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An Expeditious Synthesis of the C(1)-C(14) Subunit of Halichondrin B

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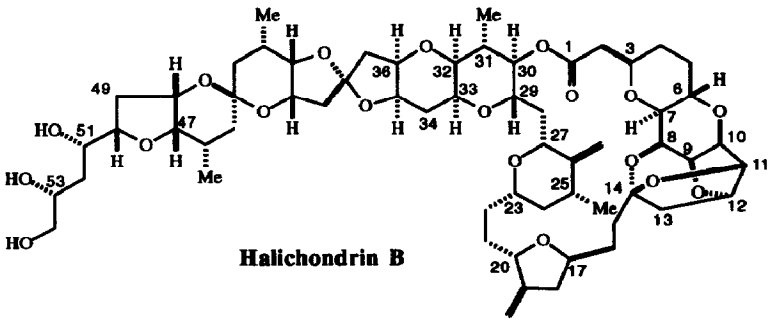
Key Words: pinacol rearrangement; intramolecular Michael addition; halichondrin B subunit

Abstract: *The synthesis of the C(1)-C(14) segment* ***1*** *of halichondrin B was achieved efficiently. Featured are the pinacol rearrangement of α-hydroxymesylate* ***9****, the intramolecular Michael addition of* ***11****, and the one-pot multistep conversion of* ***13*** *to* ***1****.*

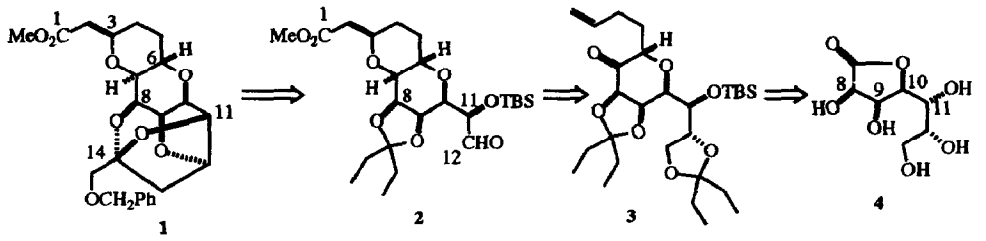
Halichondrin B (**Figure 1**) is the most potent member of a class of polyether macrolides isolated in low yield (1.8 x 10^{-8} to 3.5 x 10^{-6}%) from three different sponge genera (*Halichondria, Axinella,* and *Phakellia*).[1a-c] With a tubulin-based mechanism of action analogous to several antimitotic natural products,[1d-f] halichondrin B has displayed potent *in vivo* activity against chemoresistant human solid tumor xenografts in immune deficient mice.[1g] Preclinical development status has been recommended for halichondrin B,[1g] but the extreme scarcity of this substance and its congeners has hampered biological evaluation and detailed structure-activity studies. Synthetic approaches to the halichondrins have been described by Kishi and by Salomon, with the former group reporting a total synthesis of halichondrin B.[2] We recently reported a route to the C(22)-C(34) segment of the halichondrins,[3] and describe herein an expeditious synthesis of the bridged polycyclic C(1)-C(14) subunit.

Figure 1



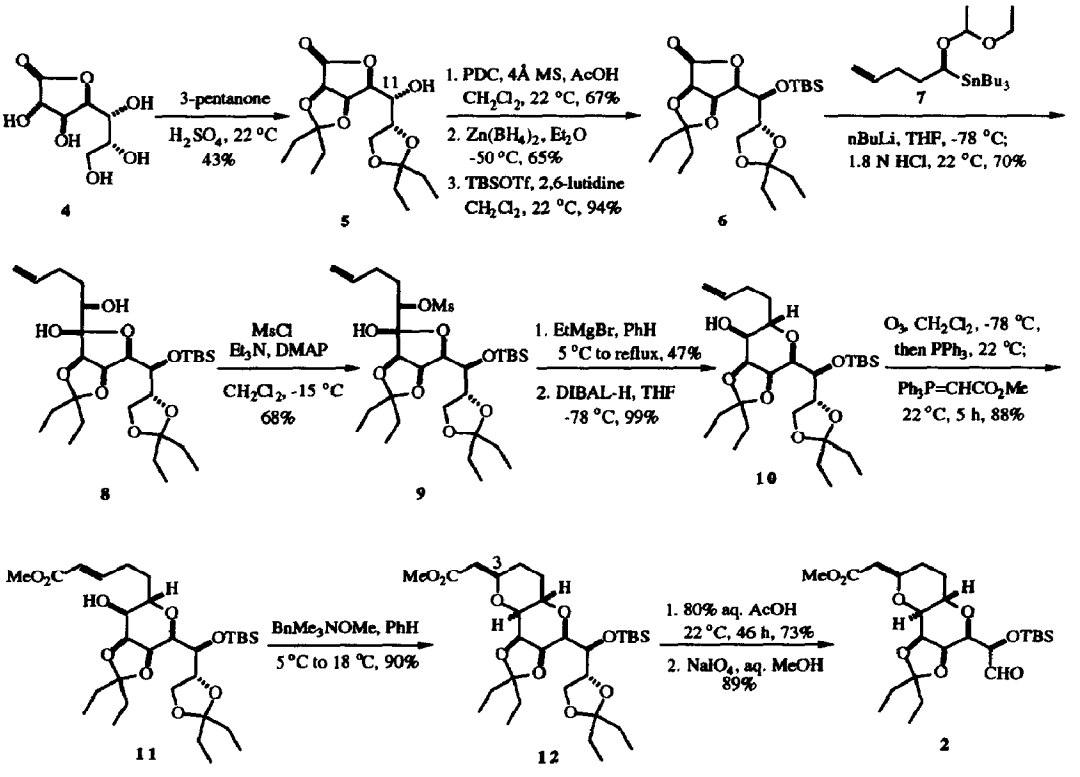
Halichondrin B

Scheme I



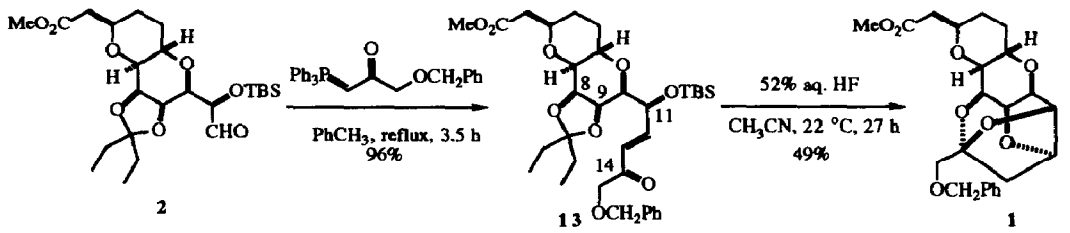
To illustrate our approach, a brief retrosynthesis is presented in **Scheme I**, utilizing Salomon's C(1)-C(14) subunit **1** as the target. The *trans*-fused dioxadecalin **2** has the appropriate functionality for establishing the cage structure in **1** via enone formation at C(12) and involvement of the C(8), C(9) and C(11) oxygen substituents. Most of the stereochemical detail in **2** is present in the pyranone **3**, which closely resembles the inexpensive carbohydrate **4** (D-*glycero*-D-*gulo*-heptono-γ-lactone), which served as the starting material for this synthesis. With the correct absolute stereochemistry at the C(8), C(9) and C(10) centers (halichondrin numbering), lactone **4** required only carbinol inversion at C(11).

Scheme II



Regioselective bis(ketalization)[4] of **4** with 3-pentanone (**Scheme II**) afforded **5**, in which the incorrect C(11) carbinol center was left unprotected. This contrasts with bis(acetonide) formation, which is known to proceed with a different regioselectivity.[4b,c] Oxidation[5] to the C(11) ketone and reduction[6] with $Zn(BH_4)_2$ gave the epimerized alcohol, which was converted to the *tert*-butyldimethylsilyl ether **6** in high yield. The α-alkoxyorganolithium reagent[7] derived from tin-lithium exchange on stannane **7** was added to lactone **6** to afford diastereomer **8** after acidic work-up. Conversion to the secondary mesylate **9** and treatment with ethylmagnesium bromide triggered a pinacol rearrangement[8] to give the pyranone **3**, which was converted to alcohol **10** upon stereoselective reduction. Ozonolysis and Wittig homologation proceeded in a one-pot operation to give the (*E*)-enoate **11** in high yield. Treatment with benzyltrimethylammonium methoxide in benzene converted **11** exclusively to the thermodynamically most stable C(3) epimer **12** via a Michael addition/ equilibration process. Selective deketalization[4b-d] of the terminal pentylidine ketal residue with 80% aqueous acetic acid and oxidative glycol cleavage gave aldehyde **2**, corresponding to the C(1)-C(12) segment of the halichondrins.

Scheme III



As shown in **Scheme III**, Wittig homologation[2h,9] of aldehyde **2** with [α-(benzyloxy)acetyl]methylenetriphenylphosphorane in toluene at reflux gave (*E*)-enone **13** in excellent yield. Treatment of **13** with 52% aqueous HF in acetonitrile (1:10 at 0.01 M) produced the polycyclic ketal **1** via a series of four *in situ* steps. Ketal and silyl ether cleavages followed by Michael addition of the C(9)-hydroxyl and ketalization of the C(14) center by the C(8) and C(11) hydroxyls all occurred in this reaction to afford the halichondrin B C(1)-C(14) segment **1**.[10]

The synthesis of **1** from inexpensive D-*glycero*-D-*gulo*-heptono-γ-lactone (**4**) required only 15 steps and proceeded in a highly stereoselective manner. Application of this route to the synthesis of halichondrins and analogs will be the subject of future studies.

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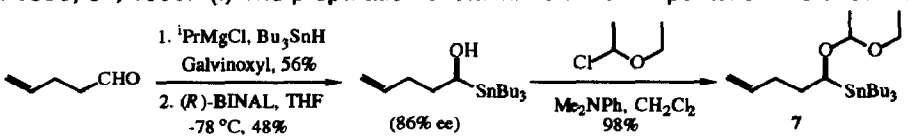

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