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New Syntheses of E7389 C14−C35 and Halichondrin C14−C38 Building Blocks: Double-Inversion Approach

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Abstract: With sequential use of catalytic asymmetric Cr-mediated coupling reactions, E7389 C14−C35 and halichondrin C14−C38 building blocks have been stereoselectively synthesized. The C19−C20 bond is first formed via the catalytic asymmetric Ni/Cr-mediated coupling, i.e., **8** + **9** → **10** (90%; *dr* = 22:1), in which vinyl iodide **8** is used as the limiting substrate. The C23−C24 bond is then formed via the catalytic asymmetric Co/Cr-mediated coupling, i.e., **13** + **14** → **4** (82%; *dr* = 22:1), in which the alkyl−iodide bond in **14** is selectively activated over the vinyl−iodide bond. The catalytic asymmetric Ni/Cr-mediated reaction is employed to couple C14−C26 segment **19** with E7389 C27−C35 segment **20** (91%; *dr* = >55:1). In this synthesis, the C23−O bond is stereoselectively constructed via a double-inversion process, i.e., **21** → **22**, to furnish E7389 C14−C35 building block **22** in 84% yield. The same synthetic sequence has been employed to synthesize halichondrin C14−C38 building block **18b**, i.e., **16a** + **19** → **18b**.

1. Introduction

Halichondrins are polyether macrolides, originally isolated from the marine sponge *Halichondria okadai* by Uemura, Hirata, and co-workers, which have received much attention due to their intriguing structure and extraordinary *in vitro* and *in vivo* antitumor activity.[1] On completion of the total synthesis of halichondrin B (Figure 1), norhalichondrin B, and homohalichondrin B (Figure 1),[2,3] 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.[4] With this crucial information, a massive drug discovery effort was undertaken by ERI, resulting in two exceptional drug candidates, one (E7389) of which is currently in the late stages

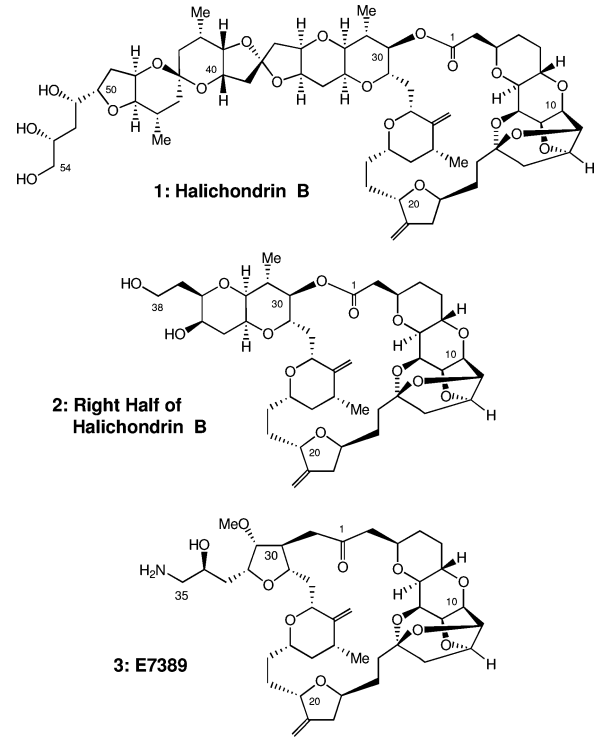


Figure 1. Structure of halichondrin B (**1**), right half of halichondrin B (**2**), and E7389 (**3**).

(1) For the isolation of the halichondrins from a marine sponge *Halichondria okadai* Kadota, see: (a) Uemura, D.; Takahashi, K.; Yamamoto, T.; Katayama, C.; Tanaka, J.; Okumura, Y.; Hirata, Y. *J. Am. Chem. Soc.* **1985**, *107*, 4796. (b) Hirata, Y.; Uemura, D. *Pure Appl. Chem.* **1986**, *58*, 701. For isolation of the halichondrins from different species of sponges, see: (c) Pettit, G. R.; Herald, C. L.; Boyd, M. R.; Leet, J. E.; Dufresne, C.; Doubek, D. L.; Schmidt, J. M.; Cerny, R. L.; Hooper, J. N. A.; Rützler, K. C. *J. Med. Chem.* **1991**, *34*, 3339. (d) Pettit, G. R.; Tan, R.; Gao, F.; Williams, M. D.; Doubek, D. L.; Boyd, M. R.; Schmidt, J. M.; Chapuis, J.-C.; Hamel, E.; Bai, R.; Hooper, J. N. A.; Tackett, L. P. *J. Org. Chem.* **1993**, *58*, 2538. (e) Litaudon, M.; Hart, J. B.; Blunt, J. W.; Lake, R. J.; Munro, M. H. G. *Tetrahedron Lett.* **1994**, *35*, 9435. (f) Litaudon, M.; Hickford, S. J. H.; Lill, R. E.; Lake, R. J.; Blunt, J. W.; Munro, M. H. G. *J. Org. Chem.* **1997**, *62*, 1868. (g) Hickford, S. J. H.; Blunt, J. W.; Munro, M. H. G. *Bioorg. Med. Chem.* **2009**, *17*, 2199.

(2) For the synthetic work on the marine natural product halichondrins from this laboratory, see: (a) Aicher, T. D.; Buszek, K. R.; Fang, F. G.; Forsyth, C. J.; Jung, S. H.; Kishi, Y.; Matelich, M. C.; Scola, P. M.; Spero, D. M.; Yoon, S. K. *J. Am. Chem. Soc.* **1992**, *114*, 3162. (b) Stamos, D. P.; Chen, S. S.; Kishi, Y. *J. Org. Chem.* **1997**, *62*, 7552. (c) Choi, H.-w.; Demeke, D.; Kang, F.-A.; Kishi, Y.; Nakajima, K.; Nowak, P.; Wan, Z.-K.; Xie, C. *Pure Appl. Chem.* **2003**, *75*, 1. (d) Namba, K.; Jun, H.-S.; Kishi, Y. *J. Am. Chem. Soc.* **2004**, *126*, 7770. (e) Namba, K.; Kishi, Y. *J. Am. Chem. Soc.* **2005**, *127*, 15382. (f) Kaburagi, Y.; Kishi, Y. *Org. Lett.* **2007**, *9*, 723. (g) Zhang, Z.; Huang, J.; Ma, B.; Kishi, Y. *Org. Lett.* **2008**, *10*, 3073. (h) Chen, C.-L.; Namba, K.; Kishi, Y. *Org. Lett.* **2009**, *11*, 409, and references cited therein.

10.1021/ja9058475 CCC: $40.75

of phase III clinical trials.[5] This is exciting news for us, partly because we have been involved in the chemistry of halichondrins from its infancy, but largely because we believe in the potential that the halichondrins offer to cancer chemotherapy. However, we should point out that, to our best knowledge, the structural complexity of the right half of halichondrin B, or E7389 (Figure 1), exceeds by far the structural complexity of synthetic drugs on the market and/or synthetic drug candidates under development. Thus, an economically feasible synthesis of the right half of halichondrin B and/or Eisai's drug candidate will play *the* key role for ultimate success of this program. It is our belief that contemporary synthetic organic chemistry has the capacity and potential to meet this type of challenge.

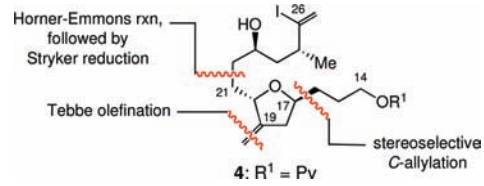
With this analysis in mind, we have continued synthesis of the halichondrins, with one of the major focuses being development of catalytic asymmetric Cr-mediated coupling reactions.[2,6] In this and the following paper,[7] we report the impact of the newly developed methods on the overall efficiency of synthesis: they allow us to shorten the synthesis, improve the overall yield, and incorporate a high degree of flexibility in synthesis.

2. Results and Discussions

2.1. Synthesis of the C14−C26 Building Block. In the first-generation synthesis, we synthesized the C14−C26 building block **4** from 2-deoxy-L-arabinose diethylthioacetal 4,5-acetonide[8] in 18 steps in approximately 20% overall yield.[2a] This synthesis relied on three C−C bond-forming reactions: (1) stereoselective *C*-allylation to form the C16−C17 bond, (2) Tebbe olefination to incorporate the exocyclic olefin at C19, and (3) Horner−Emmons olefination, followed by conjugate hydride reduction with the Stryker reagent, to form the C21−C22 bond (Scheme 1). Although lengthy, this synthesis served well not only for the first-generation total synthesis of the halichondrins but also for the discovery and development of E7389.

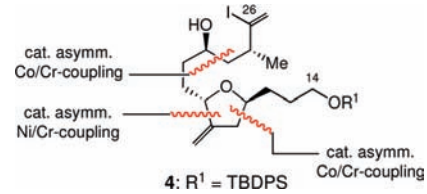
For the past several years, we have been exploring a new synthetic route and recognized the possibility of synthesizing **4** via three consecutive Cr-mediated coupling reactions: (1) Co/Cr-mediated 2-iodoallylation to form the C17−C18 bond, (2) Ni/Cr-mediated alkenylation to form the C19−C20 bond,

Scheme 1. Three C−C Bond-Forming Sites in the First-Generation Synthesis



and (3) Co/Cr-mediated alkylation to form the C23−C24 bond (Scheme 2); we reported preliminary results on the

Scheme 2. C−C Bond Formations Based on the Cr-Mediated Coupling Reactions



second and third bond-forming processes.[2c] Since then, our efforts have been focused on how to realize each of the Cr-mediated couplings in a catalytic asymmetric process at a synthetically useful level.[9]

The new synthesis of **4** started with a catalytic asymmetric Co/Cr-mediated 2-iodoallylation in the presence of Cr catalyst derived from (*S*)-sulfonamide **A** (Scheme 3). With 10 mol % catalyst loading, the coupling of aldehyde **5** with 2-iodoallyl bromide **6** furnished the desired 2-iodoolefin **7** in 85% yield with 93% *ee*.[2g] The undesired enantiomer could be removed at this stage,[10] but for practical purposes, this enantiomer mixture was directly used for the following steps (*vide infra*).

After activation of the secondary alcohol as its 2-mesitylenesulfonate (MES), the vinyl iodide was subjected to catalytic asymmetric Ni/Cr-mediated coupling with aldehyde **9** in the presence of the catalyst prepared *in situ* from $CrCl_2$ and (*R*)-sulfonamide **B**. It is noteworthy that, considering its structural complexity compared with **9**, we planned to use **8a** as the limiting substrate for this coupling. Usually, Ni/Cr-mediated couplings are carried out with a slight excess of nucleophiles, because this process often gives byproduct through leakage in the Ni catalytic cycle.[11] Under the conditions developed for the catalytic asymmetric Cr-mediated couplings, these byproducts are detected only at a low-to-insignificant level.[9] Nonetheless, the plan of using **8a** as the limiting substrate gave us an opportunity to rigorously assess leakage through the Ni catalytic cycle. Experimentally,

(3) For synthetic work by Salomon, Burke, Yonemitsu, and Phillips, see: (a) Kim, S.; Salomon, R. G *Tetrahedron Lett.* **1989**, *30*, 6279. Cooper, A. J.; Pan, W.; Salomon, R. G. *Tetrahedron Lett.* **1993**, *34*, 8193, and references cited therein. (b) Burke, S. D.; Buchanan, J. L.; Rovin, J. D. *Tetrahedron Lett.* **1991**, *32*, 3961. Lambert, W. T.; Hanson, G. H.; Benayoud, F.; Burke, S. D. *J. Org. Chem.* **2005**, *70*, 9382, and references cited therein. (c) Horita, K.; Hachiya, S.; Nagasawa, M.; Hikota, M.; Yonemitsu, O. *Synlett* **1994**, 38. Horita, K.; Nishibe, S.; Yonemitsu, O. *Phytochem. Phytopharm.* **2000**, 386, and references cited therein. (d) Henderson, J. A.; Jackson, K. L.; Phillips, A. J. *Org. Lett.* **2007**, *9*, 5299. Jackson, K. L.; Henderson, J. A.; Motoyoshi, H.; Phillips, A. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 2346, and references cited therein.

(4) Kishi, Y.; Fang, F. G.; Forsyth, C. J.; Scola, P. M.; Yoon, S. K. U.S. Patent 5338866; International Patent WO93/17650.

(5) (a) Zheng, W.; Seletsky, B. M.; Palme, M. H.; Lydon, P. J.; Singer, L. A.; Chase, C. E.; Lemelin, C. A.; Shen, Y.; Davis, H.; Tremblay, L.; Towle, M. J.; Salvato, K. A.; Wels, B. F.; Aalfs, K. K.; Kishi, Y.; Littlefield, B. A.; Yu, M. J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5551. (b) Littlefield, B. A.; Palme, M. H.; Seletsky, B. M.; Towle, M. J.; Yu, M. J.; Zheng, W. U.S. Patents 6214865, 6365759; International Patent WO99/65894. (c) Yu, M. J.; Kishi, Y.; Littlefield, B. A. In *Anticancer Agents from Natural Products*; Cragg, G. M., Kingston, D. G. I., Newman, D. J., Eds.; CRC Press: Boca Raton, FL, 2005; p41. (d) E7389 website: http://www.drugs.com/nda/e7389_08 0201.html.

(6) For reviews on Cr-mediated C−C bond-forming reactions, see ref 2 in ref 7.

(7) Dong, C.-G.; Henderson, J. A.; Kaburagi, Y.; Sasaki, T.; Kim, D.-S.; Kim, J. T.; Urabe, D.; Guo, H.; Kishi, Y *J. Am. Chem. Soc.* **2009**, *131*; http://dx.doi.org/10.1021/ja9058487.

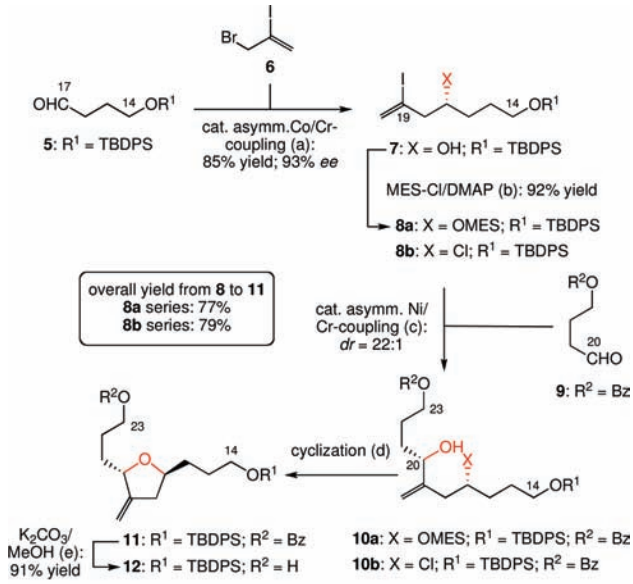
(8) Wong, M. Y. H.; Gray, G. R. *J. Am. Chem. Soc.* **1978**, *100*, 3548.

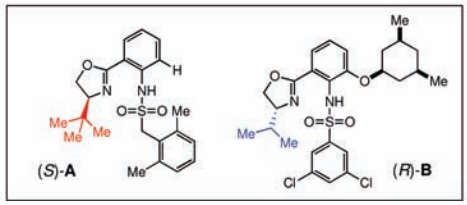
(9) Guo, H.; Dong, C.-G.; Kim, D.-S.; Urabe, D.; Wang, J.; Kim, J. T.; Liu, X.; Sasaki, T.; Kishi, Y. *J. Am. Chem. Soc.* **2009**, *131*; http://dx.doi.org/10.1021/ja905843e.

(10) The optical purity of **7** was enhanced via recrystallization of its 4-acetylphenylcarbamate and 4-[4-carbomethoxyphenyl]benzoate.

(11) Ni-mediated homodimerization of a vinyl iodide is known to be one of side reactions: see ref 1 in ref 7. For Ni(0)-mediated dimerization of aryl and alkenyl halides, see: (a) Semmelhack, M. F.; Helquist, P. M.; Jones, L. D. *J. Am. Chem. Soc.* **1971**, *93*, 5908. (b) Semmelhack, M. F.; Helquist, P. M.; Jones, L. D. *J. Am. Chem. Soc.* **1972**, *94*, 9234.

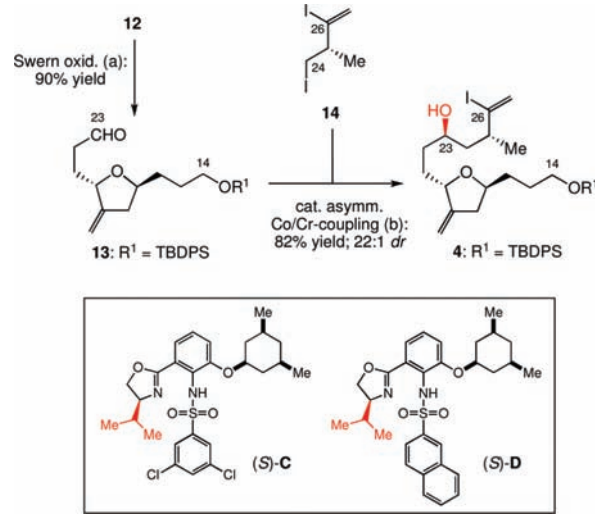
Scheme 3. Synthesis of the C14−C23 Building Block **12**[a]





[a] Reagents and conditions: (a) Catalytic asymmetric Co/Cr-mediated 2-iodoallylation in the presence of Cr catalyst prepared from (*S*)-sulfonamide **A**. (b) MES-Cl/DMAP/CH_2Cl_2/rt. (c) Catalytic asymmetric Ni/Cr-mediated coupling in the presence of Cr catalyst prepared from (*R*)-sulfonamide **B**. (d) For X = MES series, cyclization *in situ* (2 days at rt);[12] for X = Cl series, KH/18-crown-6/toluene/−78 °C → −20 °C. (e) K_2CO_3/MeOH/rt. Abbreviations: TBDPS = *t*-Bu(Ph)$_2$Si−; Bz = PhCO−; MES = 2,4,6-(Me)$_3$PhSO$_2$−; DMAP = 4-dimethylaminopyridine.

Scheme 4. Synthesis of the C14−C26 Building Block **4**[a]



[a] Reagents and conditions: (a) Swern oxidation. (b) Catalytic asymmetric Co/Cr-mediated coupling in the presence of Cr catalyst prepared from (*S*)-sulfonamide **C** or **D**.[2c]

the ratio of Cr and Ni salts was found to be critical to eliminate the byproduct forming process while maintaining the rate of coupling acceptably fast; with 20 mol % of the Cr complex and 3 mol % of $NiCl_2$·2,9-dimethyl-1,10-phenanthroline ($NiCl_2$·DMP), this coupling furnished the desired product **10a** in ca. 90% yield, accompanied with the byproduct at only <3% estimated from ^{1}H NMR. In the reaction medium, **10a** slowly cyclized and gave **11** as a 22:1 mixture of the C20 diastereomers in ca. 80% overall yield.[12]

Upon treatment with potassium carbonate in methanol, the benzoate at C23 was cleanly removed to furnish **12** as a 22:1 mixture of the C20 diastereomers. With medium-pressure chromatography on silica gel, the stereochemically homogeneous **12** was isolated in ca. 70% overall yield from **8a**.

Based on the working hypothesis discussed later, we studied the same sequence of reactions with the vinyl iodide chloride **8b**,[13] instead of the vinyl iodide mesitylenesulfonate **8a**. The catalytic asymmetric Ni/Cr-mediated coupling gave the desired allylic alcohol **10b** in 90% yield with *dr* = 22:1; the efficiency of coupling, i.e., coupling rate and catalyst loading, was noticeably improved in the **8b** series (catalyst loading ≤10 mol %) over the **8a** series (catalyst loading 20 mol %). In this series, the cyclization of **10b** was achieved by treatment with KH in toluene containing 18-crown-6, to furnish **11**. After deprotection of the C23 benzoate, **12** was isolated in 70% overall yield from **10b**. Except for the catalyst loading, the overall synthetic efficiency of the two series was comparable.

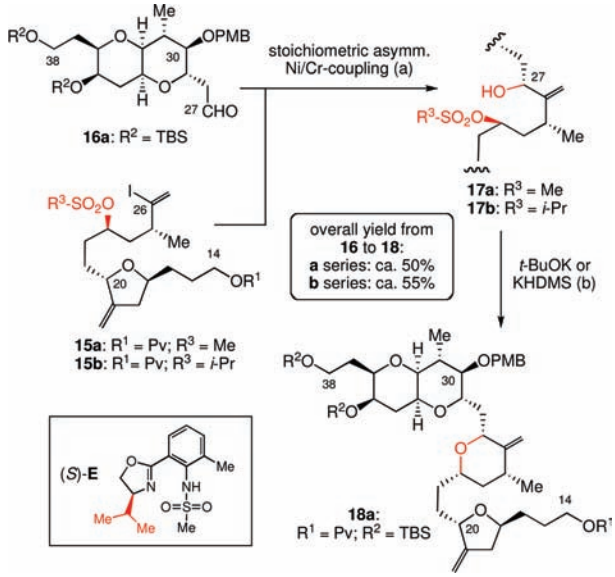
The aldehyde **13**, obtained via Swern oxidation[14] of **12**, was subjected to the next catalytic asymmetric Cr-mediated coupling reaction with diiodide **14** (Scheme 4).[15] In this coupling, activation of the alkyl−iodide bond over the vinyl−iodide bond was selectively achieved with a catalytic amount of Co-phthalocyanine (CoPc).[2c] (*S*)-Sulfonamide **C** was most effective in inducing the asymmetric process (*dr* = 33:1; 70% yield). However, for the asymmetric induction and chemical yield combined, (*S*)-sulfonamide **D** was found to be the best choice (*dr* = 22:1; 82% yield).[9]

Alcohol **4** and its C23-diastereomer exhibited a different chromatographic behavior on silica gel, allowing their separation via flash chromatography on silica gel. Taking advantage of this chromatographic behavior, we carried out the synthesis without purification at the C19−C20 Ni/Cr-coupling step and isolated homogeneous **4** chromatographically at this stage for preparative purposes. Similarly, it was possible to eliminate the purification step for the first Co/Cr-mediated 2-iodoallylation; a ca. 24:1 enantiomer mixture obtained at the 2-iodoallylation was carried through without separation, and homogeneous **4** was isolated chromatographically at this stage.[16]

Overall, the stereochemically homogeneous C14−C26 building block **4** is now available in five steps[17] with one chromatographic purification in ca. 40% and 45% overall yields from **8a**

(12) Cyclization of **10a** to **11** was effected also by treatment with pyridinium *p*-toluensufonate (PPTS).
(13) **8b** was synthesized from **5** in three steps, i.e., catalytic asymmetric Cr-mediated propargylation, CCl_3CONH_2/PPh_3, and *B*-iodo-9-BBN: Liu, S.; Kim, J. T.; Dong, C.-G.; Kishi, Y. Submitted for publication.
(14) Mancuo, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
(15) Diiodide **14** was synthesized via several synthetic routes. Two of them are outlined in the Supporting Information.
(16) Knowing the enantiomer ratio (*er* = 24:1) of **8a** used and also the asymmetric induction (*dr* ≈ 24:1) for this Ni/Cr-mediated coupling, we estimated the stereoselectivity of the coupling and the optical purity of the desired product to be *dr* = ca. 12:1 and *op* = >99.8%, respectively. Experimentally, *dr* and *op* were found to be 13:1 and >99.8%, respectively.

Scheme 5. Synthesis of Halichondrin C14−C38 Building Block **18a**[a]



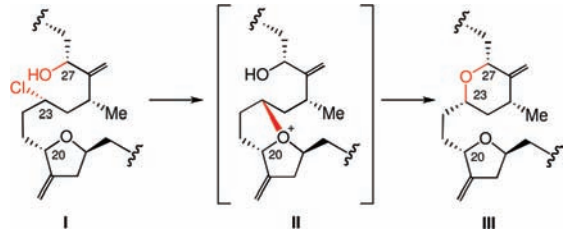
[a] Reagents and conditions: (a) Ni/Cr-mediated coupling under stoichiometric asymmetric conditions. (b) *t*-BuOK or KHMDS/THF/−15 °C. Abbreviations: TBS = *t*-Bu(Me)$_2$Si−; PMB = *p*-MeOPhCH$_2$−; Pv = (Me)$_3$CCO−; KHMDS = KN(SiMe$_3$)$_2$.

and **8b**, respectively.[18] Because of a better catalyst loading, we consider the synthesis with **8b** to be better suited for preparative purposes.

2.2. New Synthesis of Halichondrin C14−C38 and E7389 C14−C35 Building Blocks. In the first-generation synthesis, we relied on the stoichiometric non-asymmetric Ni/Cr-mediated reaction to couple **15a** and **16** (*dr* = 6:1).[2a] With use of the first-generation (*S*)-sulfonamide **E**, a stoichiometric asymmetric version was realized with a *dr* = 20:1 stereoselectivity.[2c] On treatment with *t*-BuOK or KHMDS in THF at −15 °C, the resultant allylic alcohols furnished halichondrin C14−C38 building block **18a** (Scheme 5). We should note, however, that this base-induced cyclization gave the olefin byproduct in 10−20% yield. Replacement of the methanesulfonate in **15a** (R^3 = Me) with the isopropylsulfonate (R^3 = *i*-Pr) in **15b** resulted in an improvement in the overall yield from **16a** + **15a** → **18a**, but olefin formation could not be completely eliminated.[2c]

Naturally, we were eager to improve this synthetic route; in particular, we wished to eliminate, or at least suppress, the formation of olefins upon base-induced cyclization and became interested in the double-inversion approach for three reasons (Scheme 6).

Scheme 6. Double-Inversion Strategy for the C23−O Bond Formation



First, the proposed double-inversion approach is supported by our previous observation that **15a** is readily hydrolyzed in wet THF to give the alcohol **4** (R^1 = Pv) with clean *retention* of its stereochemistry.[2a]

Second, the proposed transformation could be achieved under a condition different from base-induced cyclization and, therefore, olefin formation might be avoided or suppressed.

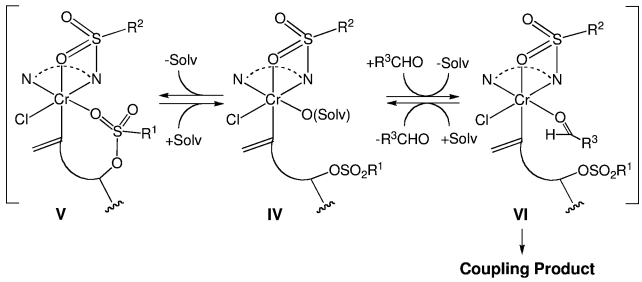
Third, as the coupling of **15a** with **16a** was found to be slow under the catalytic asymmetric conditions with the Cr catalyst derived from (*S*)-sulfonamide **E** (Scheme 5), it did not appear practical to lower the catalyst loading below 20 mol %. Interestingly, coupling with the vinyl iodide bearing OTBS at C23, instead of OMs, proceeded smoothly in the presence of 10 mol % catalyst, suggesting that the sluggishness of the coupling is associated with **15a** rather than the catalyst. Catalytic Ni/Cr-mediated coupling reactions involve at least four discrete steps: (1) oxidative addition of Ni(0) to a vinyl iodide, (2) transmetalation of the resultant vinyl-Ni(II) species to Cr(II), (3) C−C bond formation through the resultant vinyl-Cr(III) species, and (4) dissociation of the resultant product from the Cr(III) species. Based on the X-ray structure of Cr-sulfonamide complexes,[2c] we speculated that the aldehyde coordinates to the presumed active octahedral Cr species **IV**, formed via transmetalation of a vinyl-Ni(II) species, at the site indicated as "Solv". For the case of **15a**, one of the O═S bonds of the sulfonate group could occupy the coordination site "Solv", cf. **V**, thus slowing down, or shutting down, the coupling (Scheme 7). This analysis suggested that a substrate such as **19** (Scheme 8) might improve the catalyst loading.

To test the feasibility of a double-inversion approach, we prepared the C23-α-Cl substrate **19** from **4**. On treatment with (*n*-Bu)$_3$BnNCl in *N,N*′-dimethylpropylene urea (DMPU) at room temperature for 45 h, the mesylate prepared from **4** gave the desired chloride (91% isolated yield), along with C23-*β*-Cl (3%) and C17-α-Cl (0.9%).[19] It is noteworthy that DMPU is critical to obtain **19** with the inversion at C23 in high yield; for example, in DMF, C17-α-Cl was isolated in as high as 10% yield. Obviously, this byproduct was formed via an oxonium ion similar to the proposed **II** (Scheme 6).

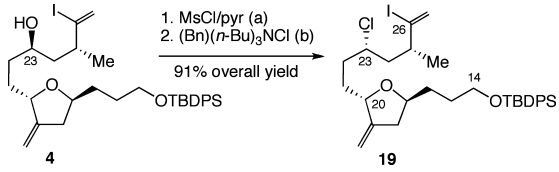
The catalytic asymmetric coupling of **19** with **20** proceeded smoothly: in the presence of Cr catalyst prepared from (*S*)-sulfonamide **F**, the desired coupling product was isolated in 91% yield with *dr* = >55:1.[20] This Ni/Cr-mediated coupling was

(17) With use of a latent aldehyde at C23, it should be possible to remove one step from the reported seven-step synthesis; indeed, we recently proved its feasibility with use of the C23 2,2-dimethylpropylene acetal corresponding to **9**.
(18) Routinely, this transformation was carried out in a one-gram scale in both **8a** and **8b** series.
(19) See the Supporting Information for the structure of this byproduct, which was proposed on the basis of the spectroscopic data (MS, ^{1}H NMR, COSY, and 1D NOE) coupled with the mechanistic considerations.
(20) The C23-*β*-Cl vinyl iodide was found to be a good substrate for the catalytic asymmetric coupling, but the resultant allylic alcohol gave olefin byproducts (10−20%) in the base-induced cyclization step.
(21) Other solvents (THF, Et$_2$O, toluene, and MeCN), silver salts (AgClO$_4$, AgF$_2$, AgNO$_3$, and Ag$_2$O), other metal salts (PbCO$_3$ and TlOEt), and additives (K$_2$CO$_3$ and molecular sieves) were also tested.
(22) The structure of the C23 diastereomer was assigned on comparison with the sample prepared via a different route; the C23-*β*-chloride corresponding to **19** was subjected to Ni/Cr-mediated coupling and then AgBF$_4$-promoted cyclization to give the C23 diastereomer of **22** as the major product.
(23) The C27 diastereomer, derived from the minor product in the Ni/Cr-coupling, was detected in the crude product by ^{1}H NMR, but only a trace amount (<0.2%).
(24) In the halichondrin series, ca. 10% of the Ni/Cr-coupling product was recovered; the yield of **18b** was ca. 83% based on the consumed starting material.

Scheme 7. Possible Intermediates Involved in Catalytic Cr-Mediated Coupling with a Sulfate Nucleophile[2c]

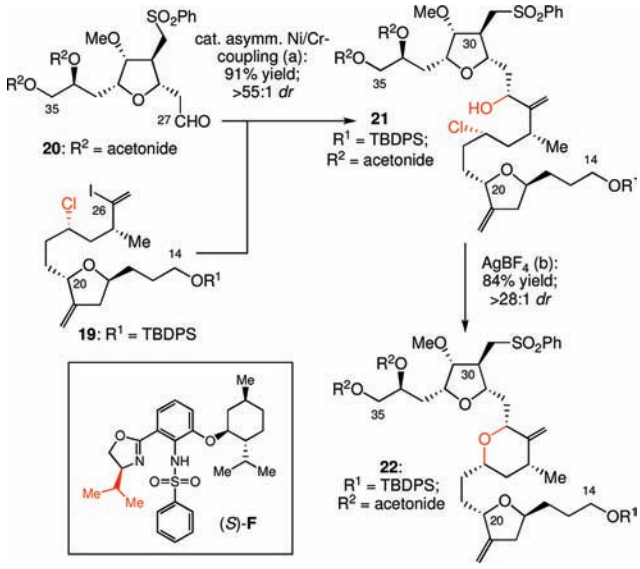


Scheme 8. Synthesis of C23-α-Chloride **19**[a]



[a] Reagents and conditions: (a) $MeSO_2Cl$/pyridine. (b) $Bn(n\text{-}Bu)_3NCl$/DMPU/rt/45 h. Abbreviation: DMPU = *N,N′*-dimethylpropylene urea.

Scheme 9. Synthesis of E7389 C14−C35 Building Block **22**[a]

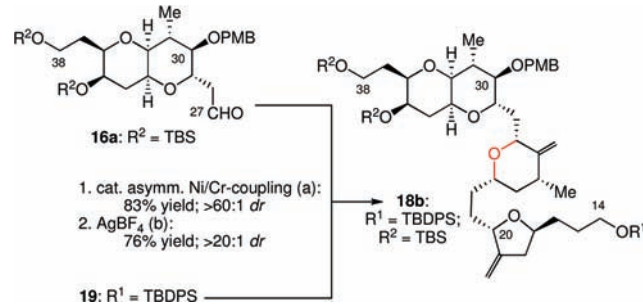


[a] Reagents and conditions: (a) Catalytic asymmetric Ni/Cr-mediated coupling in the presence of Cr catalyst prepared from (*S*)-sulfonamide **F**. (b) $AgBF_4$/DTBMP/*t*-BuOAc. Abbreviation: DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine.

routinely carried out with 1.5 equiv of **19**. We should note that, even with 1.2 equiv of **19**, the coupling reaction proceeded well but gave the product in a lower yield (ca. 80%).

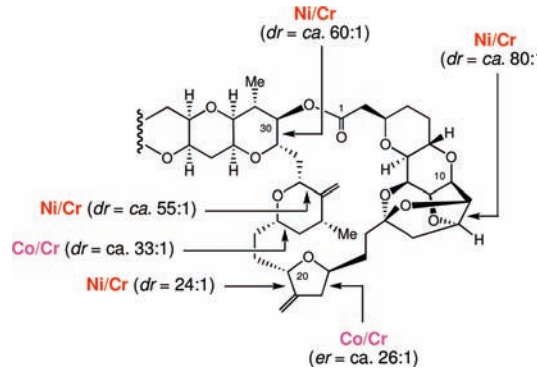
Among several conditions tested,[21] the desired double-inversion/cyclization was best achieved with $AgBF_4$ (3 equiv) in *tert*-butyl acetate containing 2,6-di-*tert*-butyl-4-methylpyridine (5 equiv) at 0 °C → rt for 9 h. With silica gel column chromatography, the desired product **22** was readily isolated in 84% yield (Scheme 9), and the product structure was confirmed by spectroscopic comparison with the authentic sample. It is noteworthy that the C23 diastereomer was also isolated, but only in a small amount (ca. 3% isolated yield),[22] indicating the efficiency of double-inversion, i.e., 84% vs 3%.[23] In this connection, it is interesting to note that the C23-β-Cl corresponding to **21** gave a ca. 8.5:1:1 mixture of products, with the major product being the expected C23 diastereomer and the minor products being the C26 diastereomer and olefin byproduct.

Scheme 10. Synthesis of Halichondrin C14−C38 Building Block **18b**[a]



[a] Reagents and conditions: (a) Catalytic asymmetric Ni/Cr-mediated coupling in the presence of Cr catalyst prepared from (*S*)-sulfonamide **F**. (b) $AgBF_4$/DTBMP/*t*-BuOAc.

Scheme 11. Catalytic Asymmetric Cr-Mediated Couplings Used in the Halichondrin Synthesis[a]



[a] Catalytic asymmetric Co/Cr-mediated 2-iodoallylation (C17−C18 bond formation), Ni/Cr-mediated alkenylation (C19−C20 bond formation), and Co/Cr-mediated alkylation (C23−C24 bond formation) are used sequentially to construct the C14−C26 building block. The C26−C27 bond is then formed through the use of catalytic asymmetric Ni/Cr-mediated alkenylation in a highly convergent manner. In addition, catalytic asymmetric Ni/Cr-mediated coupling reactions are used for the C11−C12 and the C29−C30 bond formations in the syntheses of the C1−C13 and C26−C38 building blocks.

The double-inversion approach was successfully employed to synthesize halichondrin C14−C38 building block **18b** (Scheme 10), although its overall yield was slightly lower than those in the E7389 series[24] (Scheme 10).

3. Conclusion

In summary, we have developed new concise syntheses of the E7389 C14−C35 and halichondrin C14−C38 building blocks via sequential use of Cr-mediated coupling reactions (Scheme 11). In this synthesis, the C23−O bond is constructed via a double-inversion process with excellent yield and stereoselectivity. This study demonstrates that catalytic asymmetric Cr-mediated coupling reactions allow us to assemble these molecules in a convergent and stereoselective manner, thereby dramatically improving the overall efficiency in terms of not only synthetic steps but also yields. It is also worth noting that the catalytic asymmetric Cr-mediated coupling reactions allow us to incorporate a high degree of flexibility in synthesis. In the following paper, we will address one additional critical

requirement to perform a highly convergent synthesis in a cost-effective manner.

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Supporting Information Available: Experimental details, including the syntheses outlined in Schemes 3, 4, 5, 8, 9, and 10, complete characterization of synthetic intermediates, and ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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