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Synthesis of the Ring System of Phomactin D Using a Suzuki Macrocyclization

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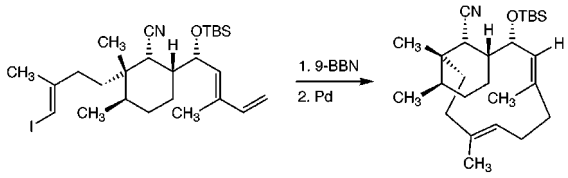
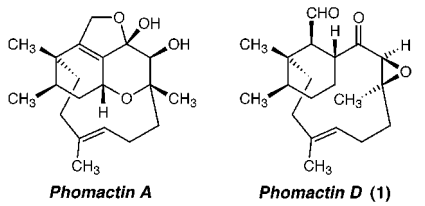
ABSTRACT



The ring system of phomactin D was synthesized in racemic form in an efficient manner from 2,3-dimethylcyclohexanone. Notable transformations include (1) an alkylation of the enolate of a vinylogous thiolester to install a quaternary stereocenter, (2) a conjugate addition of cyanide to an α,β-unsaturated aldehyde, (3) the formation of a Weinreb amide directly from a cyanohydrin, and (4) an intramolecular Pd-mediated Suzuki coupling of a *B*-alkyl-9-BBN derivative and a vinyl iodide to form the macrocyclic ring.

Platelet activating factor (PAF) is an ether-phospholipid that is responsible for several cellular functions, including mediation of anaphylaxis and platelet aggregation.[1] In recent years, the search for new molecules that inhibit the effects of PAF has resulted in the discovery of a family of naturally occurring diterpenes from the marine fungus Phoma sp. that have been given the *nom de guerre* phomactins (Figure 1).[2]



Phomactin A ***Phomactin D* (1)**

Figure 1. Structures of representative phomactins.

These compounds are structurally quite complex, and they all possess an unusual bicyclo[9.3.1]pentadecane ring system within their molecular framework. Of these compounds, phomactin D (**1**) was found to be the most biologically active. Because of their biochemical activity and unique molecular structures, the phomactins are worthy targets for the development of synthesis methods and strategies that may be broadly applicable.[3,4]

The general synthesis plan is illustrated in Scheme 1. A fundamental premise from the outset was that the epoxide moiety could be introduced in a stereoselective manner late in the synthesis.[3] Therefore, a logical intermediate would be compound **7**. Compound **7** would be synthesized as shown, using the cyclohexanone derivative **2** as a point of

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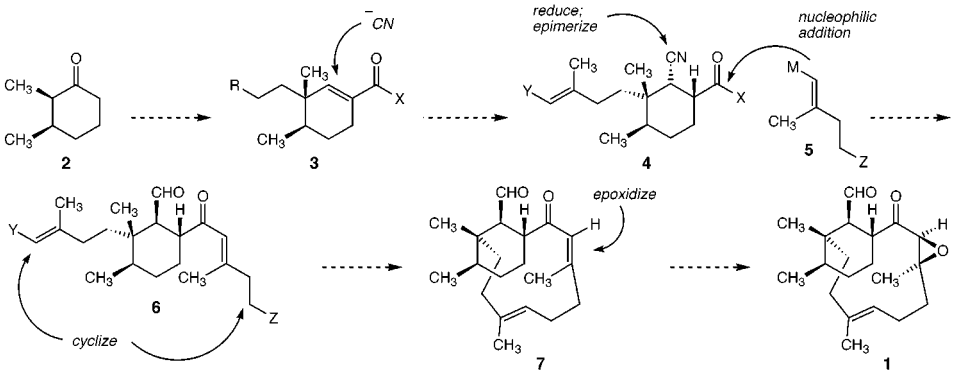
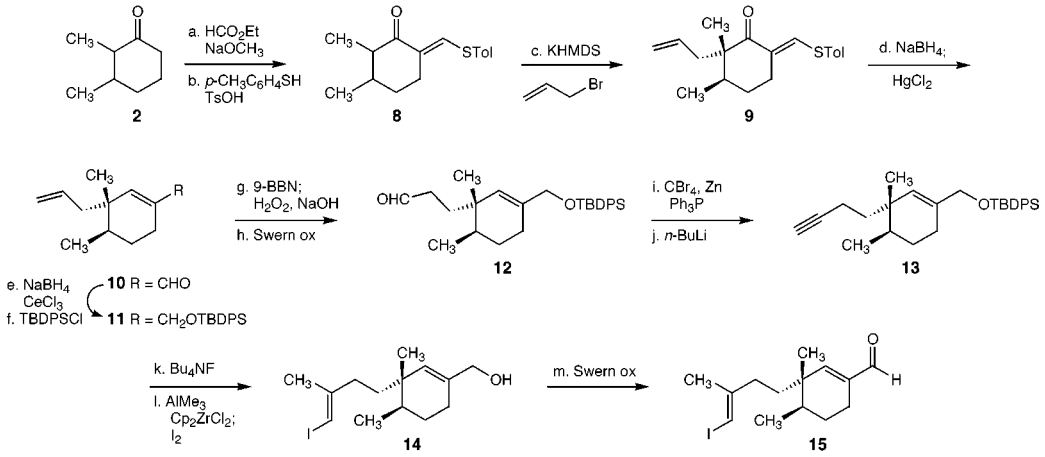
Scheme 1



departure. It was anticipated that compound **2** could be converted to the α,β-unsaturated carbonyl-containing compound **3** in a straightforward manner. A conjugate addition of a formyl anion equivalent, in actuality cyanide as described below, could potentially provide compound **4**. Although an axial addition of cyanide was in fact observed, it is reasonable to expect that the corresponding aldehyde could be epimerized to the equatorial position at a later point. Addition of a vinyl nucleophile such as **5** to the carbonyl of **4** would give **6**, which, after a macrocyclization reaction, would lead to the key intermediate **7**. This overall strategy has in fact been demonstrated to be feasible, as described in this Letter. The implementation of this general synthesis design concept, as well as the development of some novel synthesis transformations to facilitate this effort, are presented.

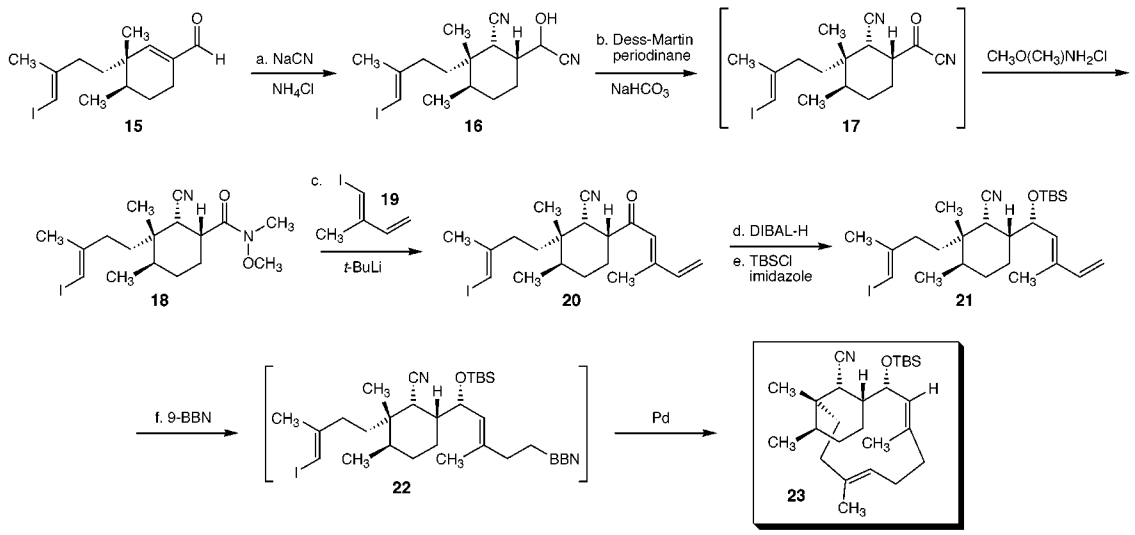
As shown in Scheme 2, the sequence began with (±)-2,3-dimethylcyclohexanone **2**.[5] Conversion to the vinylogous thiolester **8** proceeded uneventfully.[6] Alkylation of **8** with allyl bromide provided compound **9** with 15:1 diastereoselectivity at the newly formed quaternary carbon.[7] Reduction of the ketone of **9** with $NaBH_4$ and subsequent treatment with mercuric chloride provided the enal **10**.[6] In preparation for subsequent transformations, the aldehyde was reduced and protected as the *tert*-butyldiphenylsilyl ether **11** using the sequence shown. Extension of the allyl side chain was then carried out in order to both install the necessary carbons and to introduce a functional group to allow for the macrocyclization. This was accomplished first by hydroboration of the monosubstituted olefin of **11** followed by an oxidation of the resulting alcohol to give aldehyde **12**. A Corey−Fuchs procedure was then employed to introduce the alkyne moiety and produce compound **13**.[8] Interestingly, the silyl protecting group of **13** was found to be unstable to some of the subsequent transformations; therefore it was removed at this stage by treatment with fluoride. A methylzirconation reaction, combined with a quench with iodine, proceeded

Scheme 2[a]



[a] Reagents and conditions: (a) NaOMe, HCO_2Et, benzene, 0 °C to rt (97%); (b) *p*-$CH_3C_6H_4SH$, benzene, reflux (90%); (c) KHMDS, toluene, −78 °C; allyl bromide (80%); (d) $NaBH_4$, 10:1 MeOH:0.1 N NaOH, rt; $HgCl_2$, acetone/H_2O, rt (95%); (e) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, EtOH, 0 °C; (f) TBDPSCl, imidazole, DMF, rt (91% for 2 steps); (g) 9-BBN, THF, 0 °C to rt; 1.0 M NaOH, H_2O_2, 0 °C; (h) oxalyl chloride, DMSO, −78 °C; NEt_3, −78 °C to rt (98% for 2 steps); (i) Zn, PPh_3, CBr_4, CH_2Cl_2, 0 °C to rt (76%); (j) *n*-BuLi (3 equiv), THF, −78 °C to rt (92%); (k) Bu_4NF, THF, rt; (l) $AlMe_3$, Cp_2ZrCl_2 (cat.), CH_2Cl_2, 0 °C to rt; I_2, THF, −45 to 0 °C (90% for 2 steps); (m) oxalyl chloride, DMSO, −78 °C; NEt_3, −78 °C to rt (96%).

Scheme 3[a]



[a] Reagents and conditions: (a) NaCN, NH_4Cl, 8:1 CH_3CN:H_2O, reflux; (b) Dess−Martin periodinane, $NaHCO_3$, CH_2Cl_2, rt; $CH_3O(CH_3)NH_2Cl$, 0 °C (60% from **15**); (c) *t*-BuLi, ether, −78 °C; HOAc, THF −78 °C (55%); (d) DIBAL-H, toluene, −78 °C; (e) TBSCl, imidazole, DMF, 45 °C (80% for 2 steps); (f) 9-BBN, toluene, 50 °C; $Pd(dppf)Cl_2$, Cs_2CO_3, $AsPh_3$, DMF/H_2O, 50 °C (16%).

smoothly to afford vinyl iodide **14**.[9] Note that the olefin geometry in **14** was produced with the desired *E* configuration as expected. The presence of the vinyl iodide moiety allowed for a later bond formation by means of a metal-mediated coupling reaction to form the macrocycle, while also being sufficiently inert to the intervening transformations. The aldehyde was then regenerated using a Swern oxidation to provide **15**.

After investigating several formyl anion equivalents as appropriate nucleophiles for conjugate addition to **15**, it was found that cyanide met the necessary criteria for the route. Treatment of **15** with sodium cyanide and ammonium chloride in refluxing water/acetonitrile accomplished a Nagata-type reaction[10] and afforded the dicyano derivative **16** (Scheme 3). The nucleophilic addition to the β-carbon occurred from an axial direction relative to the six-membered ring, and a second equivalent of cyanide added to the aldehyde to provide the cyanohydrin group. Furthermore, the cyclohexane carbon of **16** that bears the cyanohydrin moiety possessed predominantly the stereochemical configuration shown, with the cyanohydrin occupying an equatorial position (see below). Trace amounts of products that could potentially be the epimers at the nitrile- and cyanohydrin-bearing carbons of the cyclohexane were detected by ^{1}H NMR, but sufficient quantities of material to allow unambiguous structural determination were not produced. One rationalization, among several possible hypotheses, that can be invoked to explain this observation assumes that the aldehyde intermediate that is produced after the conjugate addition is readily epimerized under the reaction conditions. In turn, the equatorial aldehyde is the one that leads to the product, because it is the predominant isomer at equilibrium and/or reacts faster than the axial aldehyde. However, this hypothesis can be neither confirmed nor disproved on the basis of the current observations.

The cyanohydrin **16** was oxidized to the acyl cyanide **17** using Dess−Martin periodinane.[11] The acyl cyanide was not isolated, rather when the oxidation step was complete, *N*,*O*-dimethylhydroxylamine hydrochloride was added directly to the reaction mixture, and amide **18** was produced in 60% overall yield from **15**.[12] Amides such as **18** are well-known to react with organometallic nucleophiles to give ketones,[13] and this property was utilized to advantage in this sequence. Treatment of **18** with the dienyllithium reagent derived from the reaction of iodide **19**[14] with *tert*-butyllithium produced ketone **20**, which possessed all of the carbons of phomactin D. Protection of the ketone of **20** was then accomplished first by reduction to the corresponding alcohol with DIBAL-H

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(11) Dess, B. D.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287.
(12) The relative configuration of the stereocenters of **18** was determined using NOE difference NMR experiments. An NOE was observed between the protons of the methyls C-19 and C-20 and between the C-19 methyl and H-15, indicating that both methyls and H-15 must be on the same face of the cyclohexane. Also, H-15 had only small coupling constants and H-1 had one large coupling constant (to H-14ax) and two small ones, indicating that H-1 must be axial and H-15 must be equatorial. See Supporting Information for complete data.
(13) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815−3818.
(14) Prepared in a manner analogous to that of 1-iodo-2-methyl-(1*Z*,3)-butadiene: Ma, S.; Negishi, E. *J. Org. Chem.* **1997**, *62*, 784−785.

and then silylation of the resulting hydroxyl group to provide **21**. Reduction of **20** proceeded smoothly at −78 °C to give a 4:1 mixture of alcohol diastereomers favoring the diastereomer shown.[15] Only the major product was carried forward in the sequence.[16]

At this point, the key macrocyclization reaction was investigated. A Suzuki coupling protocol was chosen to effect ring closure.[17] Treatment of **21** with 9-BBN provided the alkyl borane **22**.[18] This intermediate was not isolated but was directly exposed to Pd, resulting in the formation of macrocycle **23**.[19] Although the yield of the transformation is somewhat low (16%), this nevertheless constitutes a proof-of-principle. To the best of our knowledge, an example of this particular variation of the Suzuki reaction, namely, reaction of a *B*-alkyl-9-BBN derivative with a vinyl halide, to accomplish ring closure of a macrocycle of this nature has not previously been published.[20−22] Furthermore, many opportunities for optimization remain which have yet be explored, and it is strongly anticipated that this yield can be optimized to a synthetically useful level.

(15) The relative configuration of the carbon bearing the TBS ether in the major diastereomer **21** was assigned on the basis of analogy to a derivative with slightly different side chains on the cyclohexane ring whose structure was unambiguously proven by X-ray crystallography. Also, the NMR spectral characteristics (chemical shifts, splitting patterns, and coupling constants) of the protons on the cyclohexane ring for each of the two compounds were virtually identical.

(16) An alternative route to intermediates such as **21** would involve regeneration of the aldehyde from the cyanohydrin group in **16** and subsequent addition of the vinyllithium formed from iodide **19**. In practice, the approach in Scheme 3 was very efficient and produced favorable diastereomeric ratios. Therefore, alternative routes were not investigated.

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(18) Hydroboration of a similarly substituted model diene with 9-BBN in the presence of an equivalent molar amount of an appropriately substituted vinyl iodide, followed by oxidation with basic peroxide, afforded the primary alcohol almost exclusively. An analogous selective hydroboration of a similarly substituted diene has been observed previously; see ref 17a.

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In summary, a synthesis of the phomactin D ring system in racemic form was accomplished. A key reaction in the synthesis was the conjugate addition of cyanide to an α,*β*-unsaturated aldehyde with concomitant formation of a cyanohydrin. A method was developed and implemented that converted the cyanohydrin directly to a Weinreb amide in a single synthesis operation, thus installing a functional group that would allow for subsequent bond formations. Finally, an unusual intramolecular variant of the Suzuki coupling was used to effect the annulation of the macrocycle. The route presented here establishes a firm foundation for further pursuits toward a total synthesis of phomactin D. Adapting the route for a nonracemic synthesis will also be reported in due course.

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Supporting Information Available: Spectral data for compounds **8**−**15**, **18**, **20**, the alcohol precursor to **21**, and **23**. This information is available free of charge via the Internet at http://pubs.acs.org.

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