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Halichondrin B: Synthesis of a C1–C14 Model via Desymmetrization of (+)-Conduritol E

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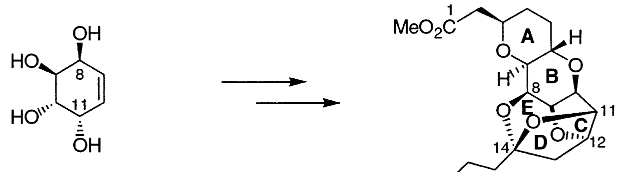
ABSTRACT



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A model C1–C14 segment (1) of halichondrin B was synthesized from (+)-conduritol E (7) in 18 steps and 2.9% overall yield. Key features of the synthesis include the novel ozonolytic desymmetrization of *C*$_2$-symmetric diol 6, the early-stage construction of the C-ring which accompanies installation of the crucial C12 stereocenter, and the use of an enol ether C14-ketone surrogate as a precursor to the CDE-"caged" ketal.

Halichondrin B (Figure 1) is the most potent member of a family of cytotoxic polyether macrolides isolated in low yield

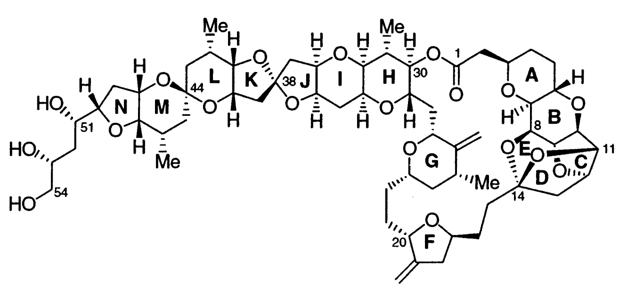

Figure 1. Halichondrin B.

(1.8×10^{-8}% to 4.0×10^{-5}%) from four different sponge genera.[1] As a mitotic inhibitor featuring a tubulin-based mechanism of action, halichondrin B displays potent in vivo activity against various human solid tumor xenografts, including LOX melanoma, KM20L colon, FEMX melanoma, and OVCAR-3 ovarian tumors.[2] It has also shown excellent in vitro activity against L1210 leukemia (IC_{50} = 0.3 nM).[3] Although halichondrin B has been recommended for stage A preclinical development by the National Cancer Institute (NCI), the scarce supply available from natural sources has made it difficult to proceed.

One potential solution to this supply issue lies in the work of Munro and co-workers on the aquacultural production of the marine sponge *Lissodendoryx* n. sp.[4] However, it has been noted that the generation of halichondrin B in quantities

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(2) (a) Personal correspondence with M. R. Boyd, M.D., Ph.D., Cancer Research Center, Frederick, MD, National Cancer Institute. Dr. Boyd shared with us data and slides that resulted in the NCI Decision Network Committee's selection of halichondrin B for drug development. (b) Personal correspondence with E. Hamel, M.D., Ph.D., National Institutes of Health, National Cancer Institute. Dr. Hamel informed us that halichondrin B cures in vivo human tumor xenografts transplanted in immune-deficient mice.

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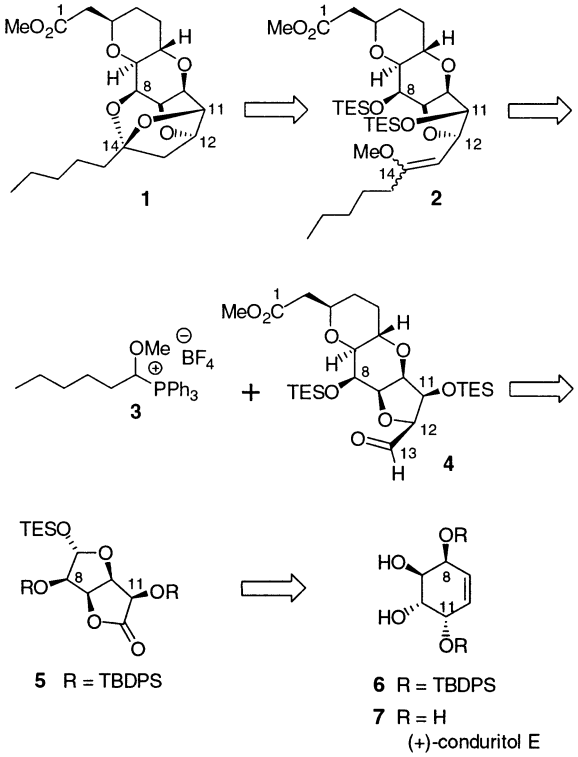
of 5 kg/year for clinical use would require quantities of sponge in excess of 5000 tons/year. Synthesis has also been explored as a means of accessing the requisite amount of natural product. Kishi and co-workers have reported syntheses of several subunits of halichondrin B[5] and have achieved the only total synthesis of this molecule to date.[5h] Salomon[6] and Yonemitsu[7] have also published synthetic approaches to halichondrin B. We have devoted considerable effort to this endeavor as well,[8] including a recent report of a synthesis of the C1−C15 subunit in 16 steps and 0.6% overall yield from inexpensive α-D-glucoheptonic acid γ-lactone.[8g] In this paper, we describe the synthesis of the known[5b] C1−C14 subunit model **1** from the C_2-symmetric natural product (+)-conduritol E.[9]

Our retrosynthesis of ketal **1** is depicted in Scheme 1. Hydrolysis of the enol ether and silyl ether functionalities of compound **2** was expected to lead directly to the 2,6,9-trioxatricyclo[3.2.2.0^{3,7}]decane framework (the CDE-ring "cage") of **1** via dehydration of the ketodiol. We were hopeful that the proximity of reactive functionality, enforced by the pre-set stereochemical configuration at C12 (halichondrin B numbering), would facilitate the desired ketalization relative to our previous work,[8g] where low and variable yields of caged ketal were attributed to poor control over the C12 stereochemistry in the final one-pot deprotection/Michael addition/ketalization cascade. Deprotonation of phosphonium salt **3** and reaction of the resultant ylide with aldehyde **4** should lead to **2**. Compound **4**, in turn, should be available from elaboration of γ-lactone **5**. Recognizing an element of local C_2-symmetry in the C8−C11 portion of **5**, we anticipated that it could be assembled from the C_2-symmetric (+)-conduritol E derivative **6** via a symmetry-breaking oxidative cleavage of the carbon−carbon double bond. The parent tetraol, (+)-conduritol E (**7**), is a known natural product which can be readily prepared from L-diethyl tartrate.[9]

Scheme 1. Retrosynthetic Analysis of Caged Ketal **1**



Our synthesis commenced with the bis(silylation) of **7** with TBDPSCl/py to provide diol **6** in good yield[10] (Scheme 2). Ozonolysis of **6** resulted in the formation of a dioxabicyclo[3.3.0]octane bearing a peroxyacetal residue at C12, which readily suffered dehydration with Ac_2O/Et_3N to provide the C7 hemiacetal **8** as a ca. 2:1 mixture of anomers. This desymmetrization protocol combines Criegee's tactic of

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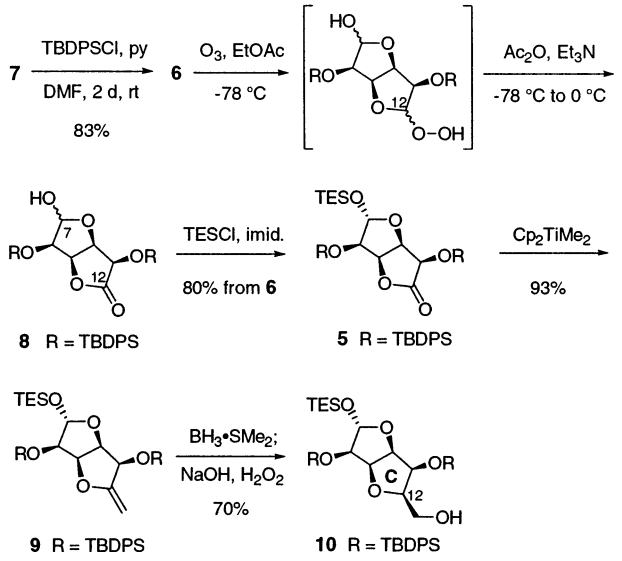
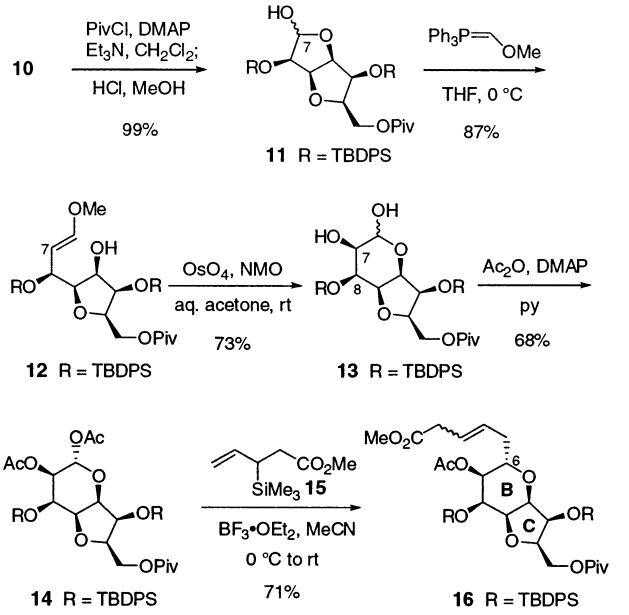
(10) A regioisomeric diol was also isolated in 19% yield.

Scheme 2. Fully Elaborated C-Ring Assembly



Scheme 3. B-Ring Assembly



trapping carbonyl oxides with suitably positioned internal nucleophiles[11] with Schreiber's ozonolytic desymmetrization of simple cycloalkenes.[12] Protection of **8** with TESCl/imidazole yielded lactone **5** as a single diastereomer, and methylenation of **5** with dimethyltitanocene[13] afforded enol ether **9**, which was purified by chromatography on silica gel without decomposition. Treatment of **9** with borane−methyl sulfide[8h,14] followed by exposure to basic hydrogen peroxide solution provided the desired 12(*R*)-hydroxymethyl-substituted C-ring **10** in good yield.[15] Use of catecholborane gave inferior yields, while 9-BBN failed to react with **9** altogether.

With the C-ring of the natural product installed, we directed our attention to the installation of the B and A rings. Pivaloate ester formation and triethylsilyl ether cleavage in a one-pot procedure starting from **10** furnished hemiacetal **11** (Scheme 3). From this point, B-ring construction was accomplished using methods previously employed by Kishi for a similar C7 hemiacetal.[5f,g] One-carbon Wittig homologation with methoxymethylene(triphenylphosphorane) provided enol ether **12**, which was subjected to catalytic osmylation to give **13** as a ca. 5:1 mixture of anomers, thereby setting the C7 carbinol center.[16] This diastereomer is predicted to be the major one based on Kishi's empirical rule.[17] Acetylation of **13** was rather sluggish, presumably due to the steric bulk of the C8 TBDPS ether, providing diacetate **14** as a single diastereomer in acceptable yield. Treatment of **14** with $BF_3{\cdot}OEt_2$ in the presence of the known[5g] allylic silane **15** afforded compound **16** as a ca. 3:1 (*E*)- to (*Z*)-mixture of olefin isomers, which contains the completed BC-ring system with a pendant β,γ-unsaturated ester moiety at C6 as a handle for A-ring construction.

It was hoped that isomerization of the carbon−carbon double bond in **16** to the α,β-unsaturated isomer would be accompanied by acetate ester cleavage and Michael addition of the resulting C7 alcohol to C3 of the enoate, thereby completing construction of the A-ring. Although Triton-B methoxide has traditionally been employed to effect similar transformations,[5f,g,8g] the acetate ester of **16** proved resistant to cleavage with this reagent. Attributing this sluggish reactivity again to the adjacent TBDPS ether, these bulky protecting groups were removed with TBAF buffered with acetic acid (Scheme 4). Subsequent treatment with a basic resin in methanol effected cleavage of the C7 acetate ester, providing triol **17**.[18] Exposure of this material to 10 equiv of DBU in refluxing toluene then afforded diol **18** as a single stereoisomer. When this reaction was conducted in refluxing benzene, a 2.9:1 mixture of **18** (major) and its C3 epimer was isolated in 94% yield. Apparently, higher temperatures are required to effect equilibration of this mixture via a retro-Michael/Michael addition pathway to the thermodynamically more stable isomer **18**, in which the C3 substituent is equatorially deployed with respect to the newly formed A-ring. Pivaloate cleavage was effected with a basic resin in refluxing methanol to give triol **19**. Protection of **19** as its tris(TES ether) and chemoselective oxidation of the primary TES ether under Swern conditions[19] then afforded aldehyde **4**.

(11) Criegee, R.; Banciu, A.; Keul, H. *Chem. Ber.* **1975**, *108*, 1642−1654.

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(15) The C12 epimer of **11** was also isolated in 13% yield.

(16) The C7 epimer of **13** was also isolated in 22% yield.

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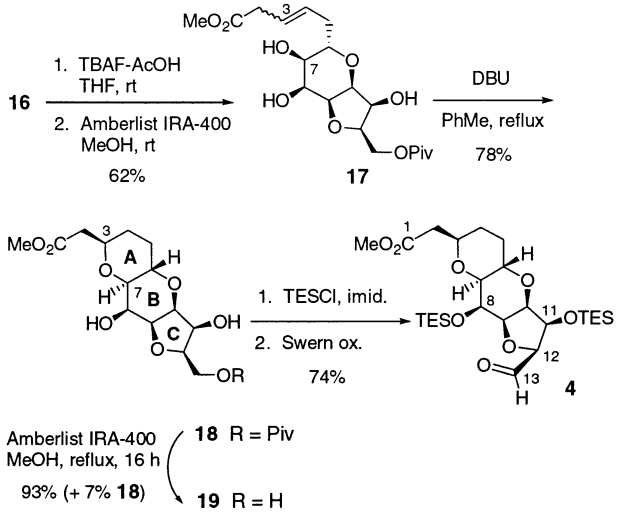
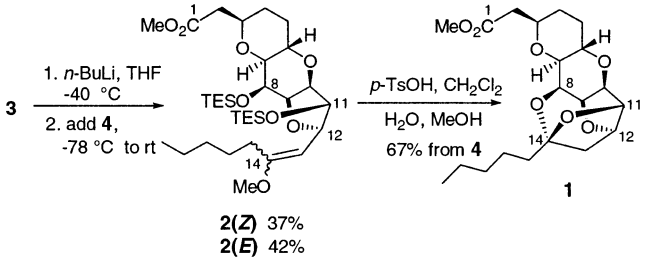
(18) A triol which had suffered C13 pivaloate migration was also isolated in 8% yield. This compound could be converted to the ABC-ring diol **18** using DBU in refluxing $PhCH_3$ as well.

Scheme 4. Synthesis of Aldehyde **4**



With **4** in hand, we focused on the simultaneous chain homologation of the C13 aldehyde and installation of an appropriate C14 ketone precursor by a method adaptable to subunit convergence in the total synthesis. For this purpose, the phosphonium tetrafluoroborate salt **3**[20] was deprotonated with *n*-BuLi at −40 °C, and the resultant ylide was allowed to react with aldehyde **4** at −78 °C followed by warming to room temperature (Scheme 5). Enol ethers **2(*Z*)** and **2(*E*)**

Scheme 5. Assembly of Caged Ketal **1**



were isolated in 37% and 42% yield, respectively, after chromatography on Florisil. Although we were successful in separating and purifying these sensitive compounds, it was more convenient to simply subject the crude mixture to acidic hydrolysis with *p*-TsOH in a mixture of CH_2Cl_2/MeOH/H_2O (ca. 4:2:1). We were pleased to observe the formation of the desired CDE-caged ketal **1** in 67% yield (two steps from **4**) under these conditions. The ^{1}H NMR data for **1** were in excellent agreement with those in the literature.[5b] Although the acid-labile ketal was stable to these conditions for several hours at ambient temperature,[21] other conditions (aq HCl/THF; aq HF/MeCN; *p*-TsOH/$CHCl_3$) gave significant amounts of C11−C14 furan byproducts. We have previously observed this undesirable reactivity manifold with related substrates and have discussed the mechanism elsewhere.[8g]

In conclusion, we have achieved the synthesis of the known ketal **1** containing the ABCDE-ring system of halichondrin B in 18 steps and 2.9% overall yield from (+)-conduritol E (**7**). This work features a novel desymmetrization of C_2-symmetric diol **6**, an early-stage installation of the densely functionalized C-ring, and takes advantage of seldom-employed α-methoxyphosphorane chemistry to extend the carbon chain at C13 and set the stage for the crucial caged ketal formation. The conjecture that control of the C12 stereocenter would improve the caged ketal formation was validated by the clean, high-yielding conversion of **4** to **1**.

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Supporting Information Available: Experimental procedures and spectral data for compounds **1**−**6**, **8**−**14**, **16**−**19**, and unnumbered intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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