# Total Synthesis of Halichondrin A, the Missing Member in the Halichondrin Class of Natural Products

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S *Supporting Information*

ABSTRACT: A total synthesis of halichondrin A, the phantom member in the halichondrin class of natural products, is reported. The highlights of synthesis include: (1) synthesis of C1−C19 building block **6b** via a catalytic asymmetric Cr-mediated coupling of **12** and **13b**; (2) synthesis of the right-half of **19** via an asymmetric Ni/Cr-mediated coupling, followed by base-induced furan formation, and Shiina macrolactonization; (3) synthesis of enone **20** via Ni/Cr-mediated coupling of **5** with **19**, followed by oxidation; (4) synthesis of halichondrin A from **20**, with use of a newly discovered, highly selective TMSOTf-mediated equilibration of C38-*epi*-halichondrin A to halichondrin A. Two pieces of evidence are presented unambiguously to establish the structure of halichondrin A thus synthesized: one is the synthesis of norhalichondrin A (**24**) from **19** and **23**, and the other is the study of the proton chemical shift difference between synthetic halichondrin A and known members of this class of natural products.
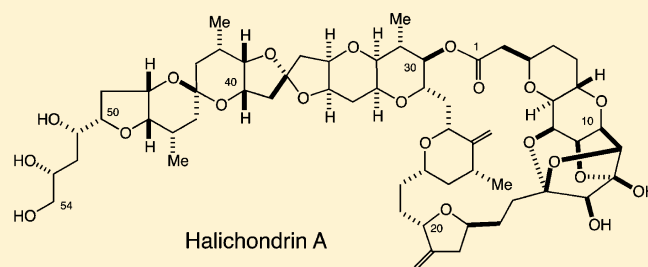
Halichondrin A

INTRODUCTION

Halichondrins are polyether macrolides, originally isolated from the marine sponge *Halichondria okadai* by Uemura, Hirata, and co-workers.[1] Several additional members, including halistatin, were isolated from various marine sponges.[2] This class of natural products displays interesting structure diversities at two sites: one being the oxidation state at C10, C12, and C13 of the C8−C14 polycycle and the other being the length of the carbon backbone. Thus, this class of natural products is subgrouped into halichondrins A−C series or the norhalichon-drin/halichondrin/homohalichondrin series. Except halichon-drin A, all the subgroup members have been isolated from the natural sources (Figure 1).[3] Due to their intriguing structural architecture and extraordinary in vitro and in vivo antitumor activity, halichondrins have received much attention from the synthetic community.[4,5] In this paper, we report a total synthesis of halichondrin A, the phantom member in this class of natural products.

SYNTHETIC ANALYSIS

We expected that unknown halichondrin A could be synthesized with the overall synthetic strategy used in the case of halichondrins B and C, i.e., halichondrins B and C were constructed from the right-half **4a,b** and the left-half **5**. Namely, we proposed a synthesis of "halichondrin A" from **4c** and **5**. We then disconnected the right-half **4c** into the C1−C19 and C20−C38 building blocks **6** and **7**. We were interested in the proposed synthetic plan primarily for four reasons. First, we recognized the possibility that the proposed synthesis of **4c** from **6** and **7** could be achieved by recently developed asymmetric Ni/Cr-mediated coupling, followed by base-
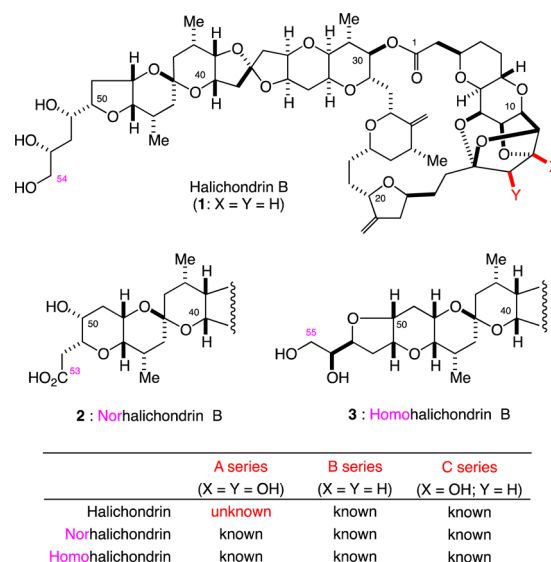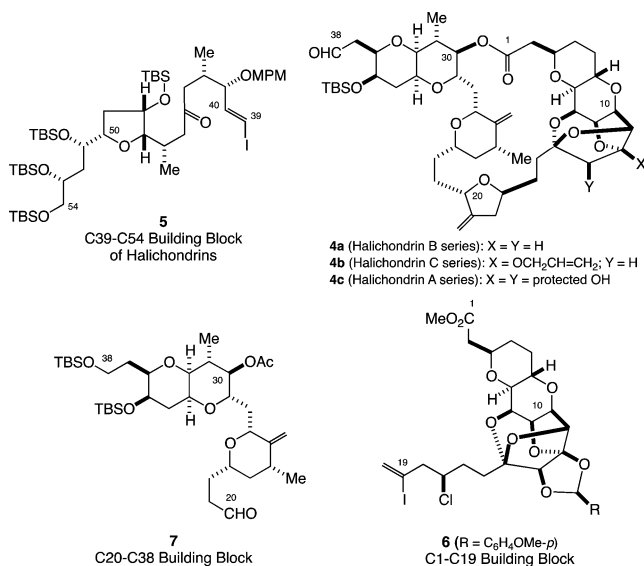

Figure 1. Structure of the halichondrin class of natural products.

induced cyclization.[6,7] Second, we should be able to utilize two blocks **5** and **7** used in the previous syntheses.[8] Third, we noticed a higher degree of convergency in this disconnection than in the previous routes.[9] Fourth, we envisioned the possibility that this approach can be extended to the synthesis of halichondrins B and C (Scheme 1).

Scheme 1. Retrosynthetic Analysis of Halichondrin A

5
C39-C54 Building Block
of Halichondrins

4a (Halichondrin B series): X = Y = H
4b (Halichondrin C series): X = OCH₂CH=CH₂; Y = H
4c (Halichondrin A series): X = Y = protected OH

7
C20-C38 Building Block

6 (R = C₆H₄OMe-*p*)
C1-C19 Building Block
of Halichondrin As

The central question for the synthesis of building block **6** was how to construct the C8−C14 polycycle of halichondrin A. Through the model studies conducted in connection with the synthesis of halichondrin C, we gained valuable information to address this question.[4b] Scheme 2 summarizes a transformation

Scheme 2. Model Studies for Construction of the C8−C14 Polycycle of Halichondrin A[a]


8
R = *n*-C₅H₁₁

E-9

Z-9

11
PhOMe-*p*

β-10

α-10
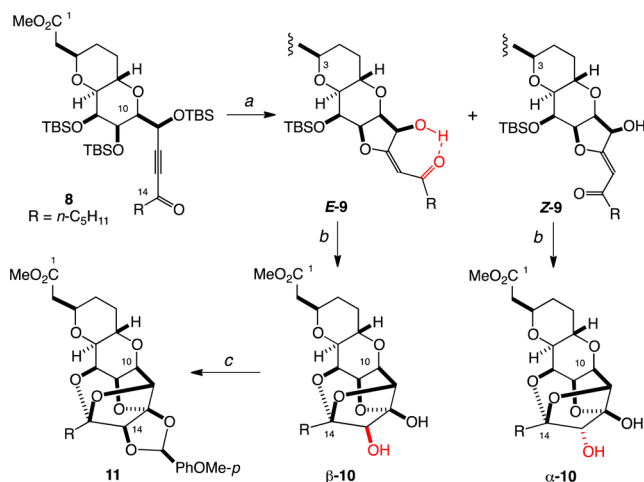
[a]Reagents and conditions: (a) HF·py, py, MeCN, rt; *E*-9: 69% and *Z*-9: 7%. (b) (1) DMDO, acetone, 0 °C; (2) CSA, CH₂Cl₂ (wet), rt; (3) HF·py, MeCN, rt; 74% for *E*-9 → **β-10** and 50% for *Z*-9 → **α-10**. (c) CSA (cat), *p*-MeOC₆H₄CH(OMe)₂, DMF, 100 °C; 67%.

of **8** into **11** possessing the C8−C14 polycycle of halichondrin A. This transformation involves: (1) selective TBS-deprotection of both C9-OTBS (equatorial) and C11-OTBS (acyclic) over C8-OTBS (axial); (2) oxy-Michael addition of the resultant C9-alcohol to ynone **8**, to form preferentially *E*-isomer with assistance of hydrogen-bonding stabilization; (3) stereoselective DMDO epoxidation from convex face; and (4) acid-promoted ketalization to form **β-10**. Interestingly, DMDO epoxidation of the corresponding *Z*-isomer *Z*-9, followed by acid-treatment, gave **α-10** noncontaminated from **β-10**, thereby

demonstrating the high stereoselectivity of DMDO oxidation. On treatment with *p*-anisaldehyde dimethyl acetal in the presence of camphorsulfonic acid (CSA), **β-10** gave single *p*-methoxybenzylidene acetal **11**.[10]

## ■ RESULTS AND DISCUSSION

Guided by the model study outlined, we began a synthesis of the C1−C19 building block **6a** (Scheme 3). The coupling of

Scheme 3. Synthesis of C1−C19 Building Block[a]

12: R = TBS

13a: X = I
13b: X = Br

14a: X = I
14b: X = Br

15

6a: X = I
6b: X = Br

16

A
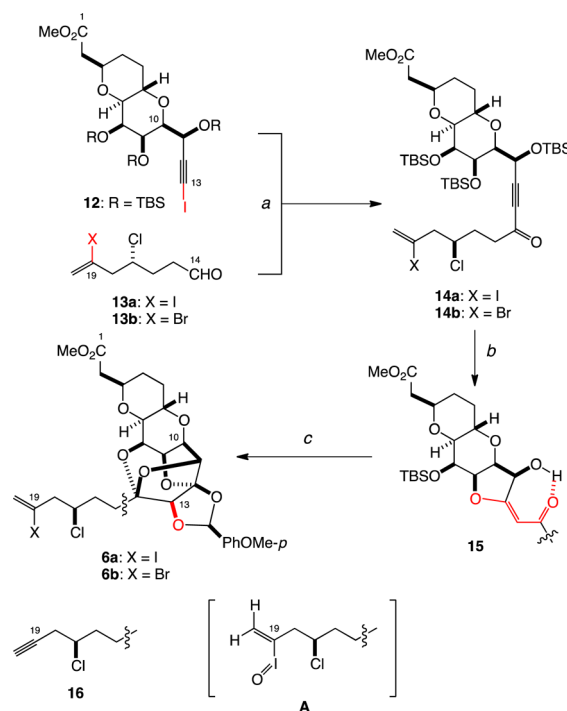
[a]Reagents and conditions: (a) (1) Ni/Cr-mediated coupling with Cr-catalyst (20 mol %) derived from (*R*)-sulfonamide-I and NiCl₂·DEP (0.03 mol %) (**12** + **13b**) → **14b**; 91%. (2) Dess−Martin oxidation, CH₂Cl₂, rt; 96%. (b) HF·py, py, MeCN, rt; 59% of **15** and 6% of its *Z*-isomer. (c) (1) DMDO, acetone, rt. (2) CSA, CH₂Cl₂ (wet), rt. (3) HF·py, MeCN, rt; 92% yield over three-steps. (4) *p*-TsOH (cat), *p*-MeOC₆H₄CH(OMe)₂, CH₂Cl₂, rt; 76% of **6b** and 12% of rsm.

aldehyde **13a** with iodoacetylene **12** was effectively achieved with catalytic asymmetric Ni/Cr-mediated coupling. This coupling deserves a few comments. First, the study by this and other laboratories showed that iodoacetylenes are far more reactive than iodoolefins in the Cr-mediated coupling.[11] This suggested the possibility that the (**12** + **13a**) coupling can be achieved without interference from the C19-iodoolefin present in **6a**. Indeed, it was found that the coupling was effectively achieved with a trace amount of Ni-catalyst or without added Ni-catalyst. At present, however, it is not clear whether a trace amount of Ni-catalyst is required for this coupling.[11b] As the resultant allylic alcohol is oxidized to the ketone, the C14 stereochemistry outcome is not an issue for this coupling. However, we noticed that the Cr-catalyst derived from a sulfonamide ligand such as sulfonamide-I (Figure 2) significantly accelerates the coupling. Interestingly, (*R*)-ligand was found to be more effective than (*S*)-ligand. Third, the coupling was conducted routinely with 15−20 mol % Cr-catalyst. However, the catalyst loading was improved up to 5 mol %
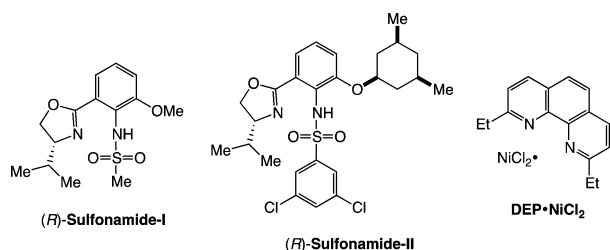
Figure 2. Sulfonamide ligands and NiCl$_2$ complex used for Ni/Cr-mediated coupling reactions.

with the iodoacetylene with TES, i.e., R = TES in **12**, without a loss of the coupling efficiency.

After oxidation of the propargyl alcohol, **14a** was subjected to the selective TBS-deprotection condition, to give enone **15** (E-isomer: 62%; Z-isomer: 6%). DMDO oxidation, followed by acid treatment and then p-anisaldehyde dimethyl acetal, furnished the desired C1−C19 building block **6a** in 45% overall yield. However, we noticed that the product thus obtained was a 2:1 mixture of desired **6a** and acetylene **16**. An NMR analysis showed that this byproduct formation took place in the DMDO step.

A literature search revealed no example known for DMDO-mediated transformation of iodoolefins to acetylenes.[12] We speculate that formation of **16** involved DMDO oxidation of the iodine to iodoso intermediate **A**, followed by syn-elimination reported by Reich.[13] In spite of some efforts, we were unable to find the oxidation condition to avoid the iodine oxidation. For this reason, we carried out the synthesis with bromoolefin aldehyde **13b**. The synthesis of this series proceeded in the parallel way with the **13a** series, except for: (1) as anticipated, there was no acetylene byproduct **16** formed and (2) the efficiency of Ni/Cr-mediated (**12** + **13b**)-coupling was slightly higher in this series (70% overall yield from **15**).

As planned, coupling of the C1−C19 building block **6b** with the C20−C38 building block **7**[14] was realized by Ni/Cr-mediated reaction in the presence of the Cr-catalyst derived from (R)-sulfonamide II (Scheme 4).[7] However, to overcome the poorer reactivity of the bromoolefin of **6b**, this coupling was carried out with 40 mol % Cr reagent. The induced cyclization of the resultant allylic alcohol with AgOTf-Ag$_2$O gave desired product **17** in 70% overall yield from **7**, with 20:1 stereoselectivity.[15]

On treatment with aq. LiOH, both acetate and methyl ester of **17** were hydrolyzed to yield the expected seco-acid, macrolactonization of which was effected with Shiina's reagent to furnish **18** in 77% overall yield.[16] Selective deprotection of the 1°-TBS at C38 over the 2°-TBS at C35 was effected with HF·py and imidazole in MeCN at 4 °C, to furnish the halichondrin-A right-half **19** in 85% yield.[17]

After Dess−Martin oxidation, **19** was subjected to Ni/Cr-mediated coupling with the halichondrin left-half **5**, followed by oxidation, to furnish the trans-enone **20** in 85% yield (Scheme 6). Once again, (S)-sulfonamide-I was used to accelerate the coupling rate.

In order to convert **20** to halichondrin A, we need to achieve the following chemical transformations: (1) deprotection of the five TBS groups; (2) hemiketal formation at C44; (3) oxy-Michael addition of the resultant hemiketal hydroxyl group to the αβ-unsaturated ketone to form the [6,6]-spiroketal at C44; (4) deprotection of the C41-MPM group; (5) formation of [5,5]-spiroketal at C38; and (6) deprotection of the anisylidene

Scheme 4. Synthesis of the Right-Half of Halichondrin A
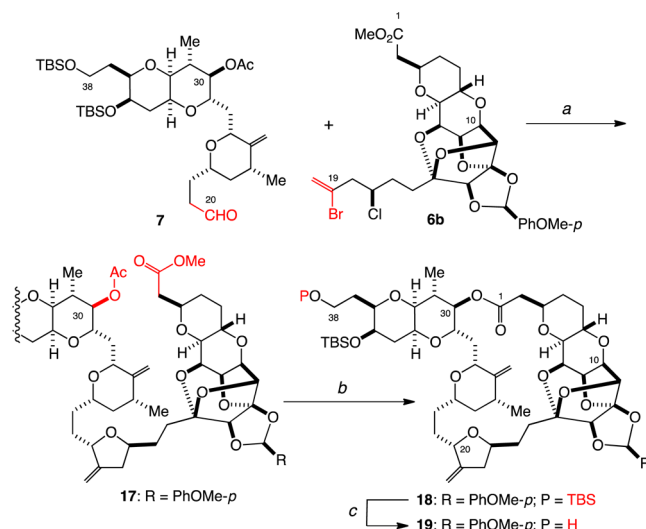
Reagents and conditions: (a) (1) Ni/Cr-mediated coupling with Cr-catalyst (40 mol %) derived from (R)-sulfonamide-II and NiCl$_2$·DEP (10 mol %); 91% yield (dr = 20:1). (2) AgOTf, Ag$_2$O, THF, rt; 78% yield. (b) (1) LiOH, aq. MeOH, rt. (2) 2-methyl-6-nitrobenzoic anhydride, i-Pr$_2$NEt, DMAP, toluene, 70 °C; 77% over two-steps. (c) HF·py, imidazole, MeCN, 4 °C; 85% yield.

group at C12/C13. In the total synthesis of halichondrins B and C, we have demonstrated that this overall transformation, except for the last anisylidene deprotection, can be achieved with the three-step protocol, i.e., TBAF, DDQ, and CSA or PPTS treatments, in a stereocontrolled manner.[4]

We expected that the anisylidene group could be removed by PPTS in protic solvent, and therefore the transformation of **20** into halichondrin A could be achieved with use of the three-step protocol with a small modification. With this analysis, we subjected **20** to TBAF, DDQ, and then PPTS treatments. Specifically, the previously established protocol was used for the first two steps, but PPTS treatment was done in i-propanol, instead of methylene chloride. In the TBAF and DDQ steps, we found that **20** exhibited the behavior perfectly parallel with that observed in the halichondrins B and C cases. In the third step (PPTS in i-propanol at RT), the anisylidene group was indeed removed, but two major products (ca. 3:2 ratio) were formed. MS and ^{1}H NMR analysis suggested that the major and minor products were likely to correspond to C38-epi-halichondrin A and halichondrin A, respectively. This result was surprising for us, as the corresponding acid-treatment step in the halichondrins B and C series furnished the desired stereoisomer as the major product.[18] Naturally, we were curious about the reason(s) why the product distribution in the halichondrin A series was noticeably different from that observed in the halichondrins B and C.

For this reason, we initiated a study on the behavior of the [5,5]-spiroketal at C38, in particular acid-catalyzed equilibration. In this connection, it is worth noting that the C11−C14 portion of halichondrins is known to be prone to furan formation under acidic conditions.[19] Related to the proposed equilibration, Blunt and Munro studied C38-epi-homohalichondrin B and its acid-catalyzed reactivity, showing that the C38 stereocenter epimerizes to yield a 1:1 mixture in TFA-CH$_2$Cl$_2$.[20] Compared with [6,6]-spiroketals,[21] the stereochemical behaviors of [5,5]-spiroketals are complex,[22] and it

is not straightforward to suggest a chemical means to favor halichondrin A over C38-*epi*-halichondrin A or vice versa. With this background, we studied the equilibration of C38-*epi*-halichonrin A (Table 1). After numerous attempts, we

Table 1. [5,5]-Spiroketal Equilibration
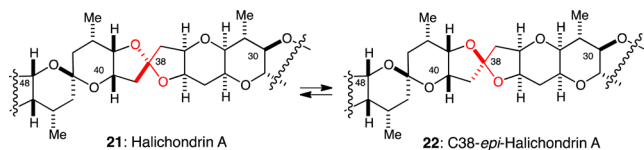
	CH$_2$Cl$_2$	Et$_2$O	MeCN	MeOH
PPTS at RT	3:2	1:1	2:1	1:2
CSA at RT	2:1	1:1	1:1	1:2
TMSOTf at −78 °C	>10:1	1:>5	3:1[a]	NA

[a] Done at −40 °C.

eventually found a simple but remarkably effective method to make the equilibration in favor to either halichondrin A (**21**) or C38-*epi*-halichondrin A (**22**); **21** and **22** were formed as the major stereoisomer on treatment with TMSOTf in CH$_2$Cl$_2$ or Et$_2$O, respectively.[23] It is worthwhile noting that no furan formation was observed under the conditions employed and that both halichondrins B and C exhibited the identical reactivity.

Realizing that solvents play the key role,[24] we would speculate a possible mechanistic explanation; the C35–C44 moiety of halichondrins provides a polyether-type cavity for cations such as Me$_3$Si$^+$ in nonoxygen-containing solvents, which shifts the equilibration in favor to halichondrin A (Scheme 5).

**Scheme 5. Possible Mechanism for the Observed Solvent-Dependent [5,5]-Spiroketal Equilibration**
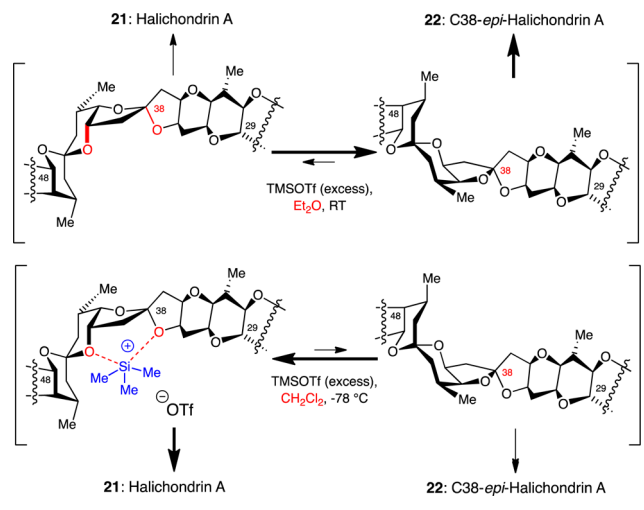
In oxygen-containing solvents, the cavity effect is canceled out with solvents and an unfavorable dipole–dipole interaction between the C38–O and C40–O bonds in halichondrin A shifts the equilibrium toward C38-*epi*-halichondrin A.

Based on the insight on the [5,5]-spiroketal behavior, we were able to complete a total synthesis of halichondrin A in a stereoselective manner. Namely, the product mixture obtained in the PPTS step was subjected to the TMSOTf-promoted equilibration, followed by chromatographic separation, to furnish synthetic halichondrin A (**21**) in 39% overall yield

from **20**, along with C38-*epi*-halichondrin A (**22**; ca. 3%). It is worth noting that **21** was *the* major product observed in this four-step transformation, although the isolated yield was modest.[25]

**Scheme 6. Completion of the Total Synthesis**
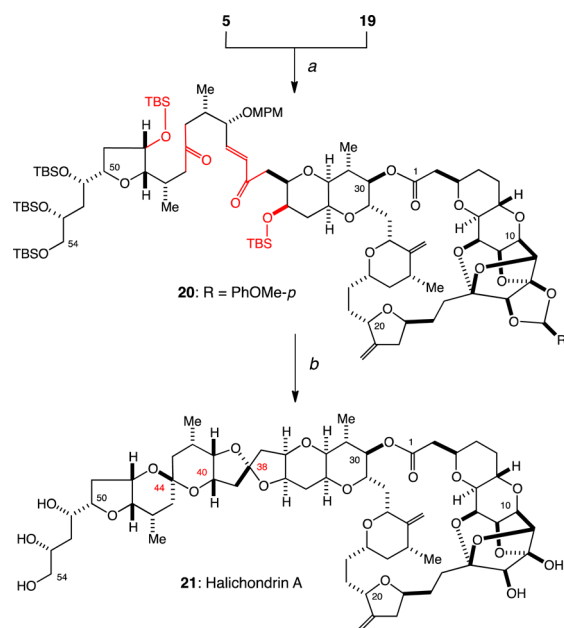
Reagents and conditions: (a) (1) Dess−Martin oxidation of **19**, CH$_2$Cl$_2$, rt; 96% yield. (2) Ni/Cr-mediated coupling with Cr-catalyst (5 equiv) derived from (*S*)-sulfonamide-I and NiCl$_2$·DEP (2 mol %). (3) Dess−Martin oxidation; 85% yield over two-steps. (b) (1) TBAF, imidazole·HCl, DMF, rt. (2) DDQ, *t*-BuOH, CH$_2$Cl$_2$, phosphate buffer (pH = 7.0), rt. (3) PPTS, *i*-PrOH, rt. (4) TMSOTf, CH$_2$Cl$_2$, −78 °C; 39% isolated yield of **21** and ∼3% of **22** over four-steps.

As mentioned in the Introduction, halichondrin A is the missing member in this class of natural products. Thus, the structure proof of synthetic halichondrin A (**21**) presented a challenge. To establish the structure of synthetic halichondrin A unambiguously, we conducted two experiments.

First, norhalichondrin A (**24**) was synthesized with coupling **19** and **23** (Scheme 7).[26,27] It should be noted that **23** was the left-half used for the synthesis of norhalichondrin B.[4a] Synthetic norhalichondrin A (**24**) thus obtained was confirmed to be identical with natural norhalichondrin A (^{1}H- and ^{13}C NMR, HR-MS, TLC), thereby establishing the structure of the halichondrin right-half **19**. Noteworthily, norhalichondrin A (**24**) played the central role in structure elucidation of this class of natural products, i.e., the X-ray structure analysis of its *p*-bromophenacyl ester.[1] Also, it should be noted that the left-half (**5**) was successfully transformed into halichondrins B and C.[4] Combined together, there was no ambiguity left on the structure of the two building blocks **5** and **19** used for the current halichondrin A synthesis.

Second, three chiral centers at C38, C40, and C44 were introduced at the transformation from the enone **20** to the final product. The fact that norhalichondrin A (**24**) was successfully obtained by using the virtually same procedure strongly suggests that the newly introduced three chiral centers match with those present in the halichondrin class natural products. Nevertheless, close NMR analysis provided us with further evidence. The panel A in Chart 1 summarizes the proton

Scheme 7. Total Synthesis of Norhalichondrin A
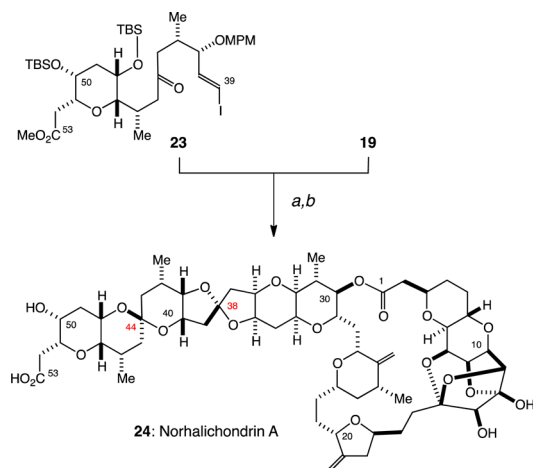
Reagents and conditions: (a) same as step (a) in Scheme 6. 83% overall yield. (b) (1–4) Same as step (b) in Scheme 6. (5) LiOH, aq. THF, rt; 30% isolated yield of **24** over five steps.

Chart 1. Proton Chemical Shift Differences[a]
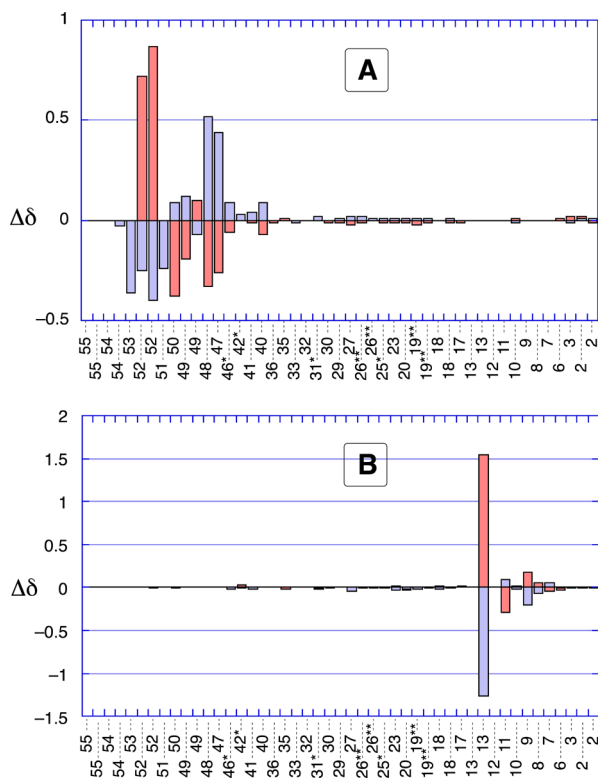
[a]The x-axis represents carbon number at which protons in question are attached. The y-axis shows proton chemical shift differences in ppm. Panel A, red: $\Delta\delta$ = (norhalichondrin A) − (synthetic halichondrin A); blue: $\Delta\delta$ = (synthetic halichondrin A) − homohalichondrin A. Panel B, red: $\Delta\delta$ = (synthetic halichondrin A) − (halichondrin B); blue: $\Delta\delta$ = (halichondrin C) − (synthetic halichondrin A). *Methyl group attached at the indicated carbon; and **exo-methylene group attached at the indicated carbon.

chemical shift differences between norhalichondrin A and synthetic halichondrin A (red) and synthetic halichondrin A and homohalichondrin A (blue). This comparison demonstrates that these three halichondrins share the same right-half

structure. Similarly, the panel B in Chart 1 shows the proton chemical shift differences between synthetic halichondrin A and halichondrin B (red) and halichondrin C and synthetic halichondrin A (blue), thereby demonstrating that these three halichondrins share the same left-half structure. The two NMR comparisons once again proved that halichondrin A obtained through the total synthesis indeed corresponds to the missing member of this class of natural products.

As mentioned in the Introduction, halichondrin A is not isolated from marine sponges thus far. With synthetic halichondrin A in hand, we are in a good position to test whether halichondrin A is present in natural sources.[28] In addition, it would be interesting to study its biological profile.

■ CONCLUSION

We have reported a total synthesis of halichondrin A, the phantom member in this class of natural products. The highlights of total synthesis include: (1) synthesis of C1−C19 building block **6b** via a catalytic asymmetric Cr-mediated coupling of **12** and **13b**; (2) synthesis of right-half **19** via an asymmetric Ni/Cr-mediated coupling, followed by base-induced furan formation and then Shiina macrolactonization; (3) synthesis of enone **20** via Ni/Cr-mediated coupling of **5** with **19**, followed by Dess−Martin oxidation; (4) synthesis of halichondrin A (**21**) from **20**, with use of a newly discovered, highly selective TMSOTf-mediated equilibration of C38-epi-halichondrin A (**22**) to halichondrin A (**21**). We have presented two pieces of evidence unambiguously to establish the structure of synthetic halichondrin A; one is the synthesis of norhalichondrin A (**24**) from **19** and **23**, and the other is the studies on the proton chemical shift difference between synthetic halichondrin A and known members of the halichondrin class of natural products.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, characterization data, and copies of spectra data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(9) In the previous synthesis of halichondrins B and C, the C8−C14 polycycle was built after the macrolactonization.

(10) Anisylidene formation of *β*-10 gave a single stereoisomer, whose stereochemistry was assigned, based on the NOE experiments done on 6a. For details, see Supporting Information.

(11) For example, see: (a) Aicher, T. D.; Kishi, Y. *Tetrahedron Lett.* **1987**, 28, 3463. (b) Usanov, D. L.; Yamamoto, H. *J. Am. Chem. Soc.* **2011**, 133, 1286.

(12) For possibly relevant examples, see: (a) Mahadevan, A.; Fuchs, P. L. *J. Am. Chem. Soc.* **1995**, 117, 3272. (b) Knapp, S.; Naughton, A. B. J.; Murali Dhar, T. G. *Tetrahedron Lett.* **1992**, 33, 1025.

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(14) For the details of synthesis, see Supporting Information.

(15) Kang, B.; Mowat, J.; Pinter, T.; Britton, R. *Org. Lett.* **2009**, 11, 1717.

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(17) In the previous syntheses, we used a four-step protocol, i.e., (1) TBAF, imidazole·HCl, THF. (2) PNB-Cl, Et$_3$N, DMAP, CH$_2$Cl$_2$, −20 °C. (3) TBSOTf, 2,6-lutidine, CH$_2$Cl$_2$, −78 °C. (4) K$_2$CO$_3$, MeOH-CH$_2$Cl$_2$, rt, for the transformation corresponding to 18→19. Each step in that transformation was very selective and high yielding (overall yield: ~90%). Although the selectivity of C38-TBS over C35-TBS deprotection was not perfect, the current method allowed transforming 18 to 19 in a single step in a yield comparable to the previous four-step procedure.

(18) We did not establish the ratio of C38-natural stereoisomer over C38-*epi*-stereoisomer in the previous synthesis of halichondrins B and C. However, ^{1}H NMR spectra of the crude products suggested that it was (4−5):1, favoring C38-natural stereoisomer.

(19) For example, see: (a) ref 20. (b) Namba, K.; Jun, H.-S.; Kishi, Y. *J. Am. Chem. Soc.* **2004**, 126, 7770.

(20) Hart, Blunt, and Munro studied acid-catalyzed reactions of homohalichondrin B with use of TFA/CH$_2$Cl$_2$/RT: Hart, J. B.; Blunt, J. W.; Munro, M. H. G. *J. Org. Chem.* **1996**, 61, 2888 Under the TFA condition employed, a significant amount of furan was formed.

(21) For analysis on the stereochemistry outcome of [6,6]-spiroketal formation, see ref 4b.

(22) For recent examples, see: (a) Phillips, S. T.; Shair, M. D. *J. Am. Chem. Soc.* **2007**, 129, 6589. Fortner, K. C.; Kato, D.; Tanaka, Y.; Shair, M. D. *J. Am. Chem. Soc.* **2010**, 132, 275. (b) Ravindar, K.; Reddy, M. S.; Lindqvist, L.; Pelletier, J.; Deslongchamps, P. *Org. Lett.* **2010**, 12, 4420. (c) Tlais, S. F.; Dudley, G. B. *Org. Lett.* **2010**, 12, 4698.

(23) TMSOTf was most effective to induce the equilibration. Other Lewis acids, including TBSOTf and BF$_3$·Et$_2$O, were also found to be effective.

(24) Solvent tested included: (a) non-oxygen containing solvents: toluene and dichloroethane; (b) oxygen-containing solvents; THF and H$_2$O.

(25) In addition to 21 and 22, one unknown product was isolated. Its molecular weight corresponded to (21 + H$_2$O), but it was not the seco-acid resulted from macrolactone hydrolysis. It is worthwhile noting that the modest yield was due to the first three steps, rather than the TMSOTf-mediated equilibration. In the halichondrin C series, the overall yield of corresponding three steps was 30%. Having learned the chemical behaviors of C-38 epimer, we re-examined the crude product obtained after the PPTS treatment, revealing that C-38 epimer was indeed present in 7∼10% overall yield from the enone.

(26) Fang, F. G.; Kishi, Y.; Matelich, M. C.; Scola, P. M. *Tetrahedron Lett.* **1992**, 33, 1557.

(27) The enone in the homohalichondrin series was also synthesized from 19 and the vinyl iodide reported as 8 in ref 25. However, the four-step protocol outlined in Scheme 6 did not give homohalichondrin A. One of the problems encountered was the difficulty in removing all the four TBS groups under the condition of TBAF, imidazole·HCl, DMF, rt; namely, one of the four TBS groups, likely one at C48, was not deprotected. With a modification on the TBAF-mediated TBS deprotection step, i.e., TBAF (50 equiv instead of 10 equiv) and reaction temperature (50 °C instead of rt), homohalichondrin A was obtained in 5% overall yield. Synthetic homohalichondrin A was found to be identical with natural homohalichondrin A (HR-MS, ^{1}H NMR, and TLC). In spite of the poor overall efficiency, this experiment has established that the C50/C51/C53/C54 stereochemistry of homohalichondrin A corresponds to the one shown in vinyl iodide 8 in ref 26.

(28) With the use of synthetic halichondrin A as the authentic sample, we searched for natural halichondrin A in a crude extract of the marine sponge *Halichondria okadai*, stored over 20 years in the Uemura laboratory, but unsuccessfully.