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Enantioselective Synthesis of the Oxadecalin Core of Phomactin A via a Highly Stereoselective Diels–Alder Reaction

Sherry R. Chemler, Ulrich Iserloh, and Samuel J. Danishefsky*

Laboratory of Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, 1275 York Avenue, Box 106, New York, New York 10021, and Department of Chemistry, Columbia University, Havemeyer Hall, New York, New York 10027

s-danishefsky@ski.mskcc.org

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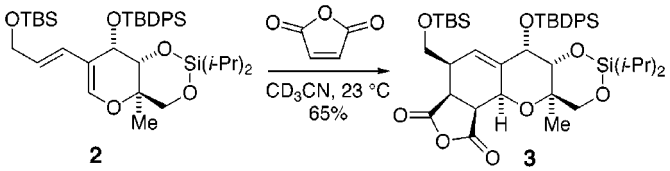
ABSTRACT



Phomactin A (1) is a selective antagonist of platelet activating factor (PAF). Herein, we report our progress toward the construction of the oxadecalin core of 1. This route is based on the Diels–Alder cycloaddition of an appropriately functionalized vinyl pyran and a complementary dienophile. A model of this reaction involving 2 and maleic anhydride was conducted. Adduct 3 contains the correct stereochemical arrangements between functional groups necessary for gaining access to phomactin A.

Phomactin A (**1**), isolated from the marine fungus *Phoma* sp. by Sugano and co-workers in 1991, is a selective antagonist of platelet activating factor (PAF), 1-*O*-alkyl-2(*R*)-(acetylglyceryl)-3-phosphorylcholine.[1] Agent **1** is one of the most structurally complex members of a class of related compounds, phomactins A−G.[2] PAF-mediated signaling has been implicated in a variety of biological effects that include platelet aggregation, hypotension, smooth muscle contraction, and vascular permeability.[3] PAF is also implicated as a causative factor in septic shock and inflammatory, respiratory, and cardiovascular diseases.[4]

Aside from the biology-driven incentives, a total synthesis exercise directed at phomactin A offers an attractive testing ground for exploring and evaluating strategy level initiatives. Indeed, several groups have reported approaches toward the synthesis of phomactin A (for the moment in racemic form). However, a solution to the problem has not yet been described.[5] Approaches toward phomactin D have also been described, and an enantioselective total synthesis of this molecule has been achieved.[6]

Phomactin A contains six stereogenic centers in its oxadecalin core. An additional ansa-like bridge connects the

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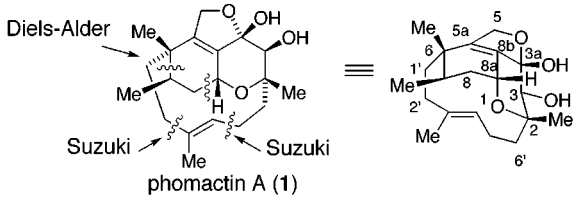
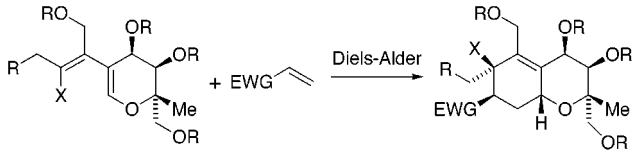


Figure 1.

C(6) quaternary carbon and the C(2) tertiary ether in a 12-membered macrocycle. Recently we described a transannular macrocyclization method that uses the *B*-alkyl Suzuki−Miyaura reaction to illustrate a $C(sp^3)-C(sp^2)$ bond forming event.[7] This method may well find application in the closure of a seco phomactin A structure, possibly through the C(4′)−C(5′) bond.

In this letter we describe our efforts directed toward the formation of the oxadecalin core of phomactin A. We envisioned a rather direct entry into this system via a Diels−Alder reaction between an appropriately functionalized diene of type **4** and an appropriately matched dienophile (cf. **5**) (Scheme 1). Such a cycloaddition could potentially install

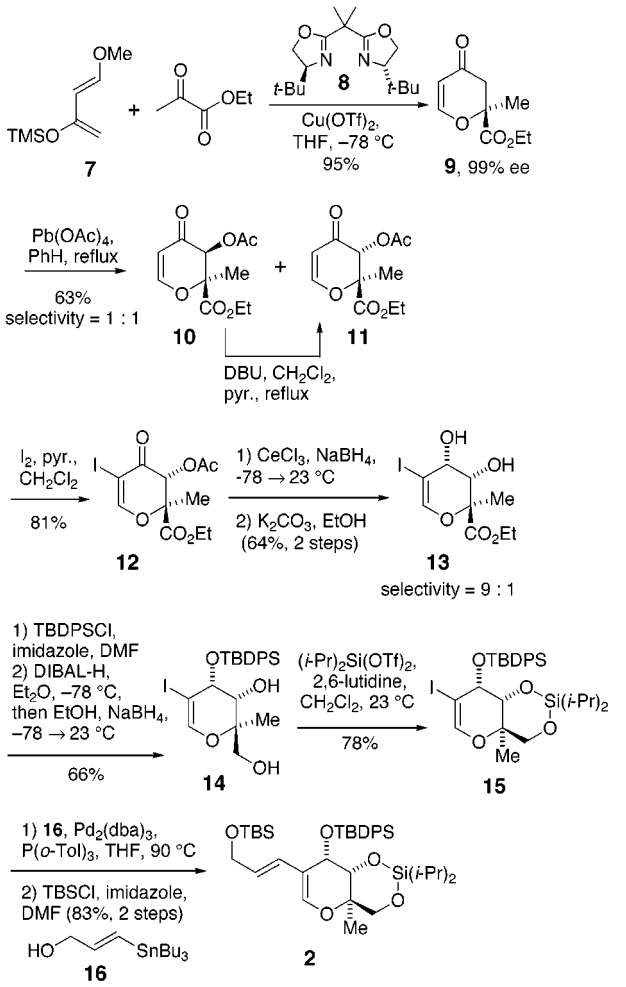
Scheme 1



the C(6), C(7) ,and C(8a) stereogenic centers, as well as the C(5a)−C(8b) endocyclic olefin of phomactin A.[8]

Synthesis of the oxadecalin core began with the cyclocondensation reaction between *trans*-1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (**7**) and ethyl pyruvate in the presence of the catalyst formed from 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] (**8**) and $Cu(OTf)_2$ (Scheme 2).[9] As reported by Jørgensen, this transformation is highly efficient and enantioselective. To date, we have used the commercially available ligand **8**, which is enantiomeric to that required for a synthesis of phomactin A. Synthesis of the required

Scheme 2



enantiomer of **8** is reported in the literature.[10] Oxidation of pyrone **9** with $Pb(OAc)_4$ in refluxing benzene[11] afforded a chromatographically separable 1:1 mixture of diastereomeric acetates **10** and **11** where **11** contains the correct relative configuration (C(3) phomactin A stereocenter). Additional quantities of **11** were obtained through an epimerization protocol, whereby acetate **10** was converted to a 1.4:1 mixture of **10** and **11** (cat. DBU, pyridine, CH_2Cl_2, reflux). Iodination of **11** afforded vinyl iodide **12**. Reduction of the ketone functionality of **12** under Luche conditions[12] afforded a mixture of acetylated regioisomeric alcohols. Treatment of this material with K_2CO_3 in 95% EtOH then afforded diol **13**, contaminated with ca. 10% of a diastereomer, presumably arising from the reduction step. Protection of the less hindered alcohol of **13** as its TBDPS ether, followed by reduction of the ester functionality led to **14**.

(6) (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.

(7) Chemler, S. R.; Danishefsky, S. J. *Org. Lett*. **2000**, *2*, 2695−2698.

(8) It should be noted that our Diels−Alder disconnection is complementary to Totah's approach toward the oxadecalin core of phomactin A. Totah's Diels−Alder disconnection of the oxadecalin core is based on the condensation of an electron-deficient pyrone with an electron-rich diene: ref 5b and (a) Chen, D.; Wang, J.; Totah, N. I. *J. Org. Chem*. **1999**, *64*, 1776−1777. (b) Seth, P. P.; Chen, D.; Wang, J.; Gao, X.; Totah, N. I. *Tetrahedron* **2000**, *56*, 10185−10195.

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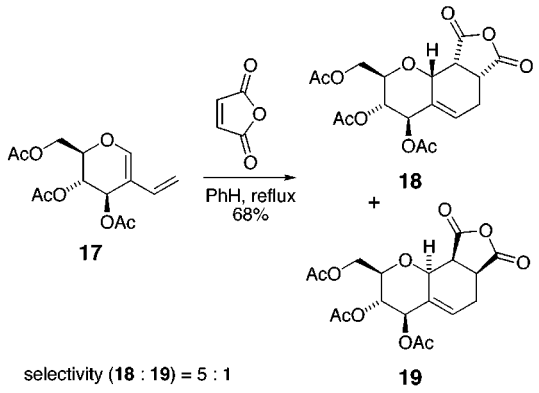
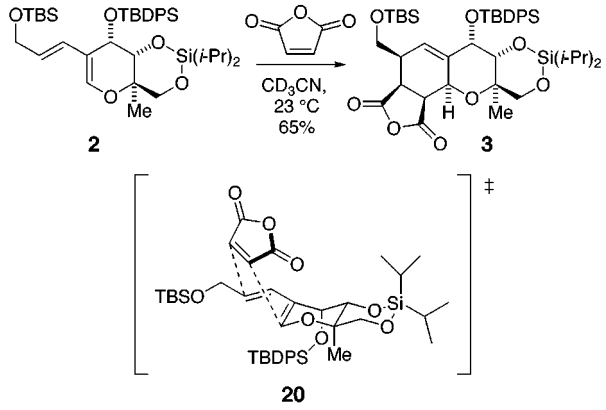
The intermediate diol **14** was converted to the silylene acetal **15** by treatment with a premixed solution of $(i\text{-Pr})_2\text{Si}(\text{OTf})_2$ and 2,6-lutidine. This protecting group was specifically chosen to enforce a rigid conformation about the pyran ring wherein *the trans-fused ring junction would force the OTBDPS and the Me groups to adopt axial positions.* We hoped that such a conformer would bias the face selectivity of the subsequent Diels−Alder reaction. Diene **2** was fashioned from **15** via Stille coupling[13] with vinylstannane **16** followed by protection of the resulting terminal alcohol as its TBS ether.

Some literature precedent existed for the thermal Diels−Alder reactions between pyran-based alkoxy-dienes and various dienophiles.[12,14] In these reactions, endo addition is highly favored with substrates such as maleic anhydride. Additionally, facial selectivity is highly influenced by the configuration of the C(3) alkoxy group. In these cycloadditions, the product distribution is consistent with approach of the dienophile from the face opposite to that group. For instance, Hayashi and co-workers have reported the reaction of **17** with maleic anhydride, where adduct **18** is favored over **19** (5:1).[13]



The origin of the strong biasing effect of the C(3) substituent is thought to be stereoelectronic in nature. Presumably, the alkoxy group adopts a pseudoaxial position on the pyran ring in the Diels−Alder transition state. *However, no examples of Diels−Alder reactions with dienes fully substituted at C(5) have been reported.*[15]

In the event, Diels−Alder reaction between **2** and maleic anhydride took place at 23 °C and with complete stereoselectivity (no other isomer observed by ^{1}H NMR analysis at 400 MHz). This result can be rationalized via transition state **20**.[16]



The stereochemistry of **3** was assigned by two-dimensional ^{1}H NMR analysis (NOESY). It will be noted that adduct **3** codes for a 1,3-*syn* relationship between the future C(8a) hydrogen and the C(2) methyl substitutents of phomactin A.

We are now well positioned to explore more advanced diene substrates in conjunction with dienophiles that are more appropriately functionalized for reaching phomactin A. Our progress along these lines will be reported.

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Supporting Information Available: Experimental procedures and full characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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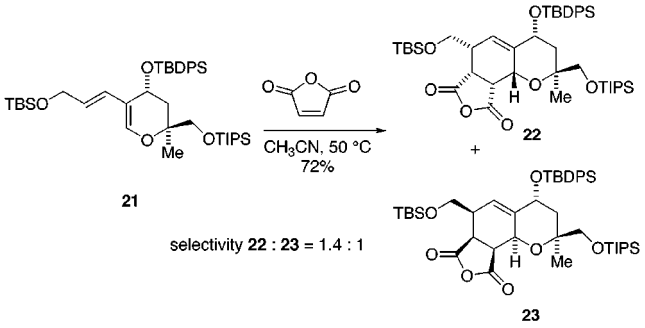
(15) It should be noted that the Diels−Alder reaction of **21** with maleic anhydride is unselective, thus indicating that conformational constraint is necessary for achieving facial selectivity.



(16) By ^{1}H NMR analysis, the conversion of **2** to **3** is very clean. We suspect the moderate isolated yield may be the result of partial decomposition of **3** during chromatography on SiO_2, perhaps due to the sensitive anhydride moiety.