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Total Synthesis of Halichondrin C

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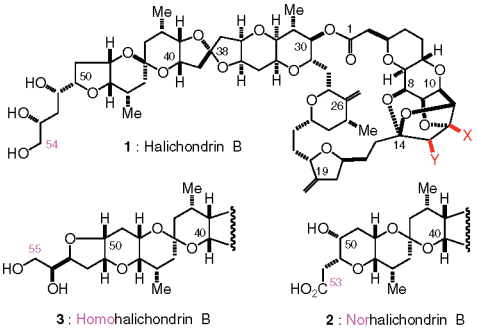
Supporting Information

ABSTRACT: The first total synthesis of halichondrin C has been completed, highlighted by development of the synthetic method to construct the C8−C14 polycycle. Cr-mediated coupling reactions are used seven times to form a new C−C bond. The acid stability of halichondrin C is studied, demonstrating that the macrolactone stabilizes the C8−C14 polycycle, relative to the one present in the C1−C16 model.

Halichondrins are polyether macrolides, originally isolated from the marine sponge *Halichondria okadai* by Uemura, Hirata, and co-workers.[1] Depending on the oxidation state at C12 and C13 of the C8−C14 polycycle or the length of the carbon backbone, halichondrins are subgrouped into the A−C series or the norhalichondrin−halichondrin−homohalichondrin series. Except halichondrin A, all the subgroup members are known (Table 1).[2]

Table 1. Subgroupings of Halichondrins

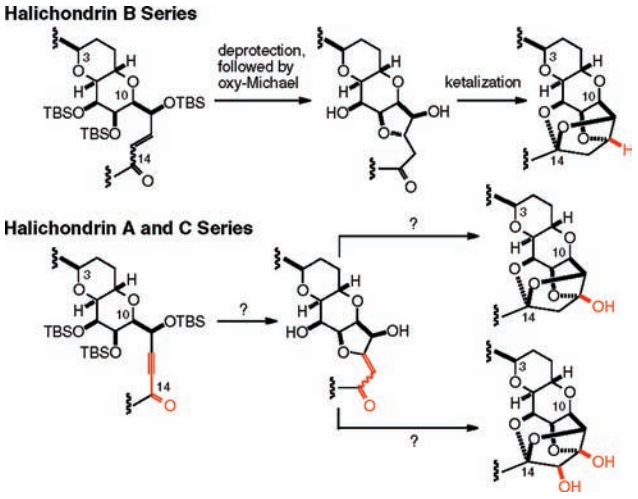


	A series (X=Y=OH)	B series (X=Y=H)	C series (X=OH;Y=H)
Halichondrin	unknown	known	known
Norhalichondrin	known	known	known
Homohalichondrin	known	known	known

In 1992, we reported the total synthesis of halichondrin B, norhalichondrin B, and homohalichondrin B.[3,4] On completion of the synthesis, we asked the late Dr. Suffness at the National Cancer Institute (NCI) and Dr. Littlefield at Eisai Research Institute (ERI) to test the *in vitro* and *in vivo* antitumor activities of the totally synthetic halichondrins, as well as several synthetic intermediates. The results were sensational: their experiments clearly demonstrated that the antitumor activities of halichondrin B reside in the right portion of the molecule,[5] which served as *the* foundation for successful development of the antitumor drug Halaven (Eribulin, E7389).[6] In this Communication, we report the first total synthesis of halichondrin C, highlighted by development of the synthetic method for construction of the C8−C14 polycycle and effective use of Cr-mediated coupling reaction seven times to form a new C−C bond.

In the halichondrin B series, the C8−C14 polycycle was constructed via an oxy-Michael reaction, followed by ketalization (Scheme 1).[3] The oxy-Michael addition gave the

Scheme 1. Plan for Construction of the C8−C14 Polycycle



desired stereoisomer as the major product, along with the undesired (minor) stereoisomer, which was recycled. Later, an ion-exchange resin-based device was developed to transform both stereoisomers to the desired product in one pot.[7] In an analogy, we hoped that the C8−C14 polycycle of both halichondrins A and C could be constructed from an ynone (Scheme 1). Specifically, we expected that an oxy-Michael addition of the C9 alcohol yields the enone, which should serve for the construction of the C8−C14 polycycle in both halichondrins A and C. Related to this plan, we should note our early work: hydrogenation of an enone similar to the one proposed took place exclusively from a convex face.[8]

We first studied the feasibility of this approach in a model system (Scheme 2). Ynone **4** was uneventfully prepared from the C1−C11 building block reported previously.[9] On treatment with HF−pyridine in MeCN, **4** gave a ca. 4:1 *E*- and *Z*- mixture of **5a** (ca. 40% combined yield) and C8/C9-ketal **6** (ca. 30% yield). Apparently, **6** was formed via oxy-Michael addition of the C8 hydroxyl to the enone **5a**; indeed, DBU treatment of the

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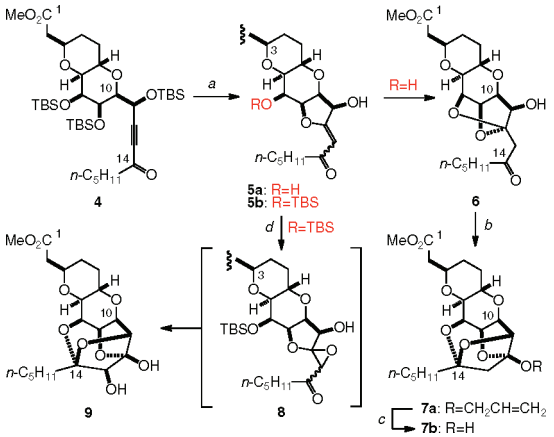
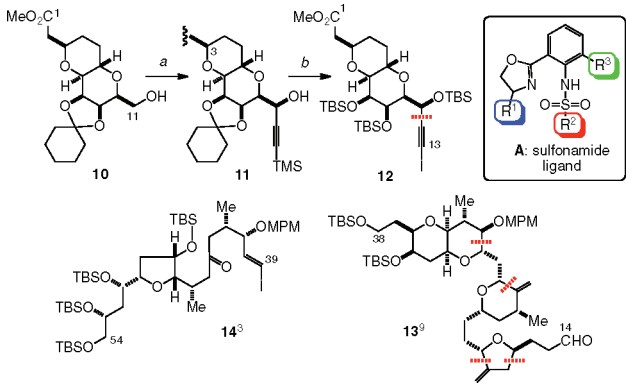
Scheme 2. Model Studies for C8−C14 Polycycle Synthesis[a]



[a]Reagents and conditions: (a) For **4**→**6**, HF-py, MeCN, rt, then DBU, rt (90%). For **4**→**5b**, HF-py, py, MeCN, rt (70%). (b) $Hf(OTf)_4$, allyl alcohol, THF, rt (59%). (c) $Pd[P(Ph)_3]_4$, dimedone, CH_2Cl_2, rt (quant). (d) DMDO, acetone, rt, followed by CSA, wet CH_2Cl_2, rt, then HF-py, THF added (74%).

Scheme 3. Three Building Blocks and C1−C13 Building Block Synthesis[a]



[a]Cr-mediated coupling was used to form the C−C bond at the sites indicated by a red broken line. Reagents and conditions: (a) i. Dess−Martin oxidation. ii. cat. asymm Ni/Cr-mediated coupling with Br-C≡C-TMS with sulfonamide **A** with R^1 = (*S*)-*i*-Pr, R^2 = $PhCl_2$-3,5/R^3 = OMe (dr: 23:1; overall yield of **11**: 75%). (b) i. TFA, wet CH_2Cl_2, rt. ii. TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C→rt. iii. NIS, $AgNO_3$, DMF, rt (94% overall yield).

crude HF−pyridine product furnished **6** in 90% overall yield from **4**. The spectroscopic data fully supported the proposed structure **6**, which was ultimately confirmed by an X-ray analysis of its *p*-nitrophenylcarbamate.[10,11]

Because of the facile, second oxy-Michael addition, it was difficult selectively to obtain the enone with a free hydroxyl group at C8. For this reason, we became interested in the possibility of converting the C8/C9-ketal into the C8−C14 polycycle. In particular, we speculated that such a transformation could be achieved with an acid in the presence of an alcohol. Because of their compatibility with protic solvents, we tested lanthanide triflates; indeed, $Sc(OTf)_3$, $La(OTf)_3$, and $Y(OTf)_3$ promoted the desired transformation. Among Lewis acids tested, $Hf(OTf)_4$ was found most effective for this transformation.[12] Methanol, allyl alcohol, and ethanethiol were effective in trapping the C12 oxonium ion in the C8−C14 polycyclic ring.[13] For the synthesis of halichondrin C, we chose to use allyl alcohol; on treatment with $Pd[P(Ph)_3]_4$,[14] the allylic ether was smoothly removed to give the C8−C14 polycycle in the halichondrin C series.[15] The structure of product was established on comparison with the ^1H and ^{13}C NMR data reported for natural halichondrin C.[1]

With the C8 hydroxyl group blocked, we sought a selective formation of the enone **5b** from **4** and eventually found that TBS deprotection with HF−pyridine in MeCN containing excess pyridine left the C8 axial TBS group intact, to furnish an 11:1 *E*- and *Z*-mixture of enone **5b** (70% combined yield). *E*- and *Z*-enones were chromatographically separable but gradually isomerized to a mixture on standing. We hoped that a Michael addition would allow us to selectively functionalize the enone, to construct the C8−C14 polycycle in the halichondrin A series. Unfortunately, we found that the enone exhibited a poor reactivity against common nucleophiles, including H_2O_2, under basic conditions.[16] In contrast, oxidation of chromatographically separated *E*-enone with DMDO and MCPBA, followed by acid treatment, gave the desired product as a dr = >30:1 (DMDO) and 1:1 (MCPBA) mixture of C13 diastereomers.[10,17] On comparison with the ^1H and ^{13}C NMR data reported for natural homohalichondrin A,[1] the major product obtained with DMDO was assigned as the desired stereochemistry at C13. The observed stereochemical outcome of DMDO oxidation is explained by the preferential convex approach, whereas that of MCPBA oxidation is a result of the C11-OH directing effect in the concave environment. These results were encouraging, yet we still need to develop a method for selectively oxidizing the enone over the exocyclic olefins at C19 and C26.[18]

With these results in hand, we began the synthesis of halichondrin C and decided to follow the synthesis of halichondrin B as closely as possible.[3] In this way, we can utilize the previously used C14−C38 and C39−C54 building blocks (Scheme 3).[3,19] We should note that the newly developed, convergent method was adopted to synthesize **13**; this method allowed stereoselectively to assemble **13** via catalytic asymmetric Cr-mediated coupling reaction at the sites indicated with a broken red line. With use of the catalytic asymmetric Ni/Cr-mediated reaction,[20−22] the remaining C1−C13 building block was synthesized from the known C1−C11 aldehyde[9] with good stereoselectivity.

Catalytic Ni/Cr-mediated reaction was used for coupling **12** with **13** (Scheme 4). Two observations are noteworthy. First, it was not necessary to use the asymmetric process, as both of the resultant allylic alcohols were oxidized to the same ynone. However, we noticed that the coupling was significantly more effective with the Cr catalysts prepared from the chiral sulfonamide ligand.[23] Second, we noticed that a Ni catalysts was required for this coupling, although activation of iodoalkynes without a Ni catalysts was recently reported.[24] The ynone thus obtained was converted to the seco-acid **15** and then to the macrolactone **16** with Shiina's reagent.[25,26]

Upon treatments with TBAF (buffered with imidazole hydrochloride) and then DBU, macrolactone **16** was cleanly converted to C8/C9-ketal **17**, which was transformed to the protected C8−C14 polycycle with $Hf(OTf)_4$ in THF containing allyl alcohol. This transformation took place in a way amazingly parallel to the model series. Finally, the functional groups at C35−C38 were adjusted to give **18** for the next Ni/Cr-mediated coupling.

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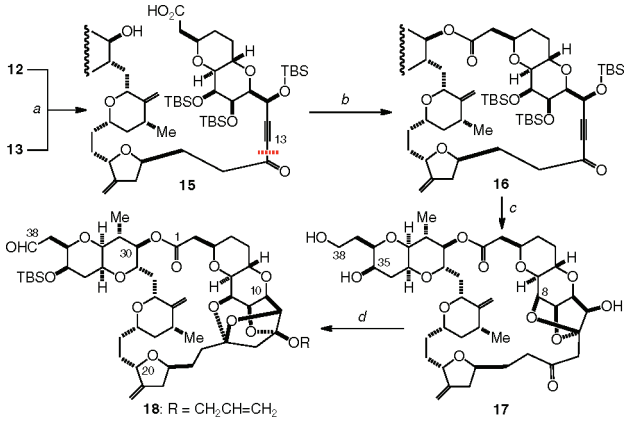
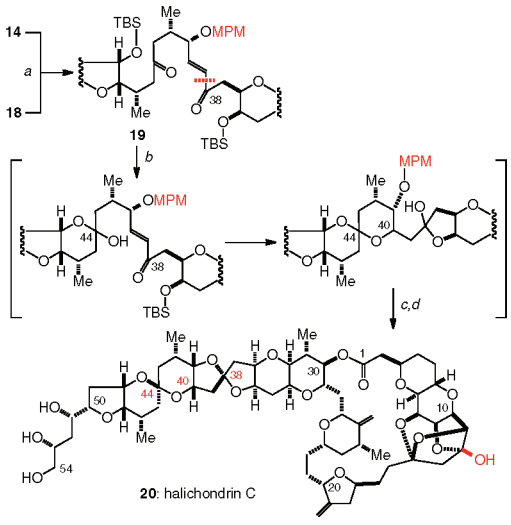
Scheme 4. Synthesis of the Right Half of Halichondrin C[a]



[a]Reagents and conditions: (a) i. cat. asymm Ni/Cr-mediated coupling with sulfonamide **A** with R^1 = (*S*)-*i*-Pr, R^2 = Me/R^3 = OMe (85%). ii. Dess–Martin oxidation, rt (94%). iii. DDQ, *t*-BuOH, CH_2Cl_2, phosphate buffer, 0 °C→rt (80%). iv. aq LiOH, THF, rt (87%). (b) $(2,6\text{-Me,NO}_2\text{PhCO})_2O$, DMAP, tol, 70 °C (high dilution) (93%). (c) TBAF-imidazole·HCl (0.5 equiv), THF, rt, then DBU, CH_2Cl_2, rt (68%). (d) i. $Hf(OTf)_4$, allyl alcohol, THF, rt (74%). ii. *p*-O_2NPhCOCl, py, CH_2Cl_2, rt (87%). iii. TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C (88%). iv. K_2CO_3, MeOH–CH_2Cl_2, rt (93%). v. Dess–Martin oxidation, rt (92%).

Scheme 5. Completion of Synthesis[a]



[a]Reagents and conditions: (a) i. stoich asymm Ni/Cr-mediated coupling with sulfonamide **A** with R^1 = (*S*)-*i*-Pr, R^2 = Me/R^3 = OMe. ii. Dess–Martin oxidation, CH_2Cl_2, rt (75% and 79% overall yield with a 1:1 and 1:2 mixture of **18** and **14**). (b) TBAF-imidazole·HCl (0.5 equiv), AcOMe, DMF, rt. (c) i. DDQ, *t*-BuOH, CH_2Cl_2, phosphate buffer, 0 °C→rt. ii. PPTS, CH_2Cl_2, rt (30% overall yield from **19**). (d) $Pd[P(Ph)_3]_4$, dimedone, CH_2Cl_2, rt (56%).

Once again, Ni/Cr-mediated reaction was used to couple **14** and **18** (Scheme 5). Because of the scale of this experiment, we opted to use a stoichiometric protocol and found that the sulfonamide ligand with R^1 = (*S*)-*i*-Pr, R^2 = Me, and R^3 = OMe greatly improved the coupling efficiency.[27] It is worth mentioning that this coupling gave a satisfactory result, even with a 1:1 molar ratio of coupling partners (75 and 79% yields with 1:1 and 1:2 ratios of **18** and **14**, respectively). The coupling product was then oxidized to enone **19**.

Following the protocol used for the synthesis of halichondrin B,[3] we subjected enone **19** to TBAF (buffered with 0.5 equiv of imidazole hydrochloride), DDQ, and PPTS treatment. This transformation involved (1) deprotection of the five TBS groups, (2) hemiketal formation at C44, (3) oxy-Michael addition of the resultant hemiketal hydroxyl group to the α,β-unsaturated ketone to form the [6,6]-spiroketal at C44, (4) deprotection of the C41-MPM group, and (5) formation of [5,5]-spiroketal at C38. To realize this transformation selectively, it was necessary to keep the C41-hydroxyl group protected at the TBAF step to avoid [5,6]-spiroketal formation at C44.

The three-step transformation introduced three stereogenic centers at C38, C40, and C44. Based on the following considerations, we anticipated that it should give the desired stereoisomer stereoselectively. In the antibiotic (−)-A23187 (calcimycin) synthesis,[28] we constructed the [6,6]-spiroketal system via a route closely related to the present case. This precedent suggested that the first two steps should give the desired stereoisomer at C40 and C44 under the kinetically and/or thermodynamically controlled conditions; indeed, TLC and ^{1}H NMR analyses indicated that it was highly stereoselective.[29] In addition, to ensure that the oxy-Michael reaction gave the desired equatorial adduct at C40, we tested a treatment of the crude product at the TBAF step with DBU and found that the DBU treatment did not noticeably affect the overall stereoselectivity. Last, the [5,5]-ketalization should yield the desired stereoisomer under the acidic (thermodynamically controlled) conditions.[27]

Preparative TLC purification furnished the C12 allyl-protected halichondrin C, cf. R = $CH_2CH{=}CH_2$ of **18**, in ca. 30% overall yield.[30] A small amount of several byproducts was isolated, but it was not clear whether any of them was a stereoisomer of halichondrin C.[28]

The final step of synthesis was to remove the allyl group at C12, which was accomplished with $Pd[P(Ph)_3]_4$,[14] to furnish synthetic halichondrin C (**20**). The synthetic material was fully characterized and confirmed to be identical with natural halichondrin C on comparison of ^{1}H and ^{13}C NMR spectra.

With synthetic halichondrin C (**20**) and C1–C16 model compound **7b** in hand, we had the opportunity to study their acid stability, thereby demonstrating a remarkable difference. Halichondrin C was found stable in CD_2Cl_2 containing CSA (0.1 equiv) at room temperature overnight, whereas the model compound was labile, yielding a ca. 1:1 mixture of two products.[31] Apparently, the macrolactone ring stabilizes the C8–C14 polycycle of halichondrin C, which is intriguing in two respects. First, the macrolactone did not affect for formation of the C8/C9-ketal and its transformation to the C8–C14 polycycle, yet stabilized the C8–C14 polycycle relative to the open-form model. Second, the observed stability of halichondrin C suggests the possibility that, once the macrolactone is introduced, the C8–C14 polycycle could be constructed from an open-form precursor under acidic conditions.

In summary, we completed the first total synthesis of halichondrin C, highlighted by development of the synthetic method to construct the C8–C14 polycycle. Cr-mediated couplings were used seven times\ to form a new C–C bond. The acid stability of halichondrin C was studied, thereby demonstrating that the macrolactone stabilizes the C8–C14 polycycle relative to the one present in the C1–C16 model.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, spectral data, crystallographic data (CIF), and complete ref 6a. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENTS

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(10) For details, see Supporting Information.

(11) The following abbreviations are used: CSA, camphor-10-sulfonic acid; DBU, 1,8-diazabicyclo[5,4,0]undec-7-ene; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DMAP, 4-dimethylaminopyridine; DMDO, dimethyldioxirane; MPM, *p*-methoxyphenymethyl; PPTS, pyridinium *p*-toluenesulfonate; TBAF, tetra-*n*-butylammonium fluoride; TBS, *tert*-butyldimethylsilyl; TMS, trimethylsilyl.

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(13) H_2O, $MeCO_2Na$, $ClCH_2CH_2OH$, and $TMSCH_2CH_2OH$ were not effective.

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(15) **7b** was also obtained from **5b** in four steps: (1) NBS, (2) $(n\text{-}Bu)_3SnH$, AIBN, (3) TBAF, and (4) PPTS, in 15% overall yield.

(16) Attempted nucleophiles included MeOH, EtSH, $MeCO_2K$, and *p*-MeOPhSH.

(17) DMDO oxidation of *Z*-enone **5b** gave the C13 diastereomer of **9** selectively.

(18) DMDO and MCPBA oxidation of a 1:1 mixture of **5b** and C14−C23 building block **11** (cited in *J. Am. Chem. Soc.* **2009**, *131*, 15636) revealed virtually no reactivity difference between the enone and the C19 exocyclic olefin.

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(23) There was no match/mismatch behavior observed between (*S*)- and (*R*)-sulfonamides for this coupling.

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(26) Macrolactone **16** was also obtained via esterification between C1-CO_2H and C30-OH, followed by macrocyclization of C13-iodoacetylene and C14-aldehyde. However, the route reported in the text gave a significantly better overall efficiency.

(27) For this coupling, we noticed a match/mismatch behavior, i.e., the coupling with the antipode of the sulfonamide ligand was significantly less satisfactory in terms of yield and coupling rate.

(28) Negri, D. P.; Kishi, Y. *Tetrahedron Lett.* **1987**, *28*, 1063.

(29) CSA and PPTS treatments of byproduct did not yield the desired product (^{1}H NMR).

(30) The overall yields of three separate experiments (8.5, 10.0, and 28 mg scales) were 32, 31, and 29%, respectively.

(31) Based on the MS and ^{1}H NMR spectra, one of the products appeared to be the C12/C14 *β*-diketone.