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Synthetic Efforts toward the C22–C36 Subunit of Halichondrin B Utilizing Local and Imposed Symmetry

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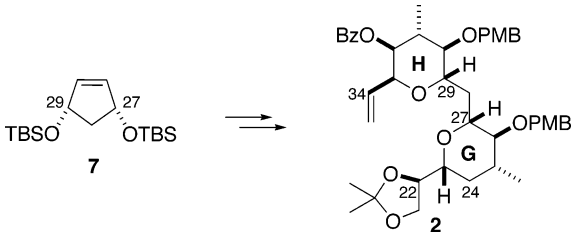
ABSTRACT



The C22–C34 portion (2) of halichondrin B was synthesized from *meso*-symmetric bis-silyl protected cyclopentenediol (7) in 20 steps and 7% overall yield. This was accomplished through a two-directional synthesis/terminus differentiation strategy that proceeded via achiral, *meso*-symmetric intermediates for eight steps and employed a Pd(0)-mediated asymmetric double cycloetherification to establish both tetrahydropyran rings.

Halichondrin B (Figure 1) is the most potent member of the halichondrin family of polyether macrolides and has been

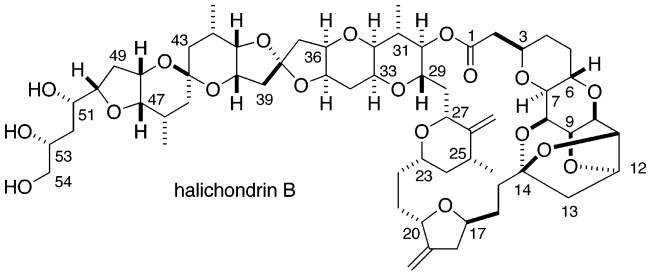


Figure 1. Halichondrin B.

isolated from several different sponge genera in extremely low yield (1.8×10^{-8} to 4.0×10^{-5} %).[1] This high potency is exemplified by its in vivo activity against various chemo-resistant human solid tumor xenografts. Binding studies showed that its mechanism of action is the inhibition of tubulin polymerization by binding near the vinca domain.[2] Because of its potential as an effective anticancer agent, the National Cancer Institute has recommended halichondrin B for stage A preclinical trials, although development has been impeded by low isolated yield from natural sources.

Several efforts have been made to address the demand for halichondrin B including aquaculture[3] and total synthesis. Kishi[4,5] has published the only total synthesis of halichondrin

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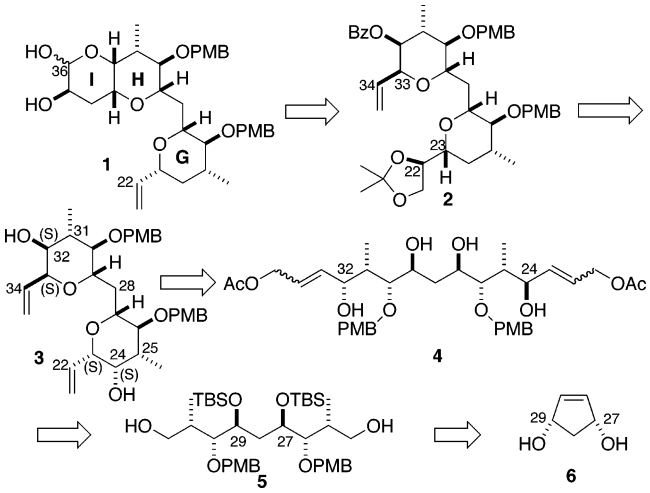
B to date and Yonemitsu[6] and Salomon[7] have each published subunit syntheses. We have completed the synthesis of the C1−C14,[8] C14−C21,[9] and C37−C54[10] subunits, and in this Letter we describe a route to the remaining C22−C36[11] subunit of halichondrin B.

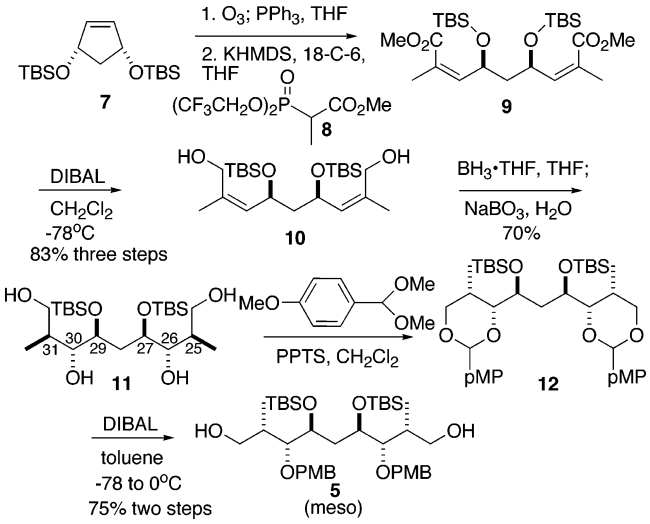
Our approach to this structurally complex natural product has been to utilize both subunit convergence and imbedded symmetry elements to significantly simplify the subunit syntheses. The retrosynthesis (Scheme 1) of this G,H,I-ring system (**1**) begins with the disconnection of the I-ring at C34 and differentiation of C23 and C33 vinyl groups to give **2**. It was envisioned that the C19 and C26 *exo*-methylenes in halichondrin B could be introduced simultaneously at a late stage in the synthesis in order to increase efficiency. It was anticipated that imposing a full measure of stereochemical and functional group symmetry, as in **3**, would optimize a two-directional synthesis strategy.[12] Note that in **3** there is local *meso*-symmetry about C28, extending from C25 through C31, which would allow *substrate*-controlled, two-directional synthesis. However, because C23 and C33 have the same configuration, as do C24 and C32, *reagent*-controlled introduction of these stereocenters in **3** via two-directional synthesis was indicated. The construction of the G- and H-rings in **3** was anticipated based on earlier success with Pd(0)-mediated asymmetric double cycloetherification,[13] leaving intermediate **4** to serve as the cyclization substrate. Our previous efforts toward the G,H-ring system revealed that introduction of the C32 oxygen functionality could not be accomplished on the dihydropyran H-ring.[14] Therefore, the C32 hydroxyl would have to be installed prior to ring formation to avoid this difficulty. Chiral cyclization precursor **4** could be obtained from *meso*-symmetric **5** after two-directional chain extension, Sharpless asymmetric epoxidation (SAE)[15] to install the C24 and C32 oxygen functionalites, and further two-directional chain extension. Finally, diol **5** could be formed from *cis*-4-cyclopentene-1,3-diol **6**[16] through two-directional elaboration.

Scheme 1. Retrosynthesis



The synthesis began with the known bis-silyl protected cyclopentenediol (**7**),[17] which was oxidatively cleaved and exposed to the Still−Gennari[18] reagent **8** to give the *Z*,*Z*-diester **9** in good yield (Scheme 2). Reduction of the diester with DIBAL gave the bis(allylic alcohol) **10** in 83% overall yield from **7**. Hydroboration with BH_3·THF occurred selectively according to Kishi's empirical rule,[19] establishing

Scheme 2



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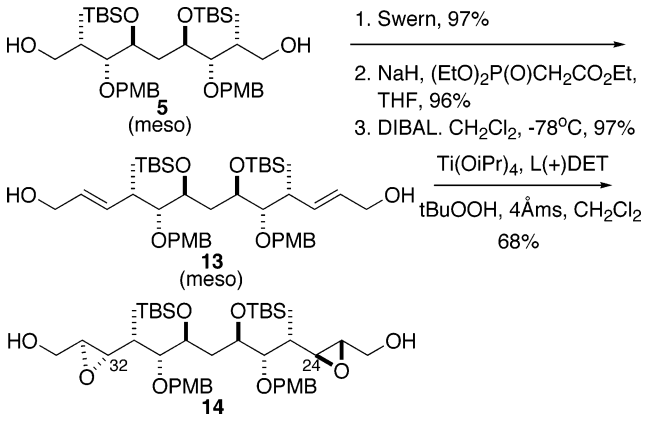
four stereocenters via substrate-controlled asymmetric induction to set the two stereotriads at C27−C25 and C29−C31 in **11**. Selective protection of the C30 and C26 secondary alcohols in **11** while leaving the primary alcohols at C32 and C24 unmasked was accomplished via the bis(*p*-methoxybenzylidine acetal), which was reduced to the diol **5** with DIBAL.[20]

Two-directional chain elongation of **5** via Horner−Wadsworth−Emmons (HWE) olefination of the derived dialdehyde and DIBAL reduction gave the *meso*-bis(allylic alcohol) **13** (Scheme 3). Symmetry breaking in **13** was

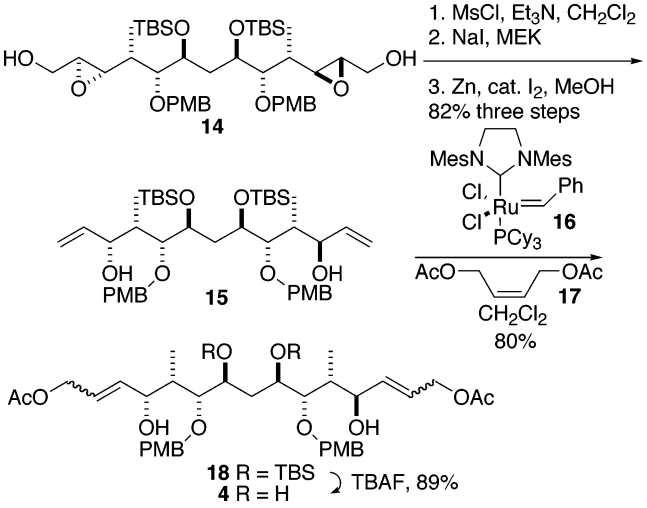
Scheme 3



accomplished via SAE[15] at each allylic alcohol unit. This (bis)epoxidation set the key C32 stereocenter along with introduction of an extraneous oxygen at C24, resulting in two sets of five contiguous stereocenters on the acyclic chain in **14**.

Installation of the allylic acetates needed for the Pd(0)-mediated asymmetric double cycloetherification started with the activation of the two primary alcohols in **14** as mesylates (Scheme 4). Treatment of the dimesylate with NaI resulted

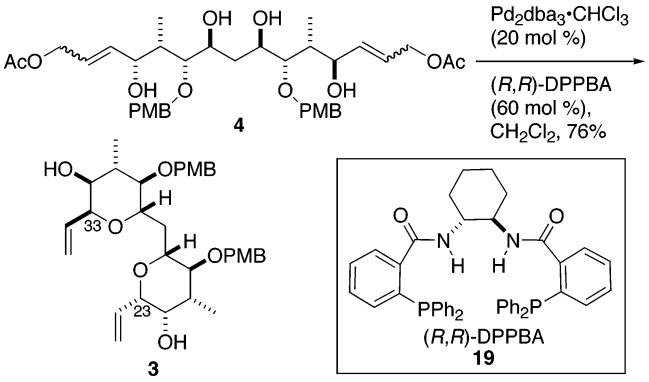
Scheme 4



in double S_N2 displacement and reductive fragmentation of the bis(iodo epoxide) using Zn powder in refluxing MeOH provided bis(allylic alcohol) **15** in good yield. Cross-metathesis employing the Grubbs catalyst **16**[21] occurred readily to install both allylic acetates in **18**.

Finally, cleavage of both TBS ethers using TBAF yielded **4**, the double cycloetherification substrate. Treatment of tetraol **4** with $Pd_2dba_3{\cdot}CHCl_3$ and the Trost (*R,R*)-DPPBA ligand **19**[22] established the bis(tetrahydropyran) G,H-rings in **3** with control of the absolute stereochemistry at C23 and C33 (Scheme 5). The stereochemistry of the product was

Scheme 5



determined by 1D NOESY experiments, which gave the enhancements shown in Figure 2.

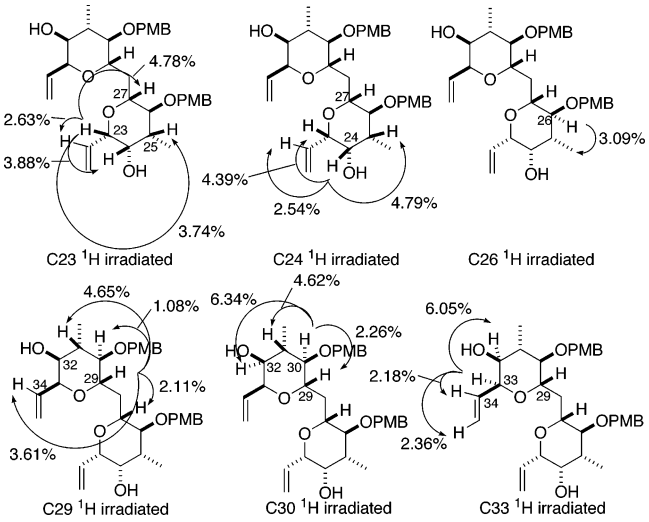
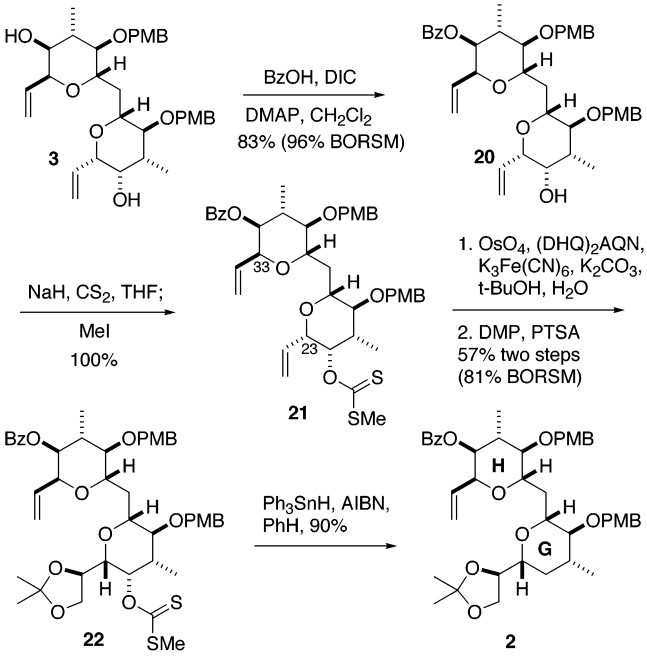


Figure 2. 1D NOESY enhancements in **3**.

At this point, differentiation of the C24 and C32 alcohols was needed in order to activate the former for removal (Scheme 6). The equatorial alcohol at C32 proved to be more reactive than the axial alcohol at C24. Selective protection using BzOH, DIC, and DMAP resulted in the ester **20** with

Scheme 6



no discernible formation of the regioisomeric benzoate. This transformation allowed for the activation of the C24 alcohol as a xanthate using standard conditions[23] to give **21** in excellent yield. Xanthate **21** was then treated with Ph_3SnH[24] and AIBN in refluxing benzene in order to promote the Barton−McCombie deoxygenation;[23] however, this resulted in a mixture of unidentifiable products, all of which appeared to be more polar than the starting **21**. Precedent exists for the deoxygenation of a homoallylic xanthate,[25] but also for its failure due to competing radical cyclization reactions.[26]

This necessitated that the G-ring vinyl substituent be converted into a spectator group to prevent any unwanted cyclization and to allow subsequent elaboration of the C33 vinyl group. Selective Sharpless asymmetric dihydroxylation of the C23 equatorial vinyl group over the C33 axial one[27] was accomplished with the $(DHQ)_2AQN$ ligand[28] to give the diol, which was protected as an acetonide to furnish **22** in moderate yield, accompanied by 30% recovery of **21**.

Exposure of **22** to Ph_3SnH and AIBN led to the deoxygenated product **2** in high yield. This resulted in the fully functionalized G- and H-rings needed for the C22−C36 segment **1**.

In summary, C22−C34 intermediate **2** was synthesized in 20 steps and 7% overall yield from the *meso*-symmetric cyclopentene **7**. Four of the stereogenic centers were set in the hydroboration of diol **10** using substrate control to form the stereotriads at C27−C25 and C29−C31. Desymmetrization was accomplished by SAE, which set the key C32 oxygen stereocenter as well as introduction of an extraneous alcohol at C24. Double cycloetherification to form the G- and H-rings simultaneously occurred using $Pd_2dba_3{\cdot}CHCl_3$ and Trost's chiral ligand **19** to establish the C23 and C33 stereocenters. Finally, removal of the extra hydroxyl group at C24 under Barton-McCombie conditions furnished the fully elaborated G- and H-rings in **2**.

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Supporting Information Available: Experimental procedures and spectral data for compounds **2**−**5, 9**−**18,** and **20**−**22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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