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Studies toward the Tricyclic Core of Phomactin A. Synthesis of the Reduced Furanochroman Subunit

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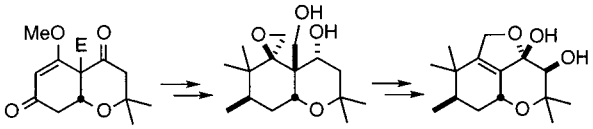
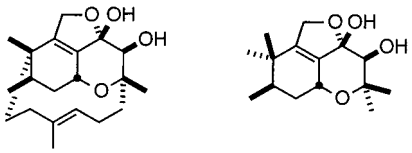
ABSTRACT



An approach to the tricyclic core of phomactin A is described via the synthesis of a reduced furanochroman model. Key elements of this study include the use of a highly functionalized 1-oxadecalone derivative as a template for the stereoselective introduction of functionality and a tandem retro aldol–epoxide opening–cyclization sequence for elaboration of the dihydrofuran ring.

Phomactin A (**1**)[1] is the most complex of a group of structurally related metabolites[2] that were recently isolated from the culture broth of *Phoma* sp. (SANK 11486). This unusual tetracyclic diterpene features a reduced furanochroman core, which is belted by a 12-membered macrocycle (Figure 1). Biological screening showed this compound to be a specific platelet activating factor (PAF) antagonist, inhibiting both PAF-induced platelet aggregation and binding of PAF to its receptors. This combination of unique molecular architecture and interesting biological properties led us to consider strategies for the preparation of this densely functionalized molecule.

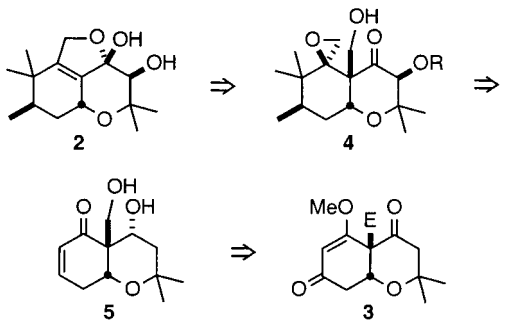


phomactin A (1) **2**

Figure 1. Phomactin A and tricyclic model system.

Our initial efforts in this area have focused on the synthesis of simplified derivatives such as **2** that represent the tricyclic core of the natural product.[3] In this regard, we anticipated that manipulation of a simple, readily available 1-oxadecalin subunit would allow an expediant entry to the basic phomactin skeleton.[4] Toward this end, preparation of the reduced furanochroman system **2** was anticipated from the readily available 1-oxadecalone derivative **3**[5] as outlined in Scheme 1.

Scheme 1



As shown, generation of the dihydrofuran ring (**2**) was envisioned at a late stage of the sequence from the hydroxy

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

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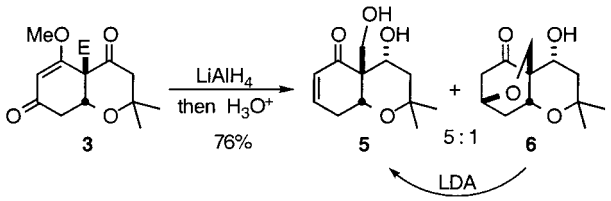
ketone **4** via retro aldol reaction and subsequent β-elimination of the resulting keto epoxide. In turn, stereoselective synthesis of this highly functionalized intermediate was anticipated from the cis-fused enone **5**, the conformational bias of which would provide a basis for stereochemical control.

In practice, reduction of oxadecalone **3** (E = CO_2Et) with $LiAlH_4$, followed by an acidic workup, provided the desired enone **5** in 64% yield, along with ca. 12% of the corresponding ether **6** that is formed via intramolecular conjugate addition of the primary hydroxymethyl function (Scheme 2).

Scheme 2

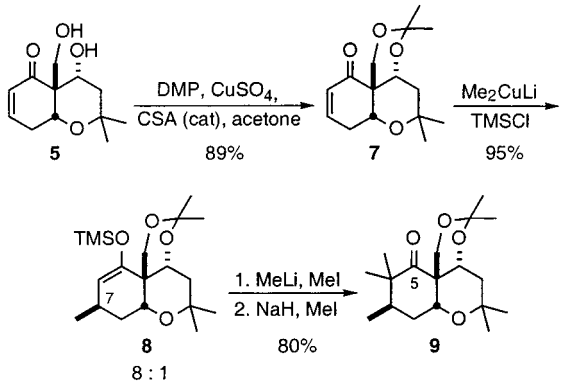


Formation of this impurity (**6**) occurs readily in the presence of acid, although its appearance can be minimized by careful control of the reaction conditions. In any event, this unwanted ether (**6**) can be cleanly recycled to the desired enone **5** upon treatment with LDA.

The diol unit of **5** was then protected as the corresponding acetonide **7**, with subsequent addition of Me_2CuLi in the presence of TMSCl[6] providing the silyl enol ether **8** as an 8:1 mixture of diastereomers (Scheme 3). Under these conditions, 1,4-addition occurs largely from the convex face to give the desired stereoisomer as the major product.[7] From here, sequential alkylation at C6 provides the *gem*-dimethyl derivative **9** in 80% yield over two steps.

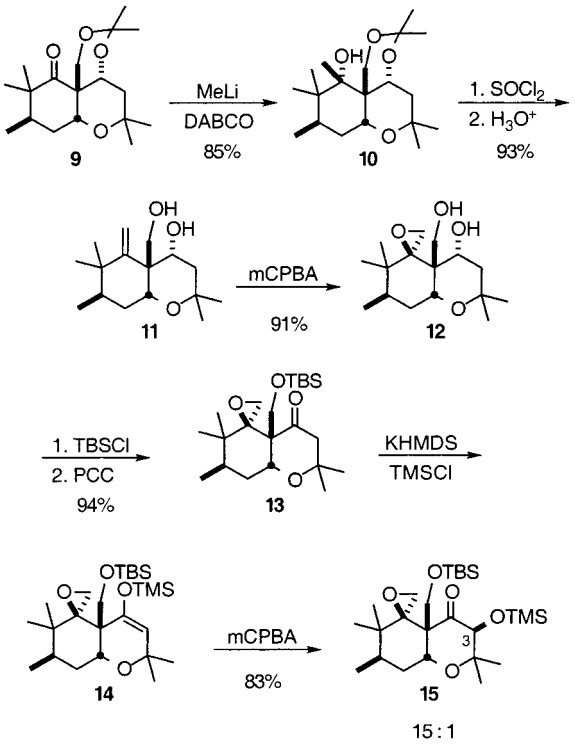
With the alkyl substituents of the carbocyclic ring in place, our next objective was methylenylation of the C5 ketone as a prelude to formation of the dihydrofuran ring. Though the steric environment of this ketone impeded attempts to effect this transformation directly, we were pleased to find that, in the presence of DABCO, MeLi adds cleanly to ketone **9** to

Scheme 3



give tertiary alcohol **10** in high yield and as a single diastereomer (Scheme 4). Subsequent elimination of the

Scheme 4



tertiary hydroxyl function ($SOCl_2$) and hydrolysis of the acetonide then provides diol **11** in high overall yield. From here, epoxidation of the exocyclic olefin with mCPBA proceeds in a highly stereoselective manner to give epoxide **12**, the stereochemistry of which was anticipated to be as shown based on the approach of the reagent from the more readily accessible convex face. Selective protection of primary alcohol **12** as the *tert*-butyldimethylsilyl (TBS) ether, followed by oxidation of the secondary alcohol at C4, provided ketone **13** which could be converted to the

(2) (a) Chu, M.; Patel, M. G.; Gullo, V. P.; Truumees, I.; Puar, M. S. *J. Org. Chem.* **1992**, *57*, 5817. (b) Chu, M.; Truumees, I.; Gunnarsson, I.; Bishop, W. R.; Kreutner, W.; Horan, A. C.; Gullo, V. P.; Puar, M. S. *J. Antibiot.* **1993**, *46*, 554. (c) Sugano, M.; Sata, A.; Iijima, Y.; Furuya, K.; Haruyama, H.; Yoda, K.; Hata, T. *J. Org. Chem.* **1994**, *59*, 564. (d) Sugano, M.; Sata, A.; Iijima, Y.; Furuya, K.; Kuwano, H.; Hata, T. *J. Antibiot.* **1995**, *48*, 1188. For the total synthesis of phomactin D, see: (e) Miyaoka, H.; Saka, Y.; Miura, S.; Yamada, Y. *Tetrahedron Lett.* **1996**, *37*, 7107.

(3) For previous work toward the synthesis of the tricyclic core of phomactin A, see: Foote, K. M.; Hayes, C. J.; Pattenden, G. *Tetrahedron Lett.* **1996**, *37*, 275.

(4) Despite the observance of the 1-oxadecalin as the central component in a variety of natural products, direct elaboration of this system is rarely observed. Rather, manipulation of the carbon framework is followed by generation of a dihydropyran at a late stage of the synthesis. See, for example: Columbo, M. I.; Zinczuk, J.; Ruveda, E. A. *Tetrahedron* **1992**, *48*, 963.

(5) Seth, P. P.; Chen, D.; Wang, J.; Gao, X.; Totah, N. I. *Tetrahedron*, in press.

(6) (a) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015; 6019. (b) Frantz, D. E.; Singleton, D. A. *J. Am. Chem. Soc.* **2000**, *122*, 3288.

(7) The stereochemistry of the major diastereomer was confirmed by NOE studies on a more advanced intermediate (cf. Figure 2).

corresponding silyl enol ether **14** upon deprotonation with KHMDS and subsequent addition of TMSCl.[8] Rubottom oxidation[9] then provides silyloxy ketone **15** as a 15:1 mixture of diastereomers.

At this stage, stereochemical assignments about the oxadecalin ring system were confirmed by NOE studies on keto epoxide **15**. Key enhancements are shown in Figure 2.

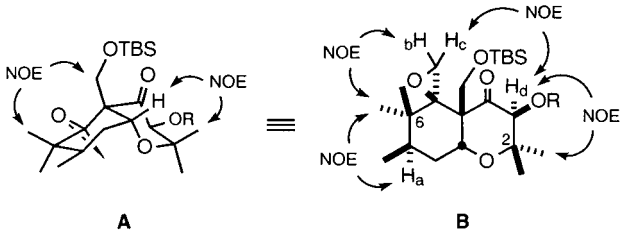
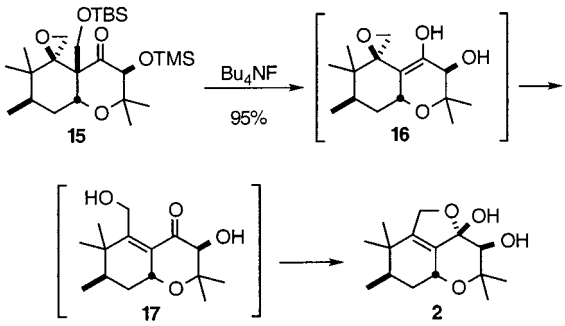


Figure 2. Determination of relative stereochemistry in keto epoxide **18**.

Individual resonances for the methyl substituents at C2 and C6 were identified in the ^{1}H NMR on the basis of chemical shift, as well as on the NOE enhancements observed between substituents at the cis-fused ring junction and methyl groups on the convex face (**A**). From here, the stereochemistry at both C3 and C5 was established upon irradiation of H_d, which resulted in an enhancement of resonances due to both H_c and the α-methyl function at C2 (**B**). In this case, NOE between H_d and H_c are expected only when both of these protons are on the concave face of this molecule. The orientation of the remaining stereogenic center at C7 then followed from enhancements observed between protons H_a and H_b and the α-methyl function at C6.

Once the relative stereochemistry of compound **15** had been established, cleavage of the silyl ethers proceeds with concomitant retro aldol reaction (**16**) and epoxide opening (**17**) to provide, upon cyclization, the desired hemiketal **2** (Scheme 5). Presumably, the facility of this process is

Scheme 5



enhanced by the relief of steric strain associated with loss of the hydroxymethyl substituent at the ring junction, as well as by ring opening of the C5 epoxide. Spectroscopic data for compound **2** is consistent with that reported for the appropriate resonances in phomactin A (**1**).[1]

In conclusion, we have prepared the tricyclic core of phomactin A in a highly stereoselective manner, with four of the six stereogenic centers in place. As part of these studies, we have demonstrated the feasibility of using a cis-fused 1-oxadecalin system such as **3** as a template for the stereocontrolled incorporation of substituents about this ring system. Furthermore, the utility of the tandem retro aldol−epoxide opening−ketalization strategy for the generation of the hemiketal moiety of phomactin A (**1**) has been established. Ongoing efforts in our laboratories are geared toward the efficient incorporation of quaternary stereogenic centers at C2 and C6 of the tricyclic core and toward the total synthesis of phomactin A.

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Supporting Information Available: Experimental procedures and characterization data for compound **2** and for key intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Upon deprotonation (e.g., **16**), *β*-elimination is presumably suppressed due to the orthogonal orientation of the *β*-alkoxy substituent relative to the enolate *π* system. See, for example: (a) Naef, N.; Seeback, D. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 1030. (b) Soo, Y. K.; Lee, A. W. M.; Masamune, S.; Reed, L. A.; Sharpless, K. B.; Walker, F. J. *Tetrahedron* **1990**, *46*, 245.

(9) Rubottom, G. M.; Vazquez, M. A.; Pelegrina, D. R. *Tetrahedron Lett.* **1974**, 4319.