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Total Synthesis of Halistatins 1 and 2

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ABSTRACT: The first total synthesis of halistatins 1 and 2 have been completed using Cr-mediated coupling reactions for the C11/C12, C17/C18 and C19/C20 bond-formation. For the C11/C12 bond-formation, a stoichiometric Ni/Cr-mediated reaction is used to couple an α-quaternary aldehyde with a vinyl iodide. The solubilized Cr-reagent, prepared from $CrCl_2$ and a sulfonamide ligand, allows to perform the coupling with ~1 equivalent of Cr-reagent. Catalytic, asymmetric Co/Cr-mediated iodoallylation is adopted to incorporate the requisite C17-C19 functionality in a stereoselective manner. Asymmetric Ni/Cr-mediated coupling is used to form the C19/C20 bond effectively. Through this study, it has been found that the stereoselectivity of [5,5]-spiroketalization dramatically depends on solvents; PTSA in 1:1 methanol-water gave a >20:1 stereoselectivity favoring the natural series. This condition is also effective to isomerize C38-*epi*-halichondrins into C38-natural halichondrins.

INTRODUCTION

Pettit and co-workers isolated two new polyether macrolides designated halistatins 1 and 2, along with halichondrin B and homohalichondrin B, from the orange sponge *Phakellia carteri* collected in the Grand Comoros Island, Republic of Comoros.[1] The structure elucidation of halistatins was carried out primarily via extensive NMR studies, suggesting that the skeleton of macrolides was reminiscent of that of halichondrins.[2] Ultimately, halistatins 1 and 2 were established as C10-hydroxyhalichondrin B and C10-hydroxyhomohalichondrin B, respectively (Figure 1).

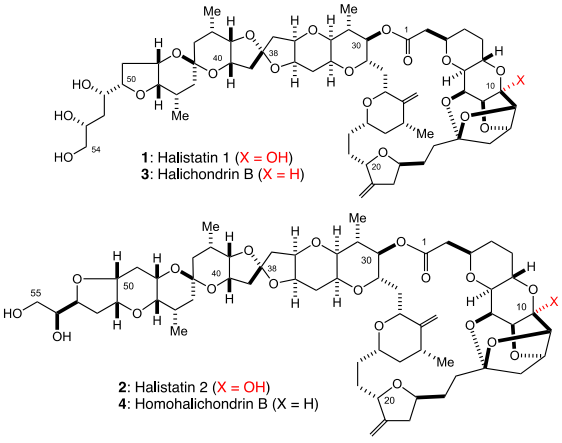


Figure 1. Structures of Halistatins 1 and 2

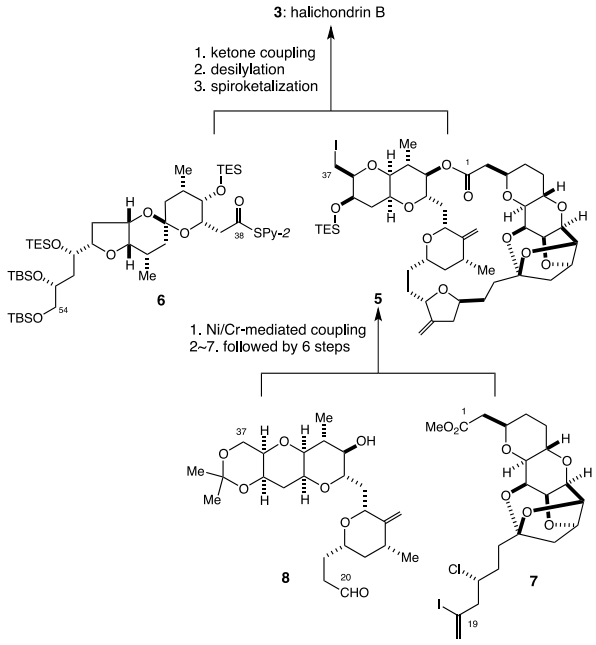
Halistatins were shown to exhibit potent cytotoxicity. In the test against the National Cancer Institute's (NCI) 60-cell line antitumor screening panel, halistatins yielded a pattern of differential cellular growth inhibition, which was highly characteristic and of comparable potency to the halichondrins.[1b]

Related to the ongoing research on the halichondrin class marine natural products,[3] we are interested in the synthesis of halistatins 1 and 2. In this paper, we report the first total synthesis of halistatins, further revealing the potentials of Cr-mediated coupling reactions.[4]

SYNTHETIC PLAN

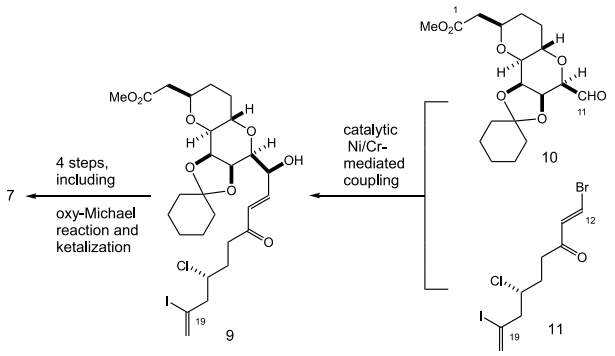
We recently reported the unified and flexible synthetic route to the halichondrin class of marine natural products. For example, halichondrin B was synthesized in a highly convergent manner (Scheme 1).[3d]

Scheme 1. Convergent Synthesis of Halichondrin B



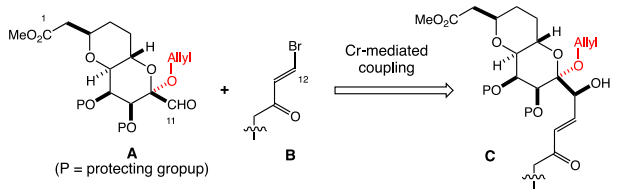
We envision that this synthetic strategy should be adaptable for a synthesis of halistatins 1 and 2, provided with the proper C1-C19 building block corresponding to **7** in the halichondrin series. The C1-C19 building block **7** was synthesized as summarized in Scheme 2, where the C11-C12 bond was effectively constructed via a catalytic, asymmetric Ni/Cr-mediated coupling reaction, commonly referred to as NHK-reaction.[5,6]

Scheme 2. Synthesis of C1-C19 Fragment of Halichondrin B



Overall, the quest for extending the unified synthetic route of halichondrins to the synthesis of halistatins is now reduced to the question of how to form the C11-C12 bond, i.e., **A** + **B** → **C** (Scheme 3). This bond-formation might be viewed by a Grignard-type carbonyl addition. For this case, however, the nucleophile generated from **B** is a "naked" vinylogous acyl anion, raising concerns of its generation and reactivity. NHK-reaction has been demonstrated to give a unique and effective solution for this type of bond-formations.[7] To the best of our knowledge, however, there is no literature precedent for NHK-reaction with an α-quaternary aldehyde such as **A**, which is presumed to be a poorer acceptor than **10**. We hoped that this study would provide us with further knowledge on the Cr-mediated coupling reactions.

Scheme 3. Proposed Cr-Mediated C11-C12 Bond Formation in Halistatins



Lastly, an allyl group was chosen as the protecting group for the C10-hydroxy group for two reasons. First, C10-hydroxy group is located in a bridgehead of the polycyclic ring, cf., **7**, and hence acid-catalyzed deprotection of RO-protecting group might become problematic.[8] Second, an allyl group was successfully used as the protecting group for the C12-hydroxy group in the halichondrin-C synthesis.[3b,d]

With these analyses, we began the experimental work.

RESULTS AND DISCUSSION

At the early phase of study, we tested the reactivity of aldehyde in the NHK-reaction. Namely, aldehyde **12** was subjected to the NHK-reaction with **11**, to give only a trace amount of the desired product. This attempt clearly showed that α-quaternary aldehyde **12** was a significantly poorer acceptor than the corresponding tertiary aldehyde **10**. Additional two aldehydes **13** and **14** were tested; **14** did not give the desired product, whereas **13** did indeed give the desired product (~8% yield). Based on these screenings, we decided to carry out the synthesis with the acetonide-aldehyde **13**.

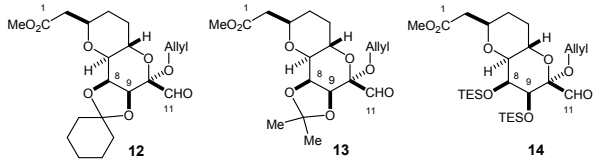
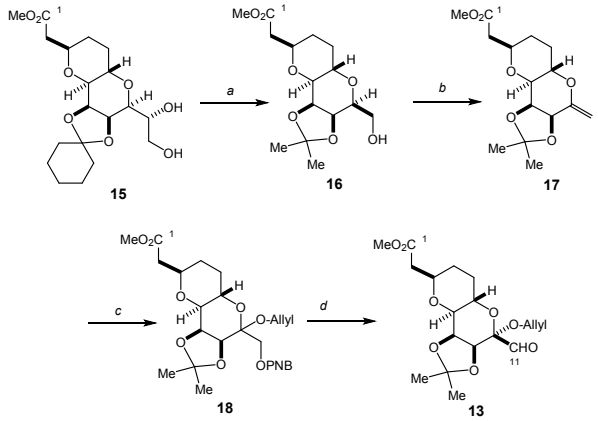


Figure 2. Aldehydes Screened for NHK-Reaction

The first synthetic route to **13** is summarized in Scheme 4. The acetonide-aldehyde **13** was synthesized from the previously reported diol **15**.[9,10] The C8/C9-protecting group of **15** was switched from the cyclohexylidene to the acetonide by six routine steps with an excellent overall yield.[11] Iodination of primary alcohol of **16**, followed by base-induced dehydrohalogenation gave *exo*-olefin **17** in 80% yield. A three-step transformation was used to construct the desired C10-quaternary stereocenter. Dihydroxylation of olefin, primary alcohol protection with *p*-nitrobenzoate, followed by acid-catalyzed etherification with triallyl orthoformate gave **18** as an 8:1 inseparable mixture of C10 diastereomers in 30% yield. The low yield of this transformation was due to the formation of two major side-products. Spectroscopic analysis suggested that these side-products were derived from acid-catalyzed cleavage of C8/C9 acetonide group, followed by allylation of the resultant diol. Without separation of C10 diastereomers, **18** was subjected to K_2CO_3-treatment, to furnish the primary alcohol as the homogeneous material. The C10-stereochemistry of the major isomer was concluded from the ^{1}H NMR comparison with the corresponding C10–OMe compound.[11] Dess-Martin oxidation of the primary alcohol gave aldehyde **13** in 86% yield.[12]

Scheme 4. First Generation Synthesis of C1-C11 Aldehyde 13[a]



[a]*Reagents and conditions:* (a) (1) $NaIO_4$ (1.2 equiv), EtOAc/pH 7 buffer (1/1), 0 °C to rt, 1 h, (2) $NaBH_4$ (1 equiv), MeOH, 0 °C, 1 h (93% for two steps), (3) benzoyl chloride (1.2 equiv), Et_3N (2 equiv), DMAP (10 mol%), CH_2Cl_2, 0 °C to rt, 3 h (97%), (4) TFA/H_2O/CH_2Cl_2 (4/1/5), 0 °C to rt, 2 h, (5) 2,2-dimethoxypropane/acetone (1/1), CSA (10 mol%), rt, 3 h (87% for two steps), (6) K_2CO_3 (2 equiv), MeOH, rt, 2 h (94%); (b) (1) PPh_3 (1.5 equiv), Imidazole (3.5 equiv), I_2 (1.2 equiv), DMF, 80 °C, 8 h (87%), (2) AgF (3 equiv), py, rt, 6 h (92%); (c) (1) OsO_4 (0.5 mol%), NMO (2 equiv), acetone/H_2O (8/2), rt, 15 h (90%), (2) PNBCl (1.2 equiv), Et_3N (2 equiv), CH_2Cl_2, 0 °C to rt, 4 h (90%), (3) Triallyl orthoformate, PTSA (10 mol%), CH_2Cl_2, 0 °C, 1 h (30%); (d) (1) K_2CO_3 (2 equiv), MeOH, rt, 2 h (94%), (2) Dess-Martin periodinane (2 equiv), $NHCO_3$ (10 equiv), CH_2Cl_2, rt, 1 h (86%). *Abbreviations*: TFA = trifluroacetic acid; CSA = camphorsulfonic acid; NMO = N-methylmorpholine N-oxide; PNBCl = 4-nitrobenzoyl chloride; PTSA = *p*-toluenesulfonic acid.

As the first generation of synthesis suffered in the overall efficiency, primarily due to the poor yield from **17** to **18**, we searched for an alternative synthetic route, resulting in the second-generation synthesis (Scheme 5). The regio- and stereo-selective introduction of the C10 allyloxy group relied on the work by Berti on a similar system.[13]

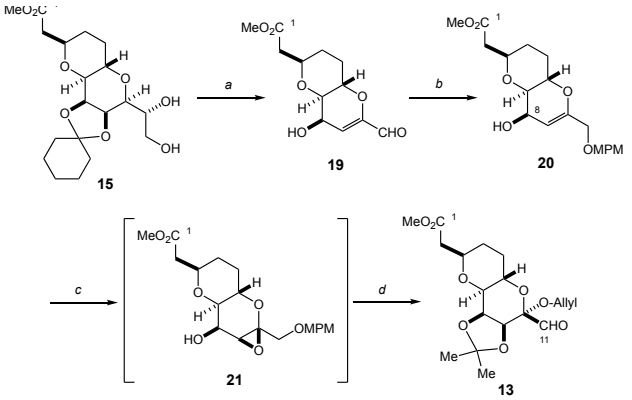
Diol **15** was subjected to oxidative cleavage, followed by a base treatment, to furnish α,β-unsaturated aldehyde **19** in excellent yield. The functional group adjustment was made in four steps to transform **19** into the desired allylic alcohol **20**, i.e., (1) acetylation of C8 alcohol, (2) reduction of aldehyde, (3) MPM-protection of C11 alcohol, and (4) deacetylation.

The next task was the C8-alcohol directed stereoselective epoxidation of olefin in **20**. Based on the classic example on stereoselective epoxidation of 1-cyclohexenol,[14] we expected to obtain *syn*-epoxide **21** from **20**. However, MCPBA-epoxidation of **20** gave a 2:3 mixture of *syn/anti*-epoxides in ~30% yield, thereby showing that the MCPBA-approach is not fully directed with the C8 hydroxy group in this ring system.

We screened several standard oxidations to obtain *syn*- and *anti*-epoxides selectively. Oxidation of **20** with dimethyldioxirane (DMDO) and oxone was effective for formation of the *anti*-epoxide. On the other hand, Sharpless VO(acac)$_2$-epoxidation was effective for formation of the *syn*-epoxide.[15] For **20**, the epoxidation was best achieved with VO(TMHD)$_2$ and cummene hydroperoxide to furnish the desired epoxide **21** selectively (stereoselectivity: >20:1).[16]

On treatment with allyl alcohol and CSA, **21** regio- and stereo-selectively gave the desired diol. Protection of the resultant diol as acetonide, followed by MPM-deprotection, Dess-Martin oxidation furnished aldehyde **13** in excellent overall yield. This synthesis was carried out in 10 g scale without any difficulties.

Scheme 5. Second Generation Synthesis of C1-C11 Aldehyde 13[a]



[a]*Reagents and conditions:* (a) (1) $NaIO_4$ (1.2 equiv), EtOAc/pH 7 buffer (1/1), 0 °C to rt, 1 h, (2) DBU (1.5 equiv), CH_2Cl_2, 0 °C to rt, 30 min (88% for two steps); (b) (1) Ac_2O (2 equiv), Et_3N (3 equiv), CH_2Cl_2, 0 °C to rt, 2 h, (2) $NaBH_4$ (1 equiv), MeOH, 0 °C, 30 min (86% for two steps), (3) MPM-imidate (2.5 equiv), CSA (20 mol%), CH_2Cl_2, 0 °C to rt, 6 h, (4) K_2CO_3 (2 equiv), MeOH, rt, 3 h (76% for two steps); (c) (1) VO(TMHD)$_2$ (10 mol%), cummene hydroperoxide (1.2 equiv), toluene, 0 °C, 6 h then allyl alcohol (3 equiv), CSA (10 mol%), 0 °C, 6 h, (2) CSA (10 mol%), 2,2-dimethoxypropane/acetone (10/1), rt, 30 min (60% for two steps); (d) (1) DDQ (2 equiv), CH_2Cl_2/pH 7 buffer (8/2), 0 °C to rt, 3 h (83%), (2) Dess-Martin periodinane (2 equiv), $NaHCO_3$ (10 equiv), CH_2Cl_2, rt, 1 h (86%). *Abbreviations*: DBU = 1,8-diazobicyclo[5.4.0]undec-7-ene; CSA = camphorsulfonic acid; TMHD = 2,2,6,6-tetramethyl-3,5-heptanedione; DDQ = 2,3-dichloro-5,6-dicyano-*p*-benzoquinone.

With the requisite aldehyde **13** in hand, we began the study on the key C11-C12 bond formation via NHK-reaction. The catalytic conditions, which was effective in the halichondrin series (Scheme 2),[5] was tested for **13**, but no product formation was observed. We then shifted our attention to the stoichiometric coupling conditions. It is worthwhile noting that the original stoichiometric conditions required 3~5 equivalents of $CrCl_2$, presumably due to its poor solubility in the reaction media.[7] However, the stoichiometric NHK-reaction is now feasible with use of ~1 equivalent of the soluble Cr-sulfonamide complexes (Figure 3).

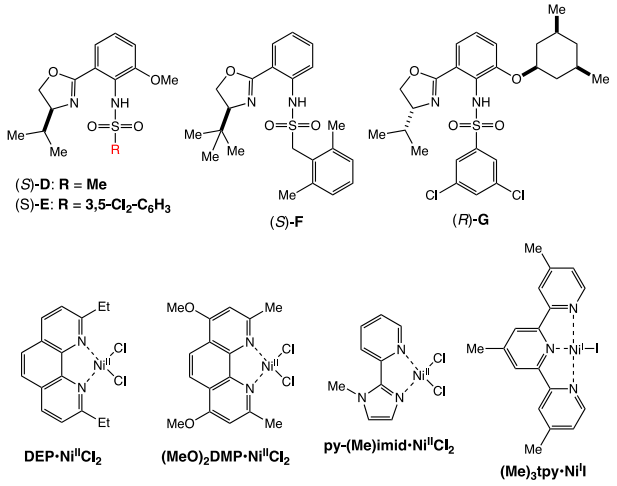


Figure 3. Sulfonamide ligands and Ni-complexes used for carbon-carbon bond formation reactions.

The NHK-coupling of **13** with **11** under the stoichiometric Ni/Cr-conditions (1 equiv of Cr-reagent derived from sulfonamide (*S*)-**D** and 5 mol% $NiCl_2$.polyether) gave a small amount of the desired product (~5%). We speculated that the low coupling efficiency might be due to a reactivity-mismatch of the coupling partners, i.e., the activation of C12-bromide in **11** with the Ni-catalyst was too fast. With this speculation, we tested **22** for the coupling under the same stoichiometric condition, but observed no C12-activation (Figure 4).[17] Replacing the C12-bromide with the C12-iodide i.e., **23** gave the desired product in an approximately 20% yield. However, the corresponding C19-iodide did not behave well in the coupling, apparently due to the competing activation at C12 vs C19. Interestingly, C12-bromo-acetylene **24** behaved well for the selective C12-activation/coupling under the catalytic conditions (~40% isolated yield). However, we were unable to hydrolyze selectively the C14-ketal at the following step.[18]

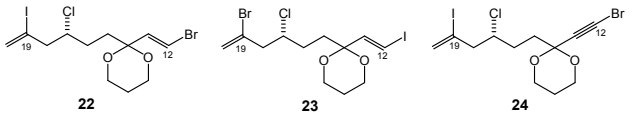


Figure 4. C12-C19 Nucleophiles Screened for NHK-Reaction

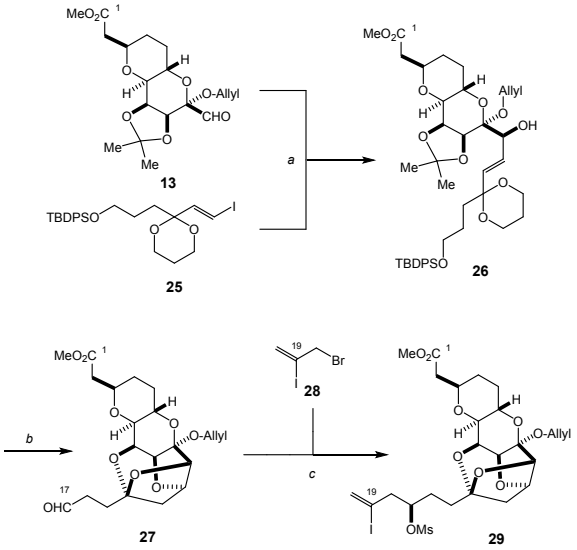
These results together demonstrated that the stoichiometric NHK-reaction was effective for a C-C bond formation even with an α-quaternary aldehyde such as **13**. However, poly-halogenated bromide **11** or its synthetic equivalents was not an acceptable coupling partner under the stoichiometric NHK-conditions, apparently because of competing activation of the C19-vinyl halide. Based on these insights, we modified the original plan to attach the C12-C19 moiety on the aldehyde **13**. To avoid the competing activation of C12 and C19 halides, we chose to use **25** for the NHK-reaction, followed by asymmetric Co/Cr-mediated haloallylation[19] to introduce the requisite C17-C19 functional group (Scheme 6).

With this plan, **13** was coupled with **25** under the stoichiometric conditions (1.0 equiv of Cr-reagent derived from sulfonamide (*S*)-**D** and 2 mol% of DEP·$NiCl_2$), to furnish the desired product **26** in 45% yield as a single product. Encouraged with this observation, we focused to improve the coupling efficiency. Ultimately, it was found that Cr-complex prepared from $CrCl_2$ and sulfonamide ligand (*S*)-**E** and $(MeO)_2$DMP·$NiCl_2$ significantly accelerated the coupling rate and improved the coupling yield up to 72%. ^{1}H-NMR analysis of the crude product demonstrated that the coupling yielded a single stereoisomer. Based on the previous precedents, we assumed the product to be the desired C11-β-stereoisomer, which was later proved via successful formation of polycyclic system, i.e., **27**.[20]

With a small modification of the protocol established in the halichondrin series,[5a] **26** was converted to the polycycle **27**. An attempted hydrolysis of C14-propylene glycol ketal and C8,C9-acetonide in **26** with aq. TFA caused also deprotection of the C17 TBDPS-group, and the resultant C17 alcohol prevented formation of the desired polycycle.[21] Therefore, the C17 alcohol was temporarily protected (step b.1), and then the previously established protocol was adopted,[5b] to yield the desired polycycle, which was converted to aldehyde **27** in two steps.

Aldehyde **27** was converted into C1-C19 building block **29** in two steps: catalytic, asymmetric Co/Cr-mediated 2-iodoallylation[19] and mesylation. With Cr-catalyst derived from sulfonamide *(S)*-**F**, the coupling of aldehyde **27** with 2-iodoallyl bromide **28** furnished the 2-iodoolefin in 77% yield with >98% stereoselectivity (^{1}H-NMR). Without separation of the minor undesired diastereomer, the crude product was treated with methanesulfonic anhydride, to furnish C1-C19 building block **29** of halistatins as the single stereoisomer in a good overall yield.

Scheme 6. Synthesis of C1-C19 Building Block 29[a]



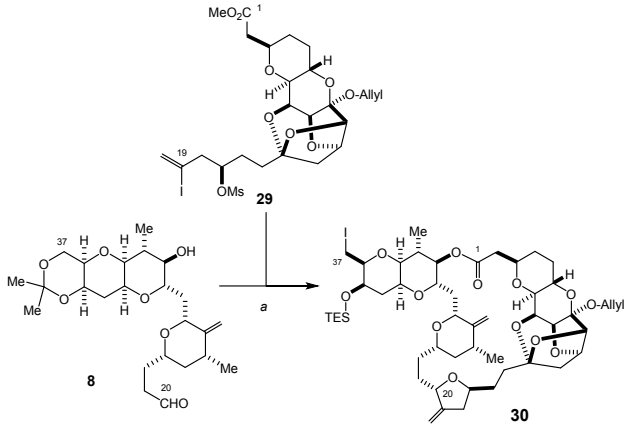
[a]*Reagents and conditions:* (a) **13** (1 equiv), **25** (1.5 equiv), $CrCl_2$ (1 equiv), proton sponge (1.05 equiv), (*S*)-**E** (1.05 equiv), LiCl (1.5 equiv), Mn (2 equiv), $NiCl_2$.DMP$(OMe)_2$ (3 mol%), MeCN, rt, 6 h (72%), (b) (1) PNBCl (1.5 equiv), Et_3N (3 equiv), DMAP (0.2 equiv), CH_2Cl_2, 0 °C to rt, 6 h (93%); (2) TFA/H_2O/CH_2Cl_2 (4/1/5), rt, 1 h, (3) K_2CO_3 (3 equiv), MeOH, rt, 30 min, (4) TBDPS-Cl (1.5 equiv), imidazole (3 equiv), CH_2Cl_2, 0 °C to rt, 2 h, (5) PPTS (2 equiv), CH_2Cl_2, rt, 2 h (43% for four steps), (6) TBAF (2 equiv), imidazole·HCl (1 equiv), THF, rt, 4 h (95%), (7) Dess-Martin periodinane (2 equiv), $NaHCO_3$ (10 equiv), CH_2Cl_2, rt, 1 h (92%); (c) (1) $CrBr_3$ (0.3 equiv), (*S*)-**F** (0.33 equiv), CoPc (0.4 mol%), **28** (2.5 equiv), Et_3N (0.33 equiv), 2,6-lutidine (0.36 equiv), Mn (3 equiv), Cp_2ZrCl_2 (1 equiv), THF, 45 °C to 0 °C, 6 h (77%), (2) Ms_2O (2 equiv), DMAP (20 mol%), CH_2Cl_2/pyridine (3/1), 0 °C, 1 h (90%). *Abbreviations*: PNBCl = 4-nitrobenzoyl chloride; TFA = trifluroacetic acid; PPTS = pyridinium *p*-toluenesulfonate; TBAF = tetrabutylammonium fluoride; DMAP = 4-(dimethylamino)pyridine.

Scheme 7 summarizes the right-half synthesis of halistatins. The synthesis followed the synthetic route developed in the halichondrin B series with two modifications.[22] The Ni/Cr-coupling of **8**[22] and **29** was carried out under the stoichiometric conditions, because we previously observed that the catalytic efficiency was low for a nucleophile bearing a C=O or S=O group in a close proximity, presumably because such a group

takes over the coordination site for an electrophile, thereby slowing down or shutting down the coupling.[23] Second, the NHK coupling was done without addition of 2,6-di-*tert*-butyl-4-methylpyridine as a base, because the C17-OMs group is eliminated under basic conditions, to form the corresponding diene.

With these modifications, the synthesis was uneventfully carried out to furnish **30** in excellent overall yield (Scheme 7). The structure was established by comparison of ^{1}H and ^{13}C NMR spectra with those in the halichondrin-B series.

Scheme 7. Synthesis of C1-C37 Building Block 30 of Halistatins[a]

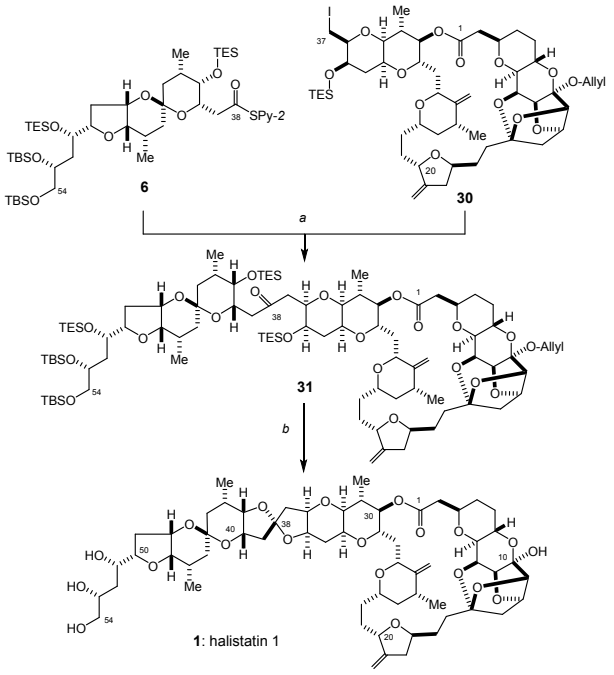


[a]*Reagents and conditions:* (a) (1) **8** (1.2 equiv), **29** (1.0 equiv), $CrCl_2$ (1 equiv), proton sponge (1.1 equiv), (*R*)-**G** (1.1 equiv), LiCl (2 equiv), Mn (2 equiv), $NiCl_2$.DMP$(OMe)_2$ (3 mol%), MeCN, rt, 4 h, (2) K_2CO_3 (10 equiv), MeOH, 60 °C, 8 h then H_2O, 3 h, (3) MNBA (6 equiv), DMAP (12 equiv), *i*-Pr_2NEt (6 equiv), toluene, 70 °C, 15 h (45% for three steps), (4) *p*-TsOH (10 mol%), CH_2Cl_2/MeOH (1/1), rt, 1 h (88%), (5) Tf_2O (1.2 equiv), 2,6-lutidine (5 equiv), CH_2Cl_2, –78 °C, 15 min, followed by addition of TESOTf (1.5 equiv), –78 °C to 0 °C, then followed by addition of NaI (5 equiv) in DMF, rt, 12 h (80% overall yield). *Abbreviations*: MNBA = 2-methyl-6-nitrobenzoic anhydride.

The completion of synthesis is outlined in Scheme 8. Recently developed Ni(I)/Ni(II)–mediated one-pot ketone synthesis was adopted to couple right-half **30** with left-half **6**[24] with a 1.0:1.2 molar ratio of coupling partners, to afford ketone **31** in 76% yield.[25]

After desilylation with buffered TBAF, ketone **31** was subjected to [5,5]-spiroketalization. In the halichondrin series, this transformation was done by a treatment with PPTS or PTSA in CH_2Cl_2 at 20 °C, to yield a (4~6):1 mixture of halichondrins and C38-*epi*-halichondrins.[3] In this study, we discovered that the stereoselectivity of [5,5]-spiroketalization dramatically depends on a solvent system; spiroketalization with PTSA in a 1:1 aqueous methanol at 20 °C yielded a >20:1 mixture of [5,5]-spiroketals (70% for two steps combined), along with a small amount of uncyclized material (~3%). On comparison of ^{1}H- and ^{13}C-NMR with halichondrin B, the major [5,5]-spriroketal was established to belong to the natural series.[26] Interestingly, both the polycyclic ring and C10 O-allyl groups were stable under the new condition.

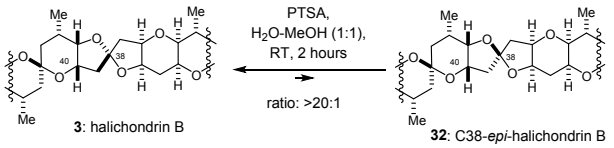
Scheme 8. Synthesis of Halistatin 1[a]



[a]*Reagents and conditions:* (a) **30** (1 equiv), **6** (1.2 equiv), py-(Me)imid·$NiCl_2$ (30 mol%), $(Me)_3$tpy·NiI (5 mol%), DTBMP (2.5 equiv), Cp_2ZrCl_2 (1.2 equiv), Zn (6 equiv), DMA/DME (1/1), rt, 1.5 h (76%); (b) (1) TBAF (10 equiv), PivOH (5 equiv), DMF, rt, 12 h, (2) PTSA (8 equiv), MeOH/H_2O (1/1), rt, 4 h (70% for two steps), (3) $Pd[PPh_3]_4$ (30 mol%), DMBA (2 equiv), MeOH, rt, 6 h (63%). *Abbreviations*: DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine; DMBA = *N,N'*-dimethylbarbituric acid.

It is worthwhile noting that the new [5,5]-spiroketalization condition was found equally effective for halichondrins. We speculated that the high stereoselectivity observed in the [5,5]-spiroketalization was due to acid-catalyzed equilibration (Scheme 9). Indeed, on treatment with PTSA in aqueous MeOH (1:1) for 2 hours at room temperature, C38-*epi*-halichondrin B, **32** was found to yield a >20:1 mixture of halichondrin B and C38-*epi*-halichondrin B. We assume that the origin of high stereoselectivity would be attributed to the double anomeric effects. This notion is supported by the [5,5]-ketal conformation found in the X-ray structure of halichondrin C.[3d]

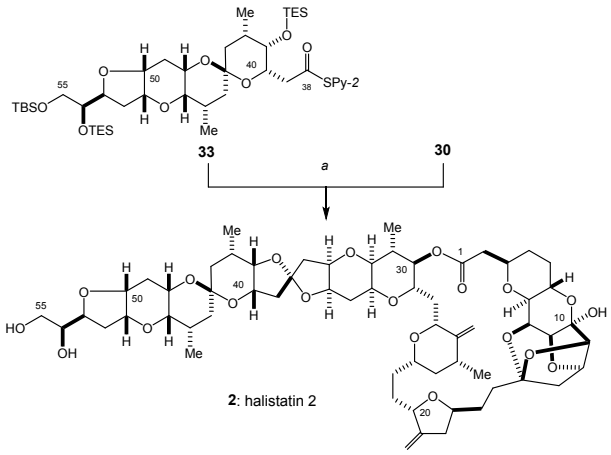
Scheme 9. Equilibration of [5,5]-Spiroketals



The final step of synthesis was to remove the C10 O-allyl group, which was accomplished with $Pd[PPh_3]_4$ in the presence of 1,3-dimethylbarbituric acid, to give synthetic halistatin 1

(Scheme 8).[27] Reverse-phase column chromatography purification furnished synthetic halistatin 1 in 63% yield. The synthetic material was fully characterized and confirmed to be identical with natural halistatin 1 on comparison of ^{1}H and ^{13}C NMR spectra (Figure 5).[28]

Scheme 10. Synthesis of Halistatin 2[a]



[a]*Reagents and conditions:* (a) Follows the synthetic sequence under the conditions defined in Scheme 8.

Following the 4-step sequence in Scheme 8, halistatin 2 was uneventfully obtained from **33**[24] and **30** in a comparable yield (Scheme 10). Synthetic halistatin 2 was isolated with reverse-phase column chromatography, fully characterized (^{1}H NMR, ^{13}C NMR, and HRMS), and confirmed to be identical with natural halistatin 2 (^{1}H and ^{13}C NMR; Figure 5).[28]

CONCLUSION

The first total synthesis of halistatins 1 and 2 has been completed using Cr-mediated coupling reactions for the C11/C12, C17/C18 and C19/C20 bond-formation. For the C11/C12 bond-formation, a stoichiometric Ni/Cr-mediated reaction was used to couple an α-quaternary aldehyde with a vinyl iodide. The solubilized Cr-reagent, prepared from $CrCl_2$ and a sulfonamide ligand, allowed to perform the coupling with 1 equivalent of Cr-reagent. Catalytic Co/Cr-mediated iodoallylation was adopted to incorporate the requisite C17-C19 functionality in a stereoselective manner. Asymmetric Ni/Cr-mediated coupling was used to form the C19/C20 bond effectively. Through this study, it was found that the stereoselectivity of [5,5]-spiroketalization dramatically depends on solvents; PTSA in 1:1 methanol-water gave a >20:1 stereoselectivity favoring the natural series. This condition was also effective to isomerize C38-*epi* halichondrins into C38-natural halichondrins.

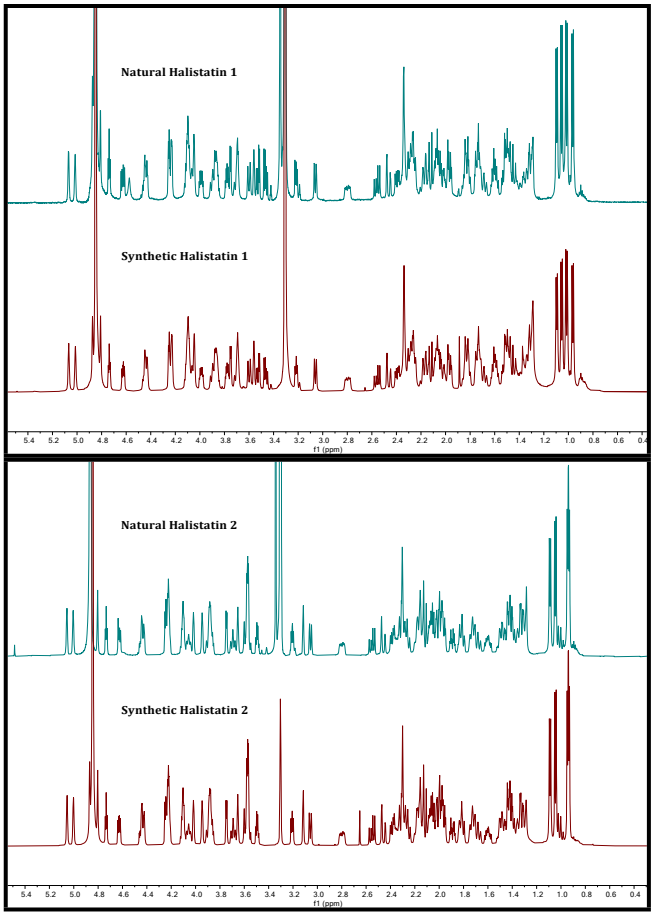


Figure 5. ^{1}H NMR Spectra of Natural and Synthetic Halistatins 1 and 2 (600 MHz; CD_3OD)

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, copies of spectra, and crystallographic data (CIF). The Supporting Information is available free of charge on the ACS Publications website.

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Author Contributions

The manuscript was written through contributions of both authors. Both authors have given approval to the final version of the manuscript.

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(17) The change of Ni-catalyst to DEP·$NiCl_2$ promoted the undesired C19-iodide activation.

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