetic interconnections within this intriguing family of natural products, complementing recent biosynthetic investigations.

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