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Total Synthesis of (+)-Phomactin A Using a *B*-Alkyl Suzuki Macrocyclization

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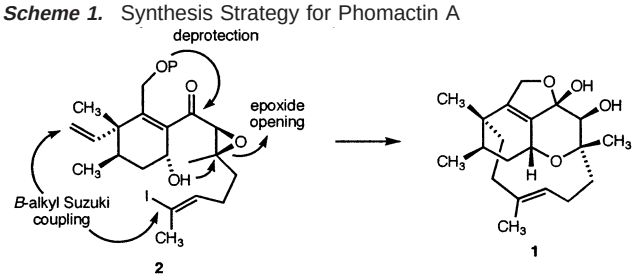
The phomactins, a class of diterpenes isolated by Sugano and co-workers[1] in the early 1990s, have drawn much attention from the synthetic community over the past few years.[2] In addition to their biological activity as platelet activating factor (PAF) antagonists, the phomactins possess a structurally unique architecture, which is marked by a highly substituted cyclohexane that is bridged by a 12-membered macrocycle. Phomactin A (**1**, Scheme 1), arguably the most structurally complex member of the phomactin family, also contains a pyran ring and a sensitive[2b,i] hydrated furan ring. This reduced furanochroman has been addressed by several groups;[2b,c,i] however, only recently has phomactin A yielded to total synthesis.[3] This manuscript reports a nonracemic total synthesis of phomactin A using a *B*-alkyl Suzuki reaction to install the macrocycle.

Scheme 1. Synthesis Strategy for Phomactin A

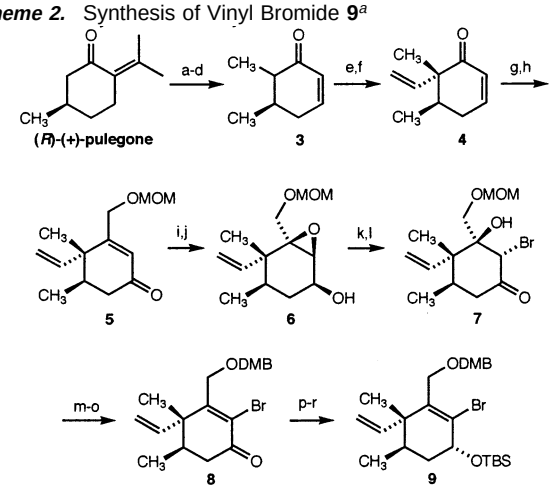


Our synthesis strategy, shown in Scheme 1, centers on substituted cyclohexene **2**. This key intermediate would possess the entire carbon framework and all relevant stereochemistry necessary to complete the total synthesis. Three crucial ring closures would then be carried out: an intramolecular epoxide opening to install the pyran ring, a deprotection of the primary hydroxyl group to spontaneously form the hydrated furan ring, and a *B*-alkyl Suzuki coupling to install the 12-membered macrocycle. The macrocyclization would be carried out last, using the rigid structure of the tricyclic core to potentially bias the system toward cyclization.

On the basis of this strategy, a convergent synthesis route to intermediate **2** was designed from two commercially available and inexpensive terpene starting materials, (*R*)-(+)-pulegone and geraniol. These two compounds were used to synthesize vinyl bromide **9** and aldehyde **13**, respectively, which were then coupled with a nucleophilic addition reaction.

Methylation of (*R*)-(+)-pulegone and subsequent retro-aldol reaction were carried out according to literature procedure[4] to give 2,3-dimethylcyclohexanone, which was converted to the corresponding enone **3** through a bromination/elimination sequence (Scheme 2). The quaternary stereocenter was then installed using an aldol reaction with phenylselenoacetaldehyde[5] to give an intermediate β-hydroxy ketone, which was cleanly converted to the vinyl-substituted enone **4** upon treatment with methanesulfonyl chloride and triethylamine.[6] This two-step sequence proceeded with complete diastereoselectivity and efficiently installed the vinyl group necessary for the pivotal *B*-alkyl Suzuki coupling. A 1,3-enone transposition was then carried out on **4** to install the MOM-protected hydroxymethyl group. Tin−lithium exchange of [(methoxymethoxy)-methyl]tributylstannane[7] and addition of the resulting anion to **4** gave a tertiary allylic alcohol, which oxidatively rearranged upon treatment with PCC[8] to give enone **5**. The vinyl bromide was then installed through an indirect sequence,[9] using an epoxide as the key intermediate. The ketone was first reduced under Luche conditions to give exclusively the pseudoequatorial alcohol, followed by directed epoxidation of the trisubstituted olefin to give **6**. Oxidation of the alcohol with Dess−Martin periodinane and regioselective epoxide opening with magnesium bromide then gave bromohydrin **7**. The tertiary alcohol was converted to the corresponding trifluoroacetate, which rapidly eliminated under the basic reaction conditions to install the vinyl bromide. The MOM-protecting group was next removed and replaced with the more labile DMB (3,4-dimethoxybenzyl) ether to give **8**.[10,11] The ketone was then reduced to the pseudoequatorial alcohol,[12] and subsequent Mitsunobu inversion gave the desired pseudoaxial alcohol, which was protected as a TBS ether to give **9**.

Scheme 2. Synthesis of Vinyl Bromide **9**[a]



[a] Reagents and conditions: a) LDA, LiCl, MeI (70%); b) KOH, reflux (75%); c) LDA, TMS-Cl, Br_2 (90%); d) Li_2CO_3, LiBr, DMF (81%); e) LDA, phenylselenoacetaldehyde (73%); f) MsCl, Et_3N (86%); g) *n*-BuLi, Bu_3SnCH_2OMOM, LiCl (70%); h) PCC (91%); i) $NaBH_4$, $CeCl_3$; j) *m*CPBA (81% for two steps); k) Dess−Martin periodinane (86%); l) $MgBr_2 \cdot Et_2O$ (83%); m) TFAA, Pyr. (95%); n) $MgBr_2 \cdot Et_2O$, BuSH (91%); o) CSA, DMB-ONPy (85%); p) $NaBH_4$, $CeCl_3$ (94%); q) PPh_3, DEAD, *p*-nitrobenzoic acid; then $NaOCH_3$ (86%); r) TBS-Cl (92%).

The synthesis of aldehyde **13** began from geraniol (Scheme 3). Geraniol was converted to known aldehyde **10** using Mori's three-step procedure.[13] Aldehyde **10** was subjected to Corey−Fuchs[14] conditions to give the corresponding terminal alkyne, which was methylated to give **11**.[15] This intermediate was then converted to the corresponding TBS-protected alcohol,[16] which was transformed to vinyl iodide **12** through a hydrozirconation/iodination sequence.[17] This reaction proceeded with excellent regioselectivity, favoring the desired vinyl iodide (12:1 mixture). The TBS group was then removed with fluoride, and the resulting allylic alcohol was

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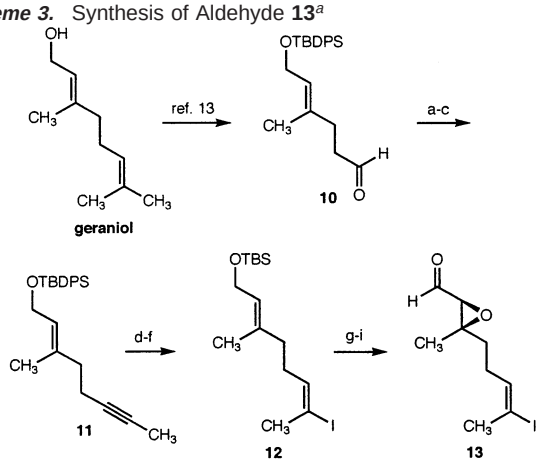
converted to aldehyde **13** by Sharpless asymmetric epoxidation,[18] followed by oxidation under Parikh−Doering[19] conditions.

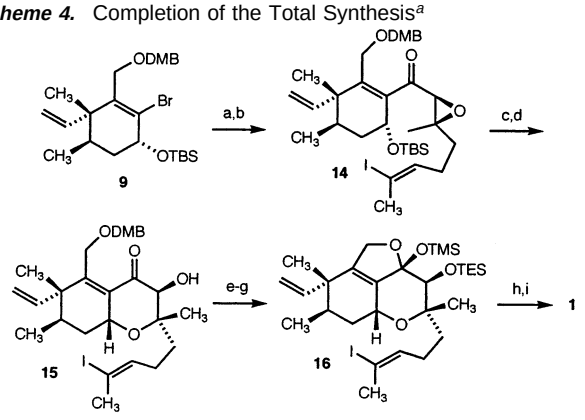
Scheme 3. Synthesis of Aldehyde **13**[a]



[a] Reagents and conditions: a) CBr_4, PPh_3, Zn; b) *n*-BuLi, Et_2O, 0 °C (92% for two steps); c) *n*-BuLi, THF, −78 °C (88%); d) TBAF; e) TBS-Cl (94% for two steps); f) Cp_2ZrHCl, 40 °C, 12 h; then I_2, 0 °C (65%); g) TBAF (92%); h) TBHP, (−)-DIPT, Ti(O-*i*Pr)$_4$, 4 Å mol. sieves; i) Pyr·SO_3, DMSO, Et_3N (66% for two steps).

The synthesis was completed as shown in Scheme 4. Lithium−halogen exchange of **9** was performed at −78 °C, and addition of the resulting vinyllithium reagent to aldehyde **13** gave an intermediate allylic alcohol which was oxidized to give ketone **14**. The TBS group was then removed to give the corresponding free secondary alcohol, which cyclized under acidic conditions to install the pyran ring and provide **15**. Alcohol **15** was protected as a triethylsilyl ether,[20] and then the DMB group was removed to give the corresponding primary alcohol, which spontaneously formed the hemiacetal and installed the hydrated furan ring. The tertiary hydroxyl group of the hemiacetal was then protected as a TMS ether to give **16**. To construct the macrocycle, a regioselective hydroboration was carried out on the terminal olefin of **16** with 9-BBN to give an intermediate alkyl borane, which cyclized using a modification[21] of Johnson's[22] conditions. This reaction illustrates the mildness of the Suzuki[23−25] reaction in that the coupling was carried out with the sensitive dihydrofuran ring in place. Treatment with TBAF then removed both silyl groups to give phomactin A (**1**). The ^{1}H and ^{13}C NMR data for synthetic **1** were in agreement with the data reported for natural phomactin A.[1a,26]

Scheme 4. Completion of the Total Synthesis[a]



[a] Reagents and conditions: a) *t*-BuLi, −78 °C, then **13**; b) Dess−Martin periodinane (45% for two steps); c) TBAF (91%); d) 1% HCl, *tert*-amyl alcohol (65%); e) TES-Cl (83%); f) DDQ (87%); g) TMS-OTf, Pyr. 0 °C (81%); h) 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%); i) TBAF (78%).

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Supporting Information Available: Full experimental detail for all new compounds, and ^{1}H NMR spectra of synthetic **1**, **4**, **13**−**16**, and other key unnumbered intermediates (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) All attempts at direct bromination of **5** failed, presumably due to the demanding steric environment and electron deficiency of the trisubstituted olefin.
(10) The MOM group introduced early in the synthesis could not be successfully removed at an appropriate later stage.
(11) 2-(3,4-Dimethoxybenzyloxy)-3-nitropyridine (DMB−ONPy) was prepared according to the procedure of Mukaiyama: Nakano, M.; Kikuchi, W.; Matsuo, J.; Mukaiyama, T. *Chem. Lett.* **2001**, 424.
(12) All attempts at reduction of the ketone to give exclusively the desired alcohol diastereomer were unsuccessful. Because the two alcohol diastereomers were not easily separated, exclusive reduction to the undesired diastereomer was carried out, followed by Mitsunobu inversion.
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(26) In $CDCl_3$ instead of CD_3OD, synthetic phomactin A showed ^{1}H NMR data which were superimposable on those reported for natural Sch 49028 from *Phoma* sp. It has been suggested that Sch 49028 is, in fact, phomactin A (**1**) and not the epoxy cyclic hemiacetal structure reported. See ref 3, and Chu, M.; Truumees, I.; Gunnarsson, I.; Bishop, W. R.; Kreutner, W.; Horan, A. C.; Patel, M. G.; Gullo, V. P.; Puar, M. S. *J. Antibiot.* **1993**, *46*, 554.

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