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A Novel Route to the F-Ring of Halichondrin B. Diastereoselection in Pd(0)-Mediated *meso* and C_2 Diol Desymmetrization

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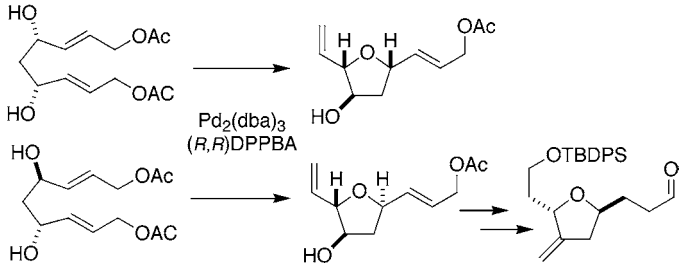
ABSTRACT



Both σ and C_2 symmetric diol diacetates were synthesized via two-directional chain elongation. A palladium-mediated, ligand-controlled C_2 diol desymmetrization provided the desired tetrahydrofuran with the correct relative and absolute stereochemistries. Simple functional group manipulation led to the desired F-ring of halichondrin B. Desymmetrization of the *meso* substrate enantioselectively provided the diastereomer, leading to a refinement of our understanding of the transition state model.

Halichondrins are a family of eight polyether macrolides that were isolated from marine sponges.[1] Among them, halichondrin B (Figure 1) was found to possess the most potent biological activity. It displays an in vitro IC_{50} value of 0.3 nM against L1210 leukemia, as well as remarkable in vivo activities against various chemoresistant human solid tumor xenographs. Potent activity against LOX melanoma, KM20L colon, FEMx melanoma, and OVCAR-3 ovarian cancer cell lines has been observed.[2]

The National Cancer Institute has recommended halichondrin B for stage A preclinical trials,[2c] but limited availability has made it difficult to proceed. Synthetic efforts have been devoted to halichondrin B by several groups, highlighted by Kishi's total synthesis.[3] Recently, it was reported that the

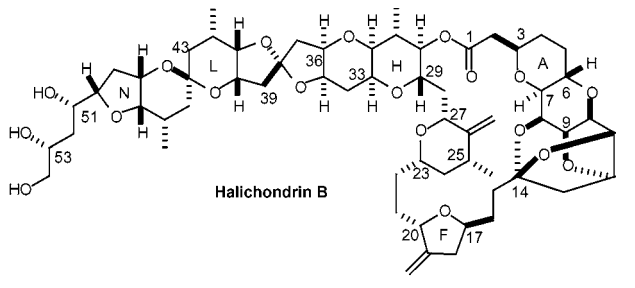


Figure 1.

(1) For isolation, see: (a) Hirata, Y.; Uemura, D. *Pure Appl. Chem.* **1986**, *58*, 701. (b) Pettit, G. R.; Herald, C. L.; Boyd, M. R.; Leet, J. E.; Dufresne, C.; Doubek, D. L.; Schmidt, J. M.; Cerny, R. L.; Hooper, J. N. A.; Rutzler, K. C. *J. Med. Chem.* **1991**, *34*, 3339. (c) Pettit, G. R.; Ichihara, Y.; Wurzel, G.; Williams, M. D.; Schmidt, J. M.; Chapuis, J. C. *J. Chem. Soc., Chem. Commun.* **1995**, 383. (d) Pettit, G. R.; Tan, R.; Gao, F.; Williams, M. D.; Doubek, D. L.; Boyd, M. R.; Schmidt, J. M.; Chapuis, J.; Hamel, E.; Bai, R.; Hooper, J. N. A.; Tackett, L. P. *J. Org. Chem.* **1993**, *58*, 2538. (e) Pettit, G. R.; Gao, F.; Doubek, D. L.; Boyd, M. R.; Hamel, E.; Bai, R.; Schmidt, J. M.; Tackett, L. P.; Rutzler, K. C. *Gazz. Chim. Ital.* **1993**, *123*, 371. (f) Litaudon, M.; Hart, J. B.; Blunt, J. W.; Lake, R. J.; Munro, M. H. G. *Tetrahedron Lett.* **1994**, *35*, 9435.

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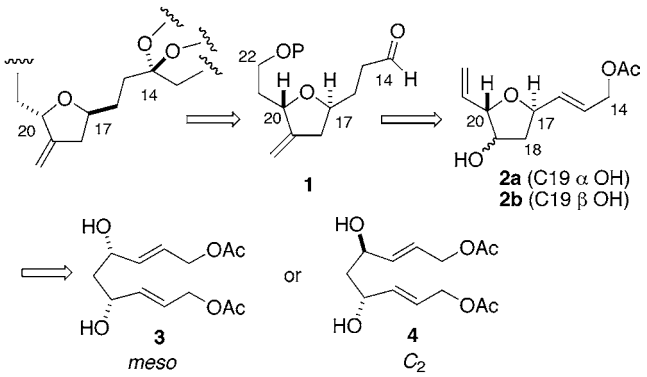
C1−C38 fragment possesses a potency similar to the natural product.[3a] Our group has successfully synthesized segments of halichondrin B including C1−C15, C20−C36, and C37−C54.[4] Herein we would like to report our synthesis of the C14−C22 portion of halichondrin B, comprising the F-ring of the natural product.

Two-directional synthesis by simultaneous chain homologation and terminus differentiation[5] has been one of our main strategies in the synthesis of complex natural products.[6] It offers not only intrinsic efficiency in skeleton synthesis but also the possibility of higher enantio- and diastereoselectivity. One possibility involves the synthesis of a *meso* symmetric intermediate. Differentiation of the termini can be simplified as a result of the fact that the two ends are enantiotopic. Of the methods commonly employed in the desymmetrization, enzymatic or chemical, the latter have the obvious advantage because they are less substrate-limited. Chiral palladium reagents have been used extensively in desymmetrization reactions.[7] We present herein the further development and application of this tactic, which leads to a better understanding of the transition state of Pd/DPPBA[8]-catalyzed allylation reactions.

Retrosynthetically (Scheme 1), the F-ring of halichondrin B is viewed as a bridge between the C1−C13 and C23−C36 subunits of the molecule. Given the success observed in selectively accessing the (trans, threo, trans)- and (cis, threo, cis)-bis(tetrahydrofuran) annonaceous acetogenin core structures via DPPBA-mediated π-allyl palladium cyclization,[9] we evaluated structure **1** in relation to that chemistry. There exists an element of hidden *meso* or C_2 symmetry about C18 in **2a** and **2b**, respectively, in that the flanking stereocenters (see **2a**) at C17 and C19 are oppositely configured and have three carbon extensions (C16−C14 and C20−C22, respectively). We recognized the possibility of a palladium-mediated, DPPBA-controlled desymmetrization reaction to set the desired stereochemistries. It was envisioned that the *meso* diol bis(allylic acetate) **3**, which should be accessible from *cis*-1,4-diacetoxy-2-cyclopentene, would only undergo monocyclization and that the biscyclization product would be too strained to form. According to the model proposed by Trost and Toste, the C20 stereochemistry would be controlled via one of the (*R*,*R*)-DPPBA π-allyl palladium intermediates shown (Figure 2). Less obvious was which of the two hydroxyl/distal allyl acetate pairs would be reactive. Although the allyl acetate groups in *meso* **3** are enantiotopic, involvement of the chiral ligand renders the two π-allyl complexes in Figure 2 diastereomeric. We reasoned (incorrectly, vide infra) that there are two factors that favor the transition state labeled Chelation: (1) a potentially favorable interaction between palladium and adjacent free hydroxyl in the Chelation Model; (2) the unfavorable steric interaction between the palladium π-allyl complex and the spectator allyl acetate chain in the Non-chelation model.

Scheme 1. Retrosynthetic Analysis



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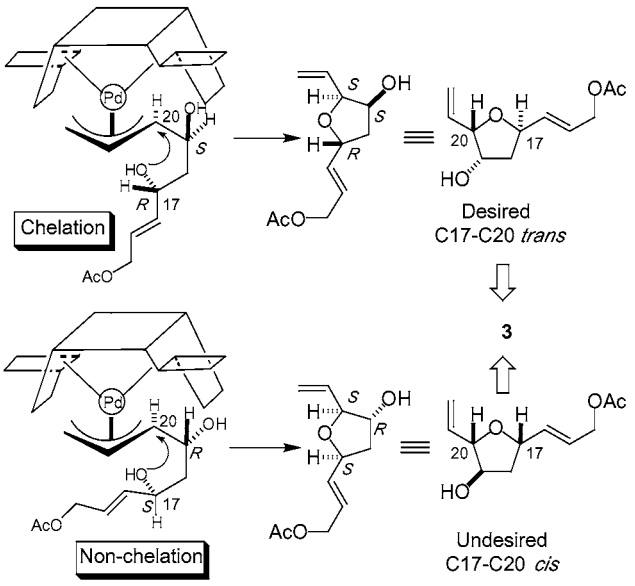
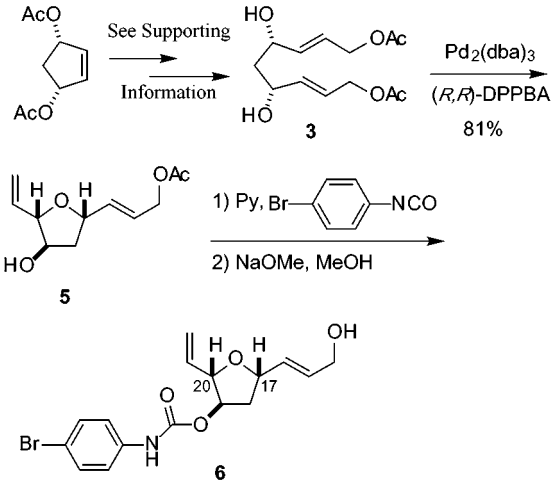


Figure 2. T.S. Model for desymmetrization of *meso* **3**.

Commercially available *cis*-1,4-diacetoxy-2-cyclopentene (Scheme 2) was converted via a straightforward sequence to the diacetate **3** via two-directional synthesis in good yield and selectivity.[10] The proposed desymmetrization of this *meso* diol diacetate proceeded smoothly, providing the tetrahydrofuran **5** (not **2a**) as the major product. To determine the stereochemical outcome of the desymmetrization, this cyclized product was transformed to a carbamate in two steps to provide the crystalline compound **6**.

Scheme 2. Attempted Cyclizations



As revealed in Figure 3, the undesired C17−C20 *cis* stereochemistry resulted in the newly formed THF ring in **5**. Apparently, an unfavorable interaction between hydrophilic hydroxyl and the hydrophobic phenyl group of the ligand disfavored the proposed chelation transition state.

(10) For details, see Supporting Information.

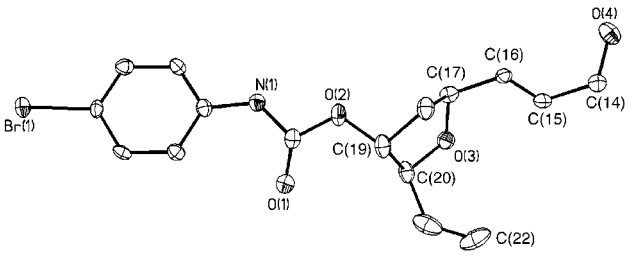
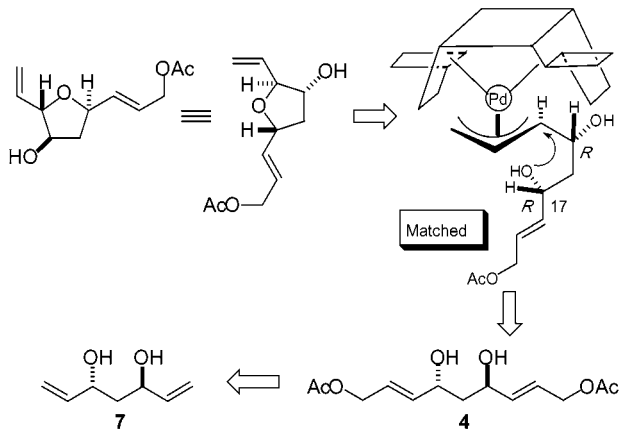


Figure 3. X-ray structure of carbamate **6**.

In light of these results, we revisited our retrosynthetic analysis (Scheme 3) and recognized that the desired stereochemistry could be set simply by switching the incipient C17 hydroxyl stereocenter on the starting diol diacetate, using **4** instead of **3**. The palladium-mediated DPPBA controlled desymmetrization reaction should be simplified since the two ends of the chain are now identical. This C_2 symmetric (*R*,*R*)-diol diacetate **4** was expected to be available from the diene diol **7**.

Scheme 3. Refined Analysis and T.S. Model for Desymmetrization of C_2 4.

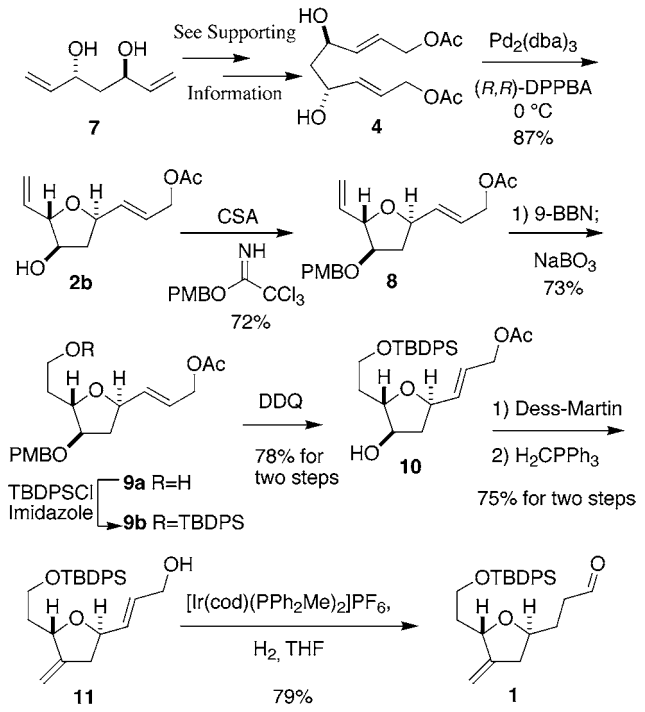


The C_2 symmetric diene diol **7**[11] was straightforwardly transformed into the desired diol diacetate **4** via two-directional synthesis in 78% overall yield. Initially, attempted desymmetrization resulted in competitive formation of the double cyclization product along with the desired mono-cyclized product. Gratifyingly, when the reaction temperature was lowered to 0 °C, the proposed desymmetrization of this C_2 diol diacetate **4** proceeded smoothly, providing a 5:1 mixture of diastereomers (^{1}H NMR). This mixture of diastereomers was treated with *p*-methoxybenzyl trichloro-

(11) For the synthesis of diene diol **7**, see: Hoffmann, R. W.; Kahrs, B. C.; Schiffer, J.; Fleischhauer, J. *J. Chem. Soc., Perkin Trans. 2*, **1996**, 2407−2413.

acetimidate under acidic conditions. The desired *p*-methoxybenzyl ether **8** was isolated as the major product (Scheme 4).

Scheme 4



Selective hydroboration of the terminal alkene afforded alcohol **9a**, providing the functionality for the future coupling of the C23−C36 subunit. Protection of the primary alcohol as TBDPS ether **9b** and subsequent removal of the PMB group with DDQ gave the secondary alcohol **10**. Oxidation of the resulting alcohol **10** with Dess−Martin periodinane proceeded uneventfully, providing the corresponding ketone. The installation of the *exo*-methylene and concomitant deacylation was accomplished with excess methylenetriphenylphosphorane to give allylic alcohol **11**,[12] without observable epimerization. To confirm the stereochemistry of the THF ring, NOE experiments on both **11** and **12** (derived from **5** in a similar way as **11** was from **2b**) were performed (Figure 4). The allylic alcohol **12** displayed significant enhancement, whereas alcohol **11** did not show any NOE between H_a and H_b. Isomerization of the allylic alcohol with a cationic Ir catalyst gave aldehyde **1**.[13]

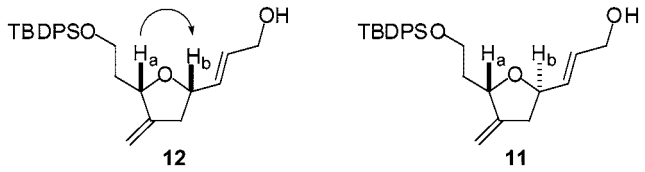


Figure 4. NOE studies.

In summary, an efficient synthesis of the C14−C22 segment of halichondrin B has been realized, featuring the desymmetrization of a C_2 symmetric diol diacetate via palladium/(*R*,*R*)-DPPBA catalysis. In this context, a refined understanding of the stereoselective desymmetrization of *meso* and C_2 symmetric substrates via this protocol has emerged.

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Supporting Information Available: Experimental procedures and spectral data for compounds **1**−**12** and crystallographic data for compound **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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