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A Nozaki–Hiyama–Kishi Ni(II)/Cr(II) Coupling Approach to the Phomactins

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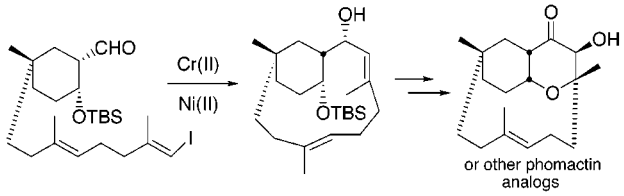
ABSTRACT



Through a unified synthetic strategy, appropriately functionalized bicyclic starting materials can be elaborated via Ni(II)/Cr(II) macrocylization to [9.3.1] bicycles. Elaboration of these core structures allows access to phomactin C/D analogues and establishes the first synthetic approach to phomactin A affording an intact octahydrochromene/macrocyclic ring system.

Several years ago, the phomactins[1] (Figure 1), including the structurally novel macrocycle phomactin A (**1**), were isolated

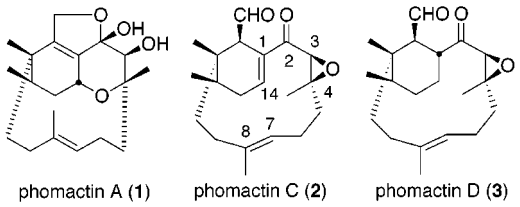


Figure 1. Representative phomactins.

from the marine fungus *Phoma* sp.[1] These metabolites have demonstrated marked biological properties, particularly platelet activating factor (PAF) antagonistic activities. Platelet activating factor (1-*O*-alkyl-2(*R*)-(acetylglyceryl)-3-phosphorylcholine) is a phospholipid mediator that is released by several cell types upon stimulation and which acts through specific receptors found on platelets, neutrophils, endothelial cells, and other cell types.[2] PAF induces a wide range of biological effects and has been implicated as an important mediator in platelet aggregation, hypotension,[3] smooth muscle contraction, and vascular permeability. Recent studies have shown PAF to contribute to chemotaxis and degranulation of polymorphonuclear leukocytes, indicating possible involvement in septic shock[4] and ischemia/reperfusion injury,[5] as well as inflammatory, respiratory,[6] and cardiovascular diseases.[6,7]

Interestingly, while phomactin A inhibits PAF-induced platelet aggregation, no effect on adenosine diphosphate, arachidonic acid, or collagen-induced platelet aggregation is observed. Thus phomactin A is a new type of PAF antagonist. Furthermore, phomactin D has been shown to possess 10−100 times the activity of other phomactins, inhibiting PAF-induced platelet aggregation with an IC_{50}

(1) (a) Phomactin A: Sugano, M.; Sato, A.; Iijima, Y.; Oshima, T.; Furuya, K.; Kuwano, H.; Hata, T.; Hanzawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 5463−5464. (b) Phomactins B−D: Sugano, M.; Sato, A.; Iijima, Y.; Furuya, K.; Haruyama, H.; Yoda, K.; Hata, T. *J. Org. Chem.* **1994**, *59*, 564−569. (c) Phomactin C: Chu, M.; Patel, M. G.; Gullo, V. P.; Truumees, I.; Puar, M. S.; McPhail, A. T. *J. Org. Chem.* **1992**, *57*, 5817−5818.

(2) Koltai, M.; Braquet, P. G. *Clin. Rev. Allergy* **1994**, *12*, 361−380.

(3) (a) Goldstein, R. E.; Feuerstein, G. Z.; Bradley, L. M.; Stambouly, J. J.; Laurindo, F. R. M.; Davenport, N. J. *Lipids* **1991**, *26*, 1250−1256. (b) Rabinovici, R.; Yue, T.-L.; Feuerstein, G. *Lipids* **1991**, *26*, 1257−1263.

(4) Heuer, H. *Lipids* **1991**, *26*, 1369−1373.

(5) (a) Bazan, N. G.; Squinto, S. P.; Braquet, P.; Panetta, T.; Marcheselli, V. L. *Lipids* **1991**, *26*, 1236−1242. (b) Uchiyama, S.; Yamazaki, M.; Maruyama, S. *Lipids* **1991**, *26*, 1247−1249.

(6) (a) Chung, K. F.; Barnes, P. J. *Lipids* **1991**, *26*, 1277−1279. (b) Page, C. P. *Lipids* **1991**, *26*, 1280−1282.

(7) (a) Godfroid, J. J.; Dive, G.; Lamotte-Brasseur, J.; Batt, J. P.; Heymans, F. *Lipids* **1991**, *26*, 1162−1166. (b) Lamotte-Brasseur, J.; Heymans, F.; Dive, G.; Lamouri, A.; Batt, J. P.; Redeuilh, C. *Lipids* **1991**, *26*, 1167−1171.

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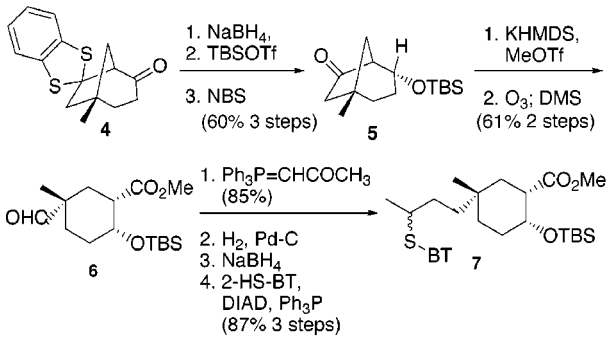
value of 8.0×10^{-7} M and inhibiting the binding of PAF to its receptors with an IC_{50} value of 1.2×10^{-7} M.[8]

Synthetic and natural PAF antagonists have also greatly facilitated molecular modeling of the PAF receptor.[6−8] Such factors, combined with the synthetic challenge of constructing the macrocyclic furochroman ring[9] unique to phomactin A, have made these compounds intriguing synthetic targets.[9,10]

With respect to prior synthetic work, Yamada and coworkers have completed the sole total synthesis of a phomactin, using an intramolecular sulfone alkylation to form the macrocycle during their construction of phomactin D (**3**).[10a] More recently, Halcomb and Kallan established a Suzuki macrocylization approach to this target.[10b] As for phomactin A, Totah[9c] has efficiently built the furochroman ring moiety, while in two reports, Pattenden described a synthesis of the tricyclic core[9b] and most recently their own[9a,11] Nozaki−Hiyama−Kishi (NHK)[12] Ni(II)/Cr(II) based approach to an oxygenated bicyclo [9.3.1]pentadecane ring system. However, to the best of our knowledge, a phomactin A approach that demonstrates the construction of a model compound containing both the octahydrochromene and macrocyclic core has not been described, nor have previous approaches shown how oxygenation levels of the various model compounds can be manipulated to allow a common route to more than one target phomactin. Thus, our aim was to develop a unified divergent synthetic strategy for the elaboration and study of phomactins A−D and allied pharmacophores.

Our approach began with the $NaBH_4$ reduction of ketone **4**,[13] which furnished the corresponding alcohol as a single stereoisomer (Scheme 1).[14] After protection with TBSOTf, the benzodithiane group was removed upon oxidation with NBS.[15,16] Resultant ketone **5** was then converted to its methyl enol ether with KHMDS/MeOTf. As this enol ether proved unstable to silica gel, it was ozonolyzed crude, providing aldehyde ester **6** in reasonable overall yield. Wittig olefination of **6** exclusively gave the *trans* enone. Selective

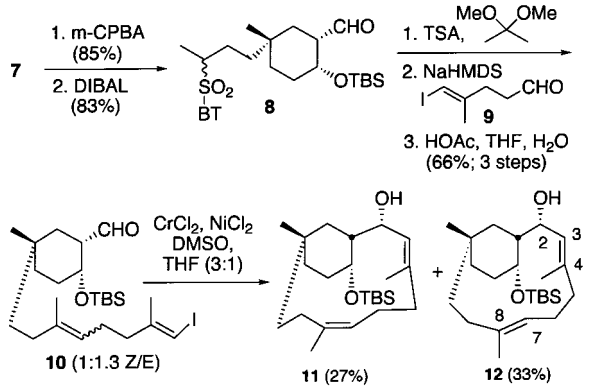
Scheme 1



saturation of that enone was carried out without chromatographic purification, setting the stage for Mitsunobu substitution with 2-mercaptobenzothiazole (2-HS-BT).[17] Thus sulfide **7** was obtained from aldehyde **6** in 74% yield over four steps.

Sulfide **7** was oxidized to the sulfone with mCPBA, after which a DIBAL reduction at −78 °C was carried out to afford aldehyde **8** in good yield (Scheme 2). The aldehyde

Scheme 2



was protected as its dimethyl acetal, which was used crude in a Julia olefination with **9**. Deprotonation of the crude sulfone with NaHMDS was followed by the addition of vinyl iodide aldehyde **9**.[18] After coupling, the crude olefination product was then stirred in a mixture of AcOH/THF/H_2O (3:1:1), freeing aldehyde **10**, which existed as an unseparable mixture of geometric isomers. The ratio and stereochemistry of the isomers were assigned according to ^{1}H NMR and NOE experiments.[19] It was discovered that performing the Julia reaction in DMF favored production of the undesired *Z*-olefin ($E/Z = 1{:}2$), whereas in DME the reaction is slightly selective

(8) Sugano, M.; Sato, A.; Saito, K.; Takaishi, S.; Matsushita, Y.; Iijima, Y. *J. Med. Chem.* **1996**, *39*, 5281−5284 and references therein.

(9) (a) Foote, K. M.; John M.; Pattenden, G. *Synlett* **2001**, 365−368. (b) Foote, K. M.; Hayes, C. J.; Pattenden, G. *Tetrahedron Lett.* **1996**, *37*, 275−278. (c) Seth, P. P.; Totah, N. I. *Org. Lett.* **2000**, *2*, 2507−2509. (d) Seth P. P.; Chen D. Q.; Wang J. Q.; Gao X. C.; Totah N. I. *Tetrahedron* **2000**, *56*, 10185−10195. (e) For a suggested approach to phomactin A, see: Chemler, S. R.; Danishefsky, S. J. *Org. Lett.* **2000**, *2*, 2695−2698.

(10) (a) Miyaoka, H.; Saka, Y.; Miura, S.; Yamada, Y. *Tetrahedron Lett.* **1996**, *37*, 7107−7110. (b) Kallan, N. C.; Halcomb, R. L. *Org. Lett.* **2000**, *2*, 2687−2690.

(11) The *Synlett* issue containing ref 9a was received several weeks after submission of this manuscript.

(12) (a) Fürstner, A. *Chem. Rev.* **1999**, *99*, 991−1046. (b) Stamos, D. P.; Sheng, X. C.; Chen, S. S.; Kishi, Y. *Tetrahedron Lett.* **1997**, *38*, 6355−6358.

(13) From methacrolein (three steps, 40% overall yield): Rigby, J. H.; Kotnis, A.; Kramer, J. *J. Org. Chem.* **1990**, *55*, 5078−5088.

(14) (a) The structure assigned to each new compound is in accord with its infrared, 300- or 500-MHz ^{1}H NMR, and 62.5- or 125-MHz ^{13}C NMR spectral data, as well as satisfactory combustion analysis, and/or appropriate ion identification by high-resolution mass spectrometry. See Supporting Information for details. (b) The stereochemical assignment of **5** was supported by NOE experiments and in accord with literature models (Watanabe, H.; Mori, K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2919−2934).

(15) Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, *36*, 3553−3560.

(16) The benzodithiane could not be deprotected by a number of other methods including treatment with $CH_3I/CaCO_3$, $PhI(CO_2CF_3)_2$, or HgO/BF_3·OEt_2.

(17) (a) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Tetrahedron Lett.* **1991**, *32*, 1175−1178. (b) Blakemore, P. R.; Kocienski, P. J.; Marzcak, S.; Wicha, J. *Synthesis* **1999**, *32*, 1209−1215. (c) Williams, D. R.; Coleman, P. J.; Nevill, C. R.; Robinson, L. A. *Tetrahedron Lett.* **1993**, *34*, 7895−7898.

(18) (a) Roush, W. R.; Barda, D. A. *Tetrahedron Lett.* **1997**, *38*, 8781−8784. (b) Zheng, Y. F.; Oehlschlager, A. C.; Hartman, P. G. *J. Org. Chem.* **1994**, *59*, 5803−5809.

(19) See Supporting Information for details.

toward *E*-olefination (*E*/*Z* = 1.3:1). In other solvents such as THF, Et_2O, or toluene or when other bases such as KHMDS or LiHMDS were utilized, the overall reaction yield of the three-step sequence dropped below 40%.

With **10** in hand, we looked at the critical macrocyclization via a NHK Ni(II)/Cr(II) coupling.[12] In practice, this approach proved quite rewarding. The yield and reaction speed of the NHK coupling was sensitive to the reaction media. With a mixture of DMF and either THF or DMSO as solvent the starting material was consumed fairly quickly (2−4 h), but macrocycle yields tended to be low. In DMSO/THF[20] (3:1), higher yields (60%) were obtained, although the reaction usually took about 24 h to reach a reasonable conversion rate (25% of **10** recovered[21]).

The *Z*-isomer of **10** was found to be slightly more reactive than the *E*-isomer. When a 2:1 *Z*/*E* mixture of isomers was subjected to the NHK coupling, **11** and **12** were formed as in a ratio of 3:1, while a 1:1.3 *Z*/*E* mixture afforded a 1:1.2 mixture of **11** and **12**. Importantly, **11** and **12** were readily separable by column chromatography. Interestingly, the NHK macrocyclization was highly stereoselective in forming the resultant carbinols. The exact structures of **11** and **12** were initially assigned according to their ^1H NMR and NOE data, with single-crystal X-ray analysis of both isomers providing the final confirmation of their structures.[19] The observed *anti*-Felkin stereoselectivity is perhaps due to steric and/or dipole repulsion from the TBS ether forcing the carbonyl into an orientation (B) that gives rise to the observed stereochemistry (Figure 2).

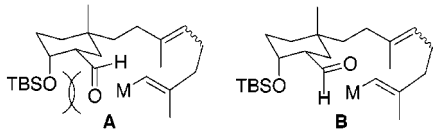
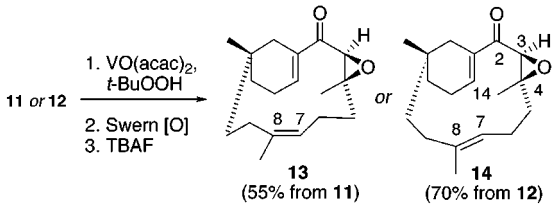


Figure 2.

With respect to the Ni(II)/Cr(II), 8.0 equiv of $CrCl_2$ containing 0.5−1% of $NiCl_2$ or $Ni(acac)_2$ was found to be optimal, with lesser amounts (4 equiv) of $CrCl_2$ lowering the conversion rate. We also found Kishi's sodium *d*,*l*-serinate workup[12b] to be exceptionally effective for sequestering chromium ion. Unfortunately, the reported benefits of 4-*tert*-butylpyridine as an additive were not observed.[12b]

With the macrocylization complete, we next sought to convert **12** into analogues of phomactins C (**2**) and D (**3**). Selective $VO(acac)_2$-mediated *t*-BuOOH epoxidation[22] of **12** proceeded in excellent yield at ambient temperature (Scheme 3). The ease of C(3)−C(4) epoxidation indicated that the C(2)-hydroxyl is well positioned to direct the epoxidation toward the desired stereochemical outcome.[23] Indeed, the stereochemistry of the epoxide derived from **12** was supported by NOE experiments.[19] Oxidation of the C(2)-hydroxyl was surprisingly sluggish. Almost no reaction was observed with SO_3−pyridine complex or the Dess−Martin periodinane. Gratifyingly, oxidation under prolonged Swern conditions was successful.

Scheme 3. Preparation of Phomactin C/D Analogues

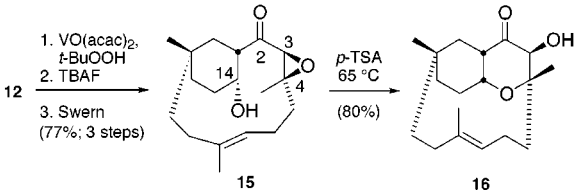


To make analogues of phomactin C (**2**) that were strategically viable intermediates in an approach to phomactin D (**3**), we sought to β-eliminate the TBS ether. Unfortunately, no elimination was observed when the β-keto ether was stirred with pyridine or DMAP for 48−52 h at room temperature, and reaction with stronger bases proved destructive. Thus it was decided to remove the TBS group and convert the resulting alcohol to the more labile mesylate. Surprisingly, reaction of the TBS ether with TBAF in THF at room temperature gave a small amount (∼25%) of β-elimination product **14** and its deconjugated isomers. Upon lowering the reaction temperature to 0 °C, the β-elimination product **14** was isolated in good yield, with no trace of the anticipated alcohol.

Because SAR studies on the C(7)−C(8) region of the phomactins were unable to examine the effect of olefin geometry,[8] we decided to exploit the formation of significant amounts of *Z*-olefin (**11**) during Julia olefination. The three-step conversion of **11** to **13** was uneventful (Scheme 3), affording the product in 55% overall yield, thus providing an additional model compound for screening of PAF antagonists.[24]

Turning our attention to a phomactin A analogue, we aimed to form the pyranyl moiety via intramolecular epoxide opening. Given our β-elimination results, it was decided that deprotection of the C(14) TBS ether should occur prior to oxidation at C(2). Thus, **12** was epoxidized as before and

Scheme 4. Preparation of a Phomactin A Analogue



(20) THF aided the solubility of **9**.

(21) Complete consumption of **10** occurred after 45 h, but the combined yield of **11** and **12** was only 29%.

(22) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136−6137.

(23) The nature of the phomactin skeleton makes representation of the relative stereochemistry through the use of wedged and dashed lines difficult and at time confusing. For example, refs 1b and 8 use dashed bonds for both the trans oriented C(3)-H and C(4)-Me groups of phomactins C (**2**), D (**3**), and allied structures.

then treated with TBAF to afford the diol (Scheme 4). Without chromatographic purification, the crude diol was subjected to Swern conditions. Oxidation occurred exclusively at the equatorially disposed C(2)-hydroxyl.[25] Heating the resultant C(14)-β-hydroxy ketone **15** in the presence of *p*-TSA effected the desired 6-exo cyclization, providing phomactin A analogue **16** in 80% yield. ^{1}H NMR and NOE studies indicated[19] that the reaction proceeded as mechanistically expected and without epimerization[26] at the C(1) position.

In summary, a unified synthetic approach to both (±)-phomactin A and (±)-phomactin C has been established. Starting with a readily available [3.2.1] bicyclic ketone, the macrocyclic core of the phomactins can be prepared via a highly stereoslective Ni(II)/Cr(II) macrocylization. This approach affords the phomactin C/D [9.3.1] bicycles in good yields. Selective epoxidation and functional group manipulation gives rise to phomactin C/D analogues and allied pharmacophores.[24] Further elaboration of the common [9.3.1] ring system provides the first synthetic approach to phomactin A affording an intact octahydrochromene/macrocyclic ring system. Studies aimed at adapting this general approach to the asymmetric syntheses of the natural products are underway and will be reported in due course.

(24) The results of biological testing will be reported elsewhere.

(25) Prolonged reaction with excess oxidant affords the diketone in 72% overall yield.

(26) AM1 semiempirical calculations suggest **16** to be ~10 kcal/mol lower in energy than its trans-fused isomer.

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Supporting Information Available: Spectroscopic data for all new compounds pictured, as well as detailed experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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