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Palladium(0)-Mediated Desymmetrization of Meso Tetraols: An Approach to the C3–C17 Bis-oxane Segment of Phorboxazoles A and B

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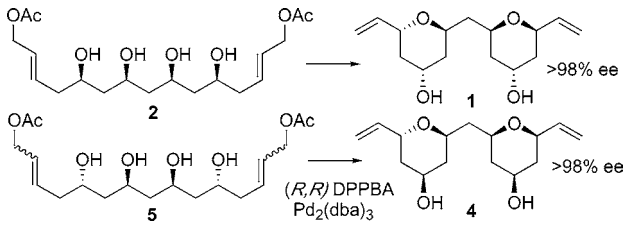
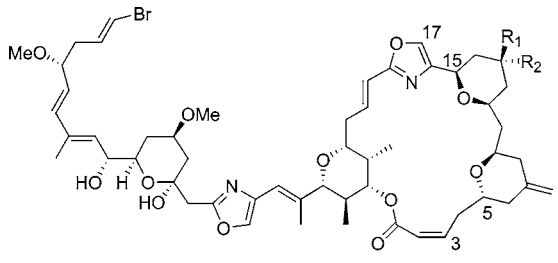
ABSTRACT



***meso*-Tetraol bis(allylic acetates) 2 and 5 were synthesized via two-directional chain elongation. A palladium-mediated, ligand-controlled desymmetrization provided the desired bis-oxanes in greater than 98% ee. Bis-oxanes 1 and 4 represent potential synthetic intermediates for the C3–C17 subunits of phorboxazoles A and B.**

Exploitation of hidden or local symmetry in complex natural products can simplify or expedite synthetic efforts. For example, our recent works on halichondrin B[1] and uvaricin[2] have employed the technique of two-directional synthesis[3] of C_2- and σ-symmetric intermediates via simultaneous chain elongation, followed by terminus differentiation to effect desymmetrization. The latter is often a substantial challenge,[3] and new methods that effect symmetry-breaking are needed to validate the two-directional chain synthesis strategy. We report herein the development of a Pd^0-mediated asymmetric allylic etherification for this purpose,[4] with meso substrates undergoing double cyclizations to potential phorboxazole bis-tetrahydropyran subunits.

First isolated from the Indian Ocean marine sponge *Phorbas.* Sp. by Molinksi[5] in 1995, the cytotoxic macrolide phorboxazoles (Figure 1) have been the subject of numerous synthetic efforts. In 1998, the first total synthesis of phorboxazole A was completed by Forsyth,[6] followed by total



Phorboxazole A : R_1=H, R_2=OH
Phorboxazole B : R_1=OH, R_2=H

Figure 1. The phorboxazoles.

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(4) See also refs 1a, 2, and: Graening, T.; Schmalz, H.-G. *Angew. Chem., Int. Ed.* **2003**, *42*, 2580.

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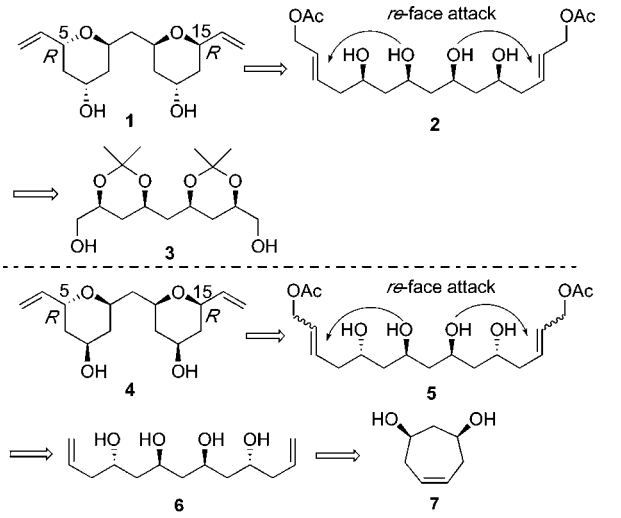
syntheses by Evans[7] (phorboxazole B), Smith,[8] Pattenden,[9] and Williams.[10] The phorboxazoles have been the focus of numerous other efforts,[11] SAR studies,[12] and a recent overview.[13]

Phorboxazole A and its C13 epimer phorboxazole B exhibit exceptional cytostatic activity. They have shown a mean GI_{50} value of $<1.6 \times 10^{-9}$ M in vitro against the NCI panel of 60 tumor cell lines.[5b] Moreover, phorboxazole A eppears to induce S-phase cell cycle arrest with no noticeable affect on microtubule stability, thus possessing a novel, albeit unknown, mechanism of action.[5b]

The C5−C15 subunits of phorboxazoles A and B can, in principle, be derived from desymmetrized bis-oxanes **1** and **4**, respectively (Scheme 1). Both lack meso symmetry

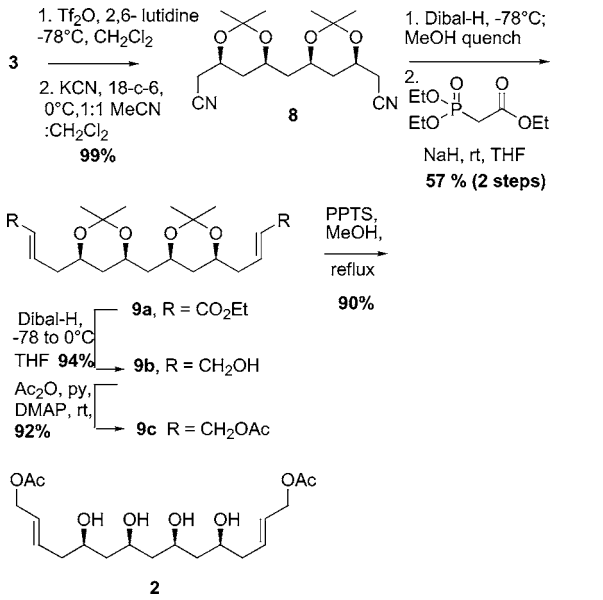
Scheme 1



because in each, the C5 and C15 stereogenic centers both have the *R*-configuration. Retrosyntheses for these intermediates are outlined in Scheme 1. Both bis-tetrahydropyran units were anticipated to arise from a chiral ligand-controlled, Pd^0-mediated double cyclization with use of Trost's catalyst system.[14] The all-syn meso tetraol precursor **2** was made by two-directional chain extension from known bis-acetonide **3**.[15] Our approach to the anti-syn-anti double cyclization precursor **5** involved application of Grubbs' second generation catalyst[16] in a double cross metathesis of **6** with *cis*-1,4-diacetoxy-2-butene. The anti-syn-anti relationship of the hydroxyls in tetraol **6** was to be set via chelation-controlled allylation of the dialdehyde derived by ozonolysis of known dihydroxycycloheptene **7**.[17]

Bis-acetonide **3**[15] was subjected to triflate formation followed by cyanide displacement to afford bis-nitrile **8** (Scheme 2) in 99% yield. Reduction of **8** with Dibal-H

Scheme 2



yielded the dialdehyde substrate for Horner−Wadsworth−Emmons elaboration to (*E*,*E*)-α,*β*-unsaturated ester **9a**. Reduction to diol **9b** and acetylation with acetic anhydride gave bis(allylic acetate) **9c**. Acetonide removal under mildly

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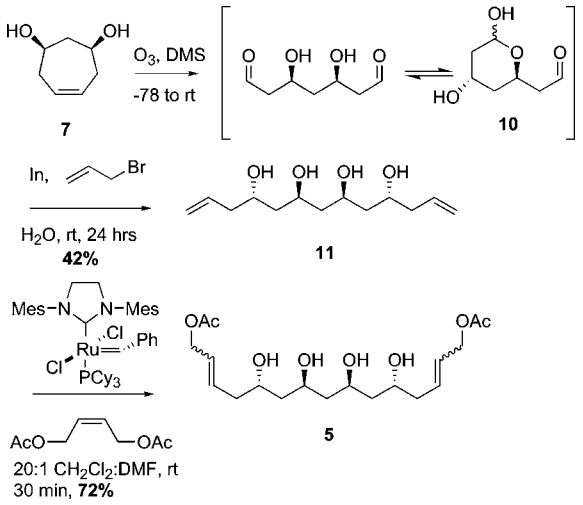
acidic conditions furnished the all-syn cyclization precursor **2** in 7 steps and 44% overall yield.

A much shorter route (Scheme 3) was devised to generate anti-syn-anti cyclization precursor **5**. Ozonolysis of cyclo-

Scheme 3



hept-5-ene-*syn*-1,3-diol (**7**),[17] followed by indium-mediated allylation[18a] of the intermediate dialdehyde afforded bis-(homoallylic alcohol) **11** in 42% yield after chromatographic separation of diastereomers. While indium-mediated allylations of β-hydroxy aldehydes have been shown to proceed with high anti selectivity,[18b] we believe that interference by hemiacetal **10** degrades the directing ability of the internal hydroxyls, reflected in the modest yield of **11**. Next, a double cross metathesis with *cis*-1,4-diacetoxy-2-butene[19] afforded directly the anti-syn-anti double cyclization substrate **5** as a mixture of *E*,*Z* isomers. Typically, the product consists of a 5:1 ratio of *E*:*Z* linkages based on ^{1}H NMR; however, as either allylic acetate geometry affords the same π-allyl palladium intermediate during the subsequent cyclization, the mixture of isomers was immaterial. Overall, the cyclization substrate **5** was synthesized from **7** in 3 steps and 30% yield, without the use of protecting groups.

On the basis of Trost and Toste's transition state model for the DPPBA ligand system (Figure 2),[20] we anticipated that cyclization of **2** with (*R*,*R*)-*N*-[2,(2′-diphenylphosphino)

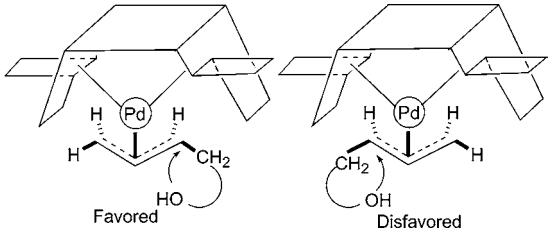
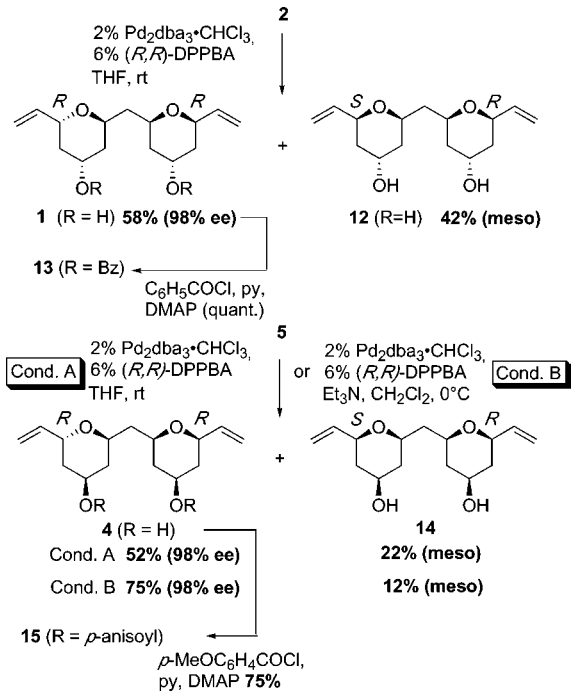


Figure 2. General T.S. Model for (*R*,*R*)-DPPBA ligand.[20]

benzamido cyclohexyl] (2′-diphenylphosphino) benzamide ligand [(*R*,*R*)-DPPBA] would effect the double cyclization to yield (*R*,*R*)-**1** (Scheme 4). Initial efforts with **2** showed

Scheme 4



that in addition to the desired desymmetrized product **1**, significant formation of meso diastereomer **12** had also occurred (d.r. 1.4:1). Subsequent benzoylation of **1** gave dibenzoate **13**, which had an enantiomeric excess of >98% by chiral HPLC analysis.[21] Cyclization of **5** with identical conditions afforded dissymmetric **4** (52%) as well as meso diastereomer **14** (22%). Further optimization[22] increased both the yield of the desired diastereomer (75%) and diastereoselectivity (~6.4:1) in the anti-syn-anti case (**5** → **4**). The enantiomeric excess of the *p*-methoxy benzoyl ester **15** was determined to be >98% by chiral HPLC analysis.[21]

Our rationale for moderate-to-good diastereoselectivity (**1** vs **12** and **4** vs **14**), yet high enantioselectivity (**1** and **4**) during the double cyclizations is outlined in Scheme 5.

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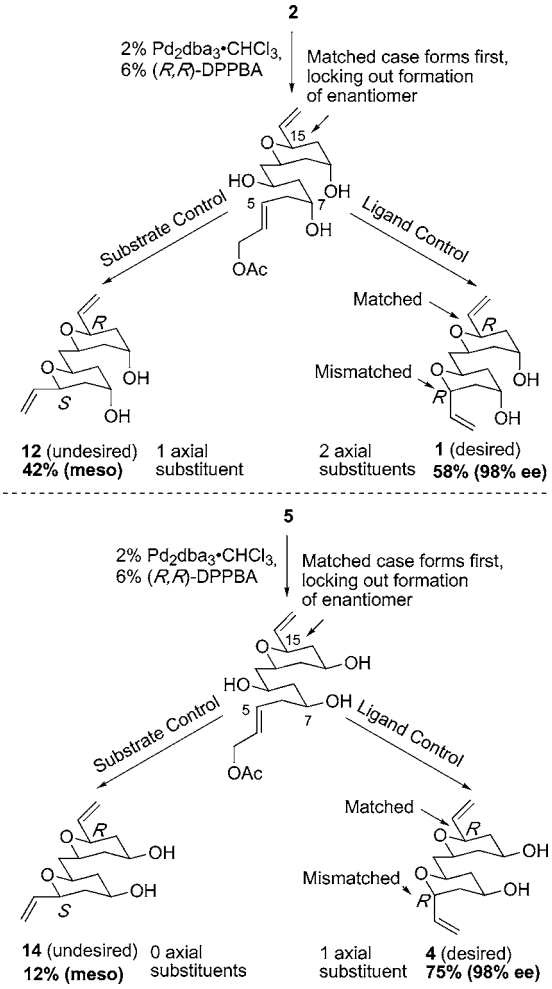
(20) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545.
(21) Absolute stereochemistry was assigned based on application of the model in Figure 2. Enantiomeric excess was determined by synthesizing the enantiomer using (*S*,*S*)-DPPBA and injecting against a standardized mixture of the two enantiomers on a Chiracel-OD HPLC column.
(22) Machacek, M. R.; Trost, B. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4693.

Scheme 5



Assuming that formation of regioisomeric Pd π-allyls is fast and reversible,[23] we propose that differing cycloetherification rates at C15 and C5 explain the observations. When all-syn tetraol **2** is subjected to the palladium-cyclization conditions, the C15 pyran forms first, the result of a matched interaction between ligand control and a steric preference to form the product with an equatorial vinyl group. Using the case of (*R*,*R*)-DPPBA as an example, one stereogenic center has been set in the *R* configuration, preventing the formation of the enantiomer. However, the second cyclization event represents a mismatched case of ligand control and intrinsic steric bias. The product of ligand control is the desired *R*,*R* isomer **1** with one equatorial (C15) and one axial (C5) vinyl group. If the substrate preference directs the second cyclization, the more stable *S*,*R* isomer **12**, with two equatorial vinyl groups, results. Thus, the major, dissymmetric product is formed in high enantiomeric excess, but a substantial quantity of meso diasteromer also is formed.

A similiar explanation applies in the case of anti-syn-anti tetraol **5**, and is consistent with the improved diastereoselectivity, favoring dissymmetric **4** over meso **14**. Again, the C15 vinyl group in both products is equatorial, while the C5 vinyl group is axial in the ligand-controlled case **4** and equatorial in the sterically favored product **14**. We suggest that the absence of a 1,3 diaxial interaction in product **4** (equatorial C7 hydroxyl) as compared to **1** (axial C7 hydroxyl) affords an increase in diastereoselectivity.

In conclusion, we have demonstrated the utility of chiral ligand-controlled, palladium-mediated desymmetrization of expeditiously prepared meso polyol chains. The target bis-tetrahydropyran systems were prepared in good yield and excellent enantiomeric excess, and their utility toward phorboxazole synthesis is under investigation.

Acknowledgment. We thank the NIH (Grant CA74394) for generous support, the Samuel H. Gellman group for assistance with chiral HPLC, and Prof. Robert H. Grubbs for helpful discussions regarding olefin cross-metathesis.

Supporting Information Available: Experimental procedures and characterization data for compounds **1**−**15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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