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New Syntheses of E7389 C14−C35 and Halichondrin C14−C38 Building Blocks: Reductive Cyclization and Oxy-Michael Cyclization Approaches

Cheng-Guo Dong, James A. Henderson, Yosuke Kaburagi, Takeo Sasaki, Dae-Shik Kim, Joseph T. Kim, Daisuke Urabe, Haibing Guo, and Yoshito Kishi*

Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford Street, Cambridge, Massachusetts 02138

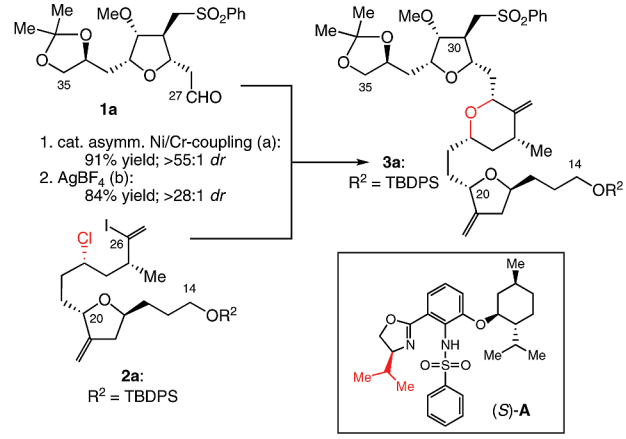
Received July 20, 2009; E-mail: kishi@chemistry.harvard.edu

Abstract: Cr-mediated coupling reactions are usually achieved with a slight excess of a given nucleophile. To develop a cost-effective use of this process, two different approaches have been studied. The first approach depends on two consecutive catalytic asymmetric Cr-mediated couplings, with use of coupling partners purposely being of unbalanced molecular size and complexity. The second approach rests on the success in identifying the nucleophile, which allows us to achieve the coupling satisfactorily with a 1:1 molar ratio of the coupling partners. The C23−O bond is stereospecifically constructed via reductive cyclization of the oxonium ion, or oxy-Michael cyclization. Both syntheses have a high overall efficiency: E7389 C14−C35 and halichondrin C14−C38 building blocks have been synthesized from the corresponding C27−C35 and C27−C38 aldehydes, respectively, in high overall yields with an excellent stereoselectivity. Because of operational simplicity, the synthesis outlined herein appears to be well suited for scaling.

1. Introduction

In the preceding paper,[1] we discussed two convergent approaches to synthesize E7389 C14−C35 and halichondrin C14−C38 building blocks. For example, a catalytic asymmetric Ni/Cr-mediated reaction is used to couple the two building blocks, e.g., **1a** + **2a** → **3a** (Scheme 1). Two aspects of this coupling are noteworthy. First, the catalyst, prepared *in situ* from $CrCl_2$ and (*S*)-sulfonamide **A**, allows us to achieve the coupling with excellent yield and stereoselectivity (yield = 91%; *dr* = >55:1). Second, this coupling gives a high level of convergency, as the target molecule is dissected into two coupling partners with roughly equal molecular size and structural complexity. However, it is achieved best with use of 1.5 equiv of the vinyl iodide for this Ni/Cr-mediated coupling. For this reason, it is not necessarily most cost-effective on the basis of **2a**, unless the synthetic cost of **2a** compensates the 1.5:1 molar ratio of the two coupling partners.[2] In this paper, we will present two approaches to address this issue.

Scheme 1. Synthesis of E7389 C14−C35 Building Block via Catalytic Asymmetric Ni/Cr-Mediated Coupling of **1a** with **2a**[a]



[a] Catalytic asymmetric Ni/Cr-mediated coupling in the presence of the Cr catalyst derived from (*S*)-sulfonamide **A**, followed by $AgBF_4$-promoted cyclization. Abbreviation: TBDPS = *t*-Bu(Ph)$_2$Si−.

2. Results and Discussions

2.1. First Approach: Unbalancing the Molecular Size and Structural Complexity of Coupling Partners. 2.1.1. C23−O Bond-Formation via S_N2 Cyclization. Cr-mediated coupling reactions are usually carried out with a slight excess, typically 1.5 equiv, of a given nucleophile.[3] Therefore, for cost-effective use of Cr-mediated couplings, one needs to pay attention not only to the relative molecular size and structural complexity of the coupling partners but also to their molar ratio. One obvious solution is to dissect a target molecule accordingly. Scheme 2 outlines such an approach. Taking these factors together into account, the target molecule **5a** is dissected into vinyl iodide **4**

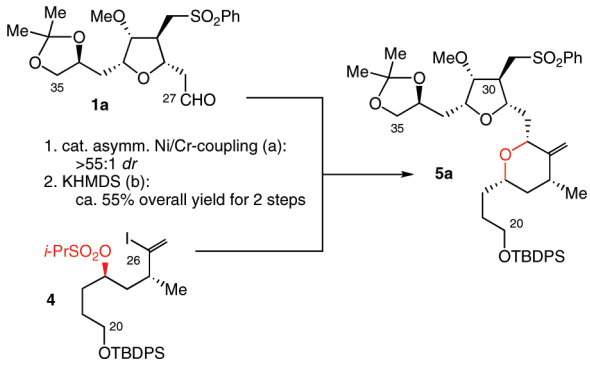
(1) Kim, D.-S.; Dong, C.-G.; Kim, J. T.; Guo, H.; Huang, J.; Tiseni, P. S.; Kishi, Y. *J. Am. Chem. Soc.* **2009**, *131*, http://dx.doi.org/10.1021/ja9058475.

(2) Two major modifications have been made on the synthesis of **1a**, reported in ref 2c in the preceding paper. In our estimation, the cost for the synthesis of **1a** now appears to be very close to, even lower than, that for **2a**.

(3) 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 and references cited therein.

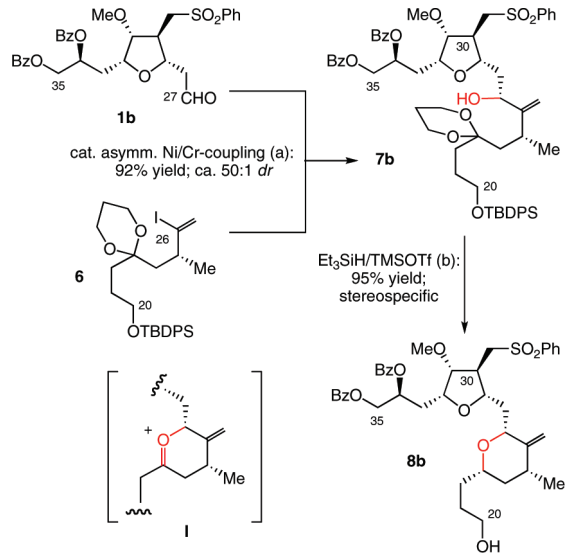
10.1021/ja9058487 CCC: $40.75

Scheme 2. Synthesis of E7389 C20−C35 Building Block **5a**[a]



[a] Reagents and conditions: (a) catalytic asymmetric Ni/Cr-mediated coupling in the presence of the Cr catalyst derived from (*S*)-sulfonamide **A**. (b) KHMDS/THF/−15 °C. Abbreviation: KHMDS = $KN(SiMe_3)_2$.

Scheme 3. Synthesis of E7389 C20−C35 Building Block **8b**[a]



[a] Reagents and conditions: (a) Catalytic asymmetric Ni/Cr-mediated coupling in the presence of the Cr catalyst derived from (*S*)-sulfonamide **A**. (b) $Et_3SiH/TMSOTf/CH_2Cl_2/-78\ °C \rightarrow 0\ °C$. Abbreviation: Bz = PhCO−; TMSOTf = $(Me)_3SiOSO_2CF_3$.

and aldehyde **1a**. The catalytic asymmetric Ni/Cr-mediated coupling of **1a** with **4** (1.5 equiv) furnished the desired coupling product in ca. 80% yield with excellent stereoselectivity (*dr* = ca. 50:1).

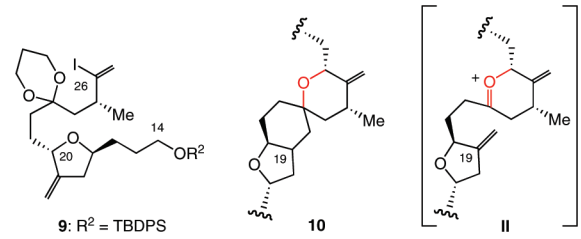
Upon treatment with a base, the resultant allylic alcohols gave the desired cyclized product in ca. 70% yield. However, as observed before,[1] the base-induced cyclization was accompanied with an olefin byproduct (ca. 10%). In order to overcome this drawback, we studied an oxonium ion route.

2.1.2. C23−O Bond Formation via Reductive Cyclization. Once again, the catalytic asymmetric coupling of aldehyde **1b** with vinyl iodide **6**[4] (1.5 equiv) furnished the expected, desired coupling product **7b** in excellent yield (92%) and stereoselectivity (*dr* = ca. 50:1) (Scheme 3).

Based on previous work from this laboratory,[5] we anticipated the desired C23-diastereomers to be preferentially formed on reductive cyclization of the resultant allylic alcohols through an oxonium ion such as **I**. Experimentally, on treatment with trimethylsilyl triflate (2 equiv) in methylene chloride containing

(4) For the preparation of vinyl iodide **6**, see the Supporting Information.

Scheme 4. Attempted Synthesis of E7389 C20−C35 Building Block **3b** via the Oxonium Route



triethylsilane (10 equiv) at −78 °C, the crude allylic alcohols gave the cyclized products with the C20 silyl protecting group intact.

When this reaction mixture was warmed to 0 °C before the workup, the C20 silyl protecting group was cleanly removed *in situ*, to furnish directly the deprotected product **8b** in 95% yield from the Ni/Cr-mediated coupling product. NMR and TLC analyses demonstrated that the reductive cyclization did not yield the undesired C23-diastereomer at detectable levels.[6]

Related to the synthesis outlined in Scheme 3, we should comment on our attempt to extend the oxonium ion approach to the vinyl iodide **9** (Scheme 4).[7] The catalytic asymmetric Ni/Cr-mediated coupling worked well, but the following reductive cyclization gave a mixture of two products. On comparison with the authentic sample, one of the products was found to be the desired product. The spectroscopic data (MS and NMR) suggested the other product to be **10**, which presumably arose through participation of the C19-exocyclic olefin to the oxonium ion **II**. In spite of extensive efforts (varying reducing agents, Lewis acids, and solvents), we were unable to prevent formation of this byproduct.

The primary alcohol **8b** was oxidized to the corresponding aldehyde **11b** and then subjected to catalytic asymmetric Ni/Cr-mediated coupling, followed by base-induced cyclization, to furnish stereochemically homogeneous E7389 C14−C35 building block **3b** (Scheme 5). This transformation deserves several comments. First, considering the unbalanced molecular size and structural complexity, the coupling was carried out with an excess (1.5 equiv) of the vinyl iodide to give the products in 85% yield based on the aldehyde.[8] However, it is noteworthy that the coupling efficiency was not noticeably affected by the use of 1.2 equiv of vinyl iodide. Second, as discussed in the preceding paper, asymmetric induction (*dr* = ca. 32:1) was best achieved with the Cr catalyst derived from (*R*)-sulfonamide **B**. Interestingly, this Cr catalyst gave a higher asymmetric induction for a structurally complex aldehyde such as **11b** than for structurally simple aldehydes previously reported.[1] Third, the base-induced cyclization was effected with KH in toluene containing 18-crown-6 at −78 °C → −20 °C with no detectable level of olefin byproduct.

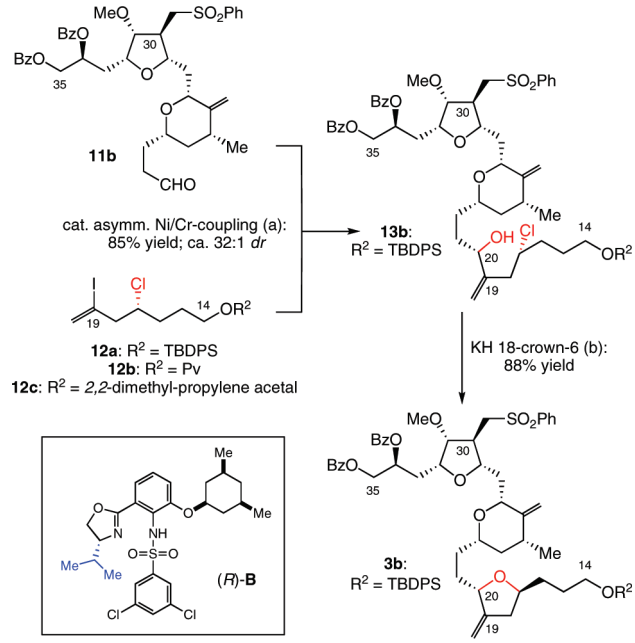
(5) (a) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976. For recent examples, see: (b) Ayala, L.; Lucero, C. G.; Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 15521. (c) Henderson, J. A.; Jackson, K. L.; Phillips, A. J. *Org. Lett.* **2007**, *9*, 5299.

(6) The ethylene glycol ketal corresponding to **6** gave virtually the same results as summarized in Schemes 3 and 5.

(7) Xie, C.; Nowark, P.; Kishi, Y. *Org. Lett.* **2002**, *4*, 4427. For an alternative synthesis of this alcohol, see the Supporting Information in one of our preceding papers.

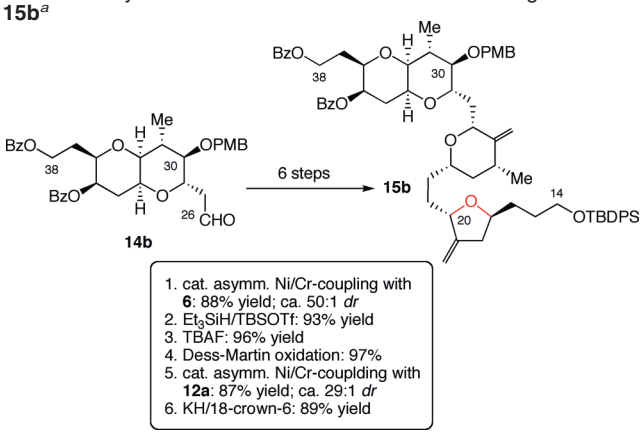
(8) The catalytic asymmetric Ni/Cr-mediated coupling with the vinyl iodide bearing C17 α-2,4,6-trimethylbenzenesulfonate (2 equiv) gave results similar to **12**.

Scheme 5. Synthesis of E7389 C14−C35 Building Block **3b**[a]



[a] Reagents and conditions: (a) Catalytic asymmetric Ni/Cr-mediated coupling in the presence of the Cr catalyst derived from (*R*)-sulfonamide **B**. (b) KH/18-crown-6/toluene/−78 °C → −20 °C. Abbreviation: Pv = $(Me)_3CCO-$.

Scheme 6. Synthesis of Halichondrin C14−C38 Building Block **15b**[a]



[a] Reagents and conditions: see Schemes 3 and 5. Abbreviation: TBAF = tetra-*n*-butylammonium fluoride; PMB = *p*-methoxybenzyl.

The minor C20 diastereomer was readily removed by flash chromatography on silica gel.

The synthesis in Scheme 5 was illustrated with the vinyl iodide **12** with the TBDPS protecting group at C14. It is worth noting that (1) the transformation of **11b** + **12** → **13b** → **3b** was equally effective for two additional vinyl iodides bearing OPv and 2,2-dimethylpropylene acetal at C14 and (2) the C34 and C35 benzoate protecting groups were selectively removed without affecting the C14 protecting group in all the series.[9] Thus, the protecting group in **3b** is readily adjustable as required.

Halichondrin C14−C38 building block **15b** was synthesized via the same synthetic sequence, with one minor modification (Scheme 6). On the reductive cyclization in the halichondrin series, the C30 protecting group (PMB = *p*-methoxybenzyl) was concomitantly removed under the conditions given in Scheme 3. Therefore, a stepwise protocol was used to obtain the C20 primary alcohol, i.e., reductive cyclization at −78 °C, followed by TBDPS deprotection. The overall yield in the halichondrin series was 60%.[10,11]

In summary, E7389 C14−C35 building block **3b** and halichondrin C14−C38 building block **15b** have been synthesized from **1b** and **14b** in five and six steps, respectively, in 60−65% overall yields with excellent stereoselectivities. This synthesis route relies on (1) two consecutive catalytic asymmetric Cr-mediated couplings, utilizing coupling partners with unbalanced molecular size and complexity for consideration of cost-effectiveness, and (2) stereoselective reductive cyclization to form the C23−O bond. We should also note that none of the steps outlined in Schemes 3 and 5 presents any apparent problem on scaling. In our view, this synthesis offers several appealing features, including high overall yield, high stereoselectivity, operational simplicity, and overall cost-effectiveness.

2.2. Second Approach: Convergent Synthesis with Approximately Equal Size and Complexity of Coupling Partners in a ca. 1:1 Molar Ratio. In order to take advantage of the highest degree of convergency, it is ideal to find a coupling reaction that can be efficiently achieved with a 1:1 mixture of coupling partners with approximately equal molecular size and structural complexity. The case shown in Scheme 1 used coupling partners with approximately equal molecular size and structural complexity. However, to achieve this coupling with a high efficiency, an excess (1.5 equiv) of the nucleophile was required.

As previously noted, the Ni/Cr-mediated couplings involve at least four discrete steps.[3] Based on the X-ray structure for two Cr-sulfonamide complexes,[12] we speculated that a group or atom with a high Cr affinity present in the nucleophile could occupy the coordination site for the electrophile. With this speculation, we proposed a possible approach to improve the catalyst loading.[3] At the same time, we noticed that this working hypothesis might be applicable to improve the molar ratio of coupling partners.

With this background, we searched for a nucleophile with no capacity for coordination to the Cr metal center and found that the C14−C26 building block **16**, previously reported from this laboratory,[13] exhibits the ideal property for our purpose. Even with a 1:1 molar ratio of the coupling partners,[14] the catalytic asymmetric Ni/Cr-mediated coupling in the presence of the Cr catalyst derived from (*S*)-sulfonamide **A** proceeded smoothly to furnish the expected, desired product **17** in ca. 80% yield in both the E7389 and halichondrin series (Scheme 7). For preparative purposes, we routinely used a 1:1.2 molar ratio and obtained the coupling product in a better than 85% yield.

(9) For details, see the Supporting Information.

(10) As expected, a change of the C30-protecting group from PMB to $MeOCH_2CO$ allowed for the reductive cyclization and C20-deprotection in one pot in the halichondrin series as well.

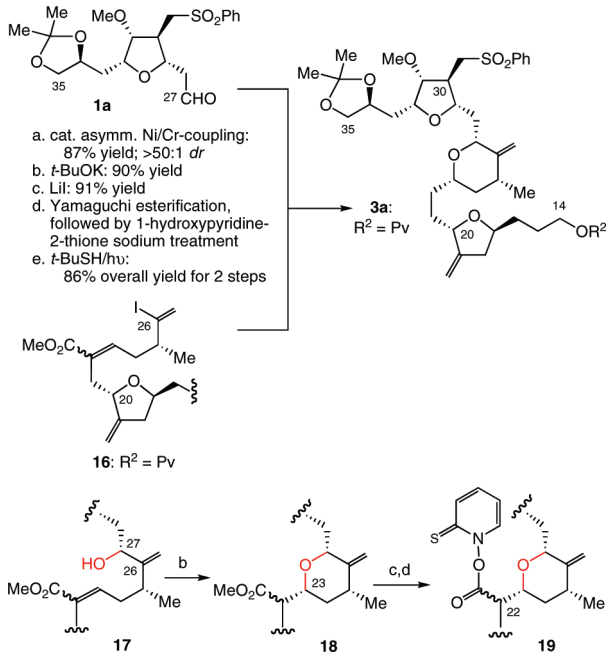
(11) The ethylene glycol ketal corresponding to **6** gave virtually the same results as summarized in Schemes 3 and 5.

(12) Wan, Z.-K.; Choi, H.-w.; Kang, F.-A.; Nakajima, K.; Demeke, D.; Kishi, Y. *Org. Lett.* **2002**, *4*, 4431.

(13) See ref 2b in the preceding paper.

(14) The following yields were obtained with varied ratios of the coupling partners: **1a**:**16** = 1:1 (85% yield), 1:1.2 (91%), 1:1.5 (90%). Similar results were observed for the coupling with the Cr catalyst derived from (*S*)-sulfonamide with R^1 = *i*-Pr, R^2 = Me, and R^3 = OMe: 1:1 (85%), 1:1.2 (90%), and 1:1.8 (>90%). However, the stereoselectivity with this catalyst was ca. 15:1.

Scheme 7. Oxy-Michael Route to E7389 C14−C35 Building Block **3a**[a]



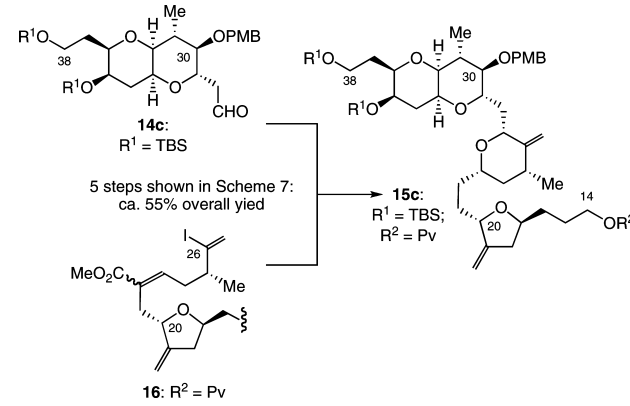
[a] Reagents and conditions: (a) Catalytic asymmetric Ni/Cr-mediated coupling in the presence of the Cr catalyst derived from (*S*)-sulfonamide **A**. (b) *t*-BuOK/CH_2Cl_2/0 °C. (c) LiI/pyridine/110 °C. (d) 2,4,6-Cl_3PhCOCl/ polymer-supported Hünig base, followed by 1-hydroxypyridine-2-thione sodium salt/C_6H_6. (e) *t*-BuSH/*hν*.

The vinyl iodide **16** used in this study was a 1.4:1 mixture of *E*- and *Z*-unsaturated esters. Interestingly, *E*- and *Z*-isomers were consumed at roughly the same rate to yield the coupling products composed of a 1.4:1 mixture of *E*- and *Z*-unsaturated esters. As might be expected, *E*- and *Z*-isomers of **16** gave products with similar stereoselectivity; for example, in the coupling with **1a**, a stereoselectivity of ca. 55:1 was observed for both *E*- and *Z*-isomers.[15]

The allylic alcohols were then subjected to the base-induced oxy-Michael reaction to furnish the cyclization products in 90% yield with excellent stereoselectivity, e.g., **17** → **18**. NMR and TLC analyses at this stage, as well as after decarboxylation, showed that the oxy-Michael reaction yielded no C23-diastereomer at detectable levels.

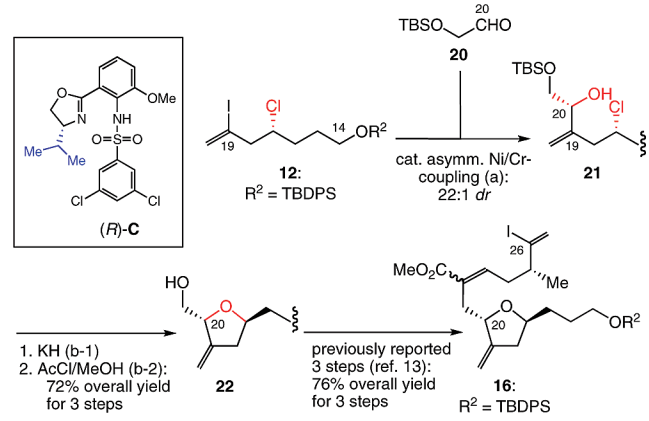
After hydrolysis of the C20 methyl ester to the corresponding carboxylic acid, the oxy-Michael product was subjected to Barton decarboxylation, e.g., **18** → **19** → **3a**;[16] this process was best achieved with use of Yamaguchi's protocol for activation of carboxylic acids[17] to furnish the E7389 C14−C35 building block in 65% overall yield from aldehyde **1a**.[18] It is worth noting that the decarboxylation should be carried out in the absence of molecular oxygen; otherwise byproduct hydroxylated at C22 was formed in up to ca. 10% yield.[19]

Scheme 8. Synthesis of Halichondrin C14−C38 Building Block **15c**[a]



[a] Reagents and conditions: (a) Catalytic asymmetric Ni/Cr-mediated coupling in the presence of the Cr catalyst derived from (*S*)-sulfonamide **A** (86% yield). (b) *t*-BuOK/CH_2Cl_2/0 °C (88% yield). (c) LiI/pyridine/110 °C (90% corrected yield). (d) 2,4,6-Cl_3PhCOCl/ polymer-supported Hünig base, followed by 1-hydroxypyridine-2-thione sodium salt/C_6H_6. (e) *t*-BuSH/*hν* (82% overall yield for two steps).

Scheme 9. Synthesis of Vinyl Iodide **16**[a]



[a] Reagents and conditions: (a) Catalytic asymmetric Ni/Cr-mediated coupling in the presence of Cr catalyst prepared from (*R*)-sulfonamide **C**. (b) 1. KH/18-crown-6/toluene/−78 °C → −20 °C; 2. AcCl/MeOH.

With the same sequence of reactions, the halichondrin C14−C38 building block **15c** was synthesized (Scheme 8). The overall yield (∼55%) in this series was slightly lower than that in the E7389 series, primarily due to a partial cleavage of the C38 silyl protecting group on the LiI-promoted transformation of the methyl ester to the carboxylic acid.

Last, we should comment on the new synthesis of **16**. Once again, we relied on the catalytic asymmetric Ni/Cr-mediated reaction to couple aldehyde **20** and vinyl iodide **12** (Scheme 9). Under the conditions discussed in the preceding paper,[1] the Cr catalyst derived from (*R*)-sulfonamide **C** smoothly effected the coupling to furnish the desired allylic alcohol **21** (*dr* = 22:1). Interestingly, for coupling of aldehyde **20** with vinyl iodide **12**, the sulfonamide **C** performed better than the sulfonamide reported in the preceding paper. The

(15) Although tedious, *E*- and *Z*-unsaturated esters **17** were chromatographically separable. Using the separated *E*- and *Z*-unsaturated esters, we confirmed the stereoselectivity for each diastereomer.

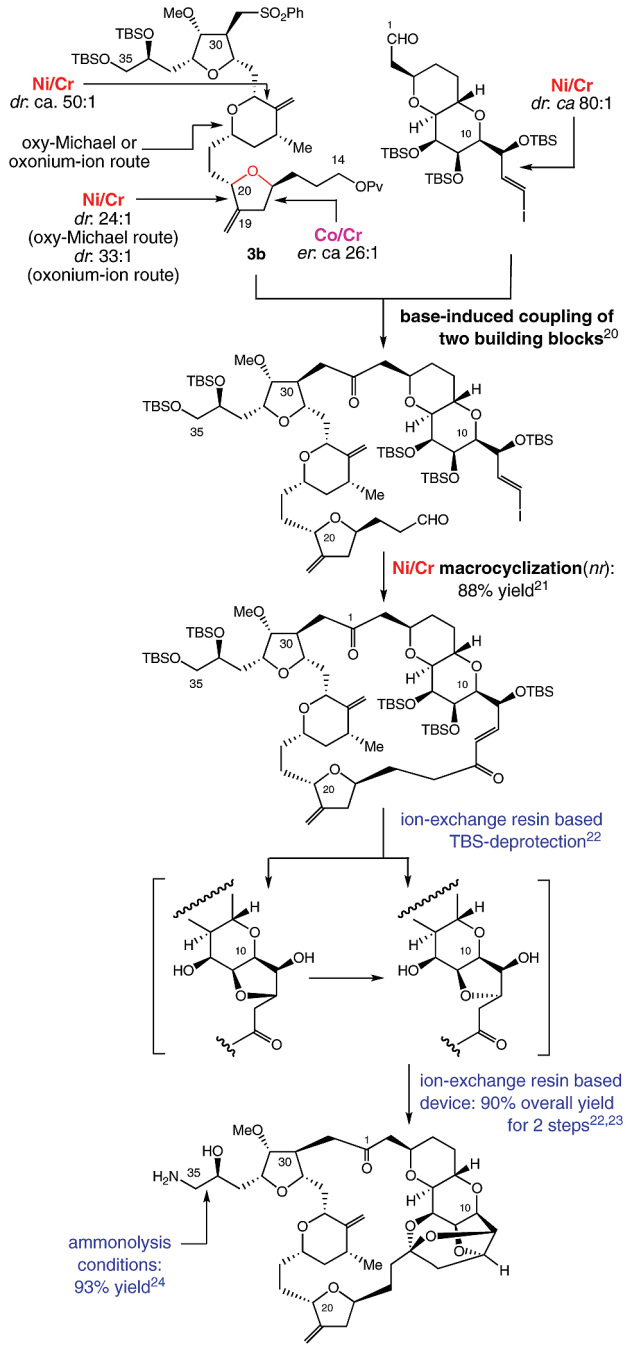
(16) (a) Barton, D. H. R.; Dowlatshahi, H. A.; Motherwell, W. B.; Villemin, D. *J. Chem. Soc., Chem. Commun.* **1980**, 732. (b) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *J. Chem. Soc., Chem. Commun.* **1983**, 939.

(17) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

(18) In the halichondrin series, the TBS group at C38 was partially deprotected on treatment with LiI/py/120 °C. Thus, the reaction was stopped at approximately 75% completion.

(19) Using the nucleophile with an α,β-unsaturated nitrile group in **16**, the synthesis paralleling the one shown in Scheme 7 was carried out to yield the oxy-Michael product in a high overall yield. However, attempted reductive decyanation and DIBAL reduction/decarbonylation did not give promising results.

Scheme 10. Summary of the Current E7389 Synthesis from This Laboratory[a]



[a] Catalytic asymmetric Ni/Cr- and Co/Cr-mediated couplings are used for bond formation at the indicated sites. After coupling of **3b** with C1−C13 building block under the Eisai protocol,[20] the macrocyclization was effected by use of the Cr catalyst prepared from 3,3′-dimethyl-2,2′-dipyridyl.[21] A convenient ion-exchange resin-based method is developed to deprotect TBS groups.[22] A device composed of two ion-exchange resin columns allows us to construct the polycyclic ring system from the deprotected enone quantitatively.[23] In addition, a new condition is developed for ammonolysis to introduce an amino group at C35.[24] Abbreviation: *nr* = not relevant.

crude product was then subjected to the base-induced cyclization, followed by acid treatment in methanol, to yield **22** in 80% overall yield from **12** as a 22:1 diastereomeric mixture at C20. The undesired C20-diastereomer was readily removed with medium-pressure column chromatography or selective hydrolysis of the corresponding acetate by Amano lipase PS-800 to afford stereochemically homogeneous **22**. Following the method previously reported,[13] **22** was then converted to **16** in a good overall yield.

3. Conclusion

In summary, Cr-mediated coupling reactions are usually achieved best with an excess of a given nucleophile, calling attention not only to the relative molecular size and structural complexity of the coupling partners but also to their molar ratio. To employ this reaction in a cost-effective manner, two different approaches have been studied. The first approach depends on two consecutive catalytic asymmetric Cr-mediated couplings with use of coupling partners purposely being of unbalanced molecular size and complexity. The second approach rests on the success in identifying the nucleophile, which allows us to achieve the coupling satisfactorily with a 1:1 ratio of the coupling partners. Both syntheses have a high overall efficiency: E7389 C14−C35 and halichondrin C14−C38 building blocks are obtained from the corresponding C27−C35 and C27−C38 aldehydes, respectively, in high overall yields with an excellent stereoselectivity. Because of operational simplicity, we feel that the synthesis outlined in Schemes 3 and 5 is well suited for cost-effective scaling. The progress reported here has had a major impact on the overall synthetic efficiency of E7389 as well as the right half of halichondrin B. Scheme 10 summarizes the current E7389 synthesis from this laboratory. With the use of additional key transformations (highlighted), the C14−C35 building block is converted into E7389.[20−24]

Acknowledgment. We are grateful to the National Institutes of Health (CA 22215) and to the Eisai Research Institute for generous financial support. D.U. gratefully acknowledges a postdoctoral fellowship from Japan Society for the Promotion of Science (JSPS).

Supporting Information Available: Experimental details, including the syntheses outlined in Schemes 2, 3, 5, 6, 7, 8, and 9, 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.

JA9058487

(20) See ref 5 in the preceding paper.
(21) Namba, K.; Kishi, Y. *J. Am. Chem. Soc.* **2005**, *127*, 15382.
(22) Kaburagi, Y.; Kishi, Y. *Org. Lett.* **2007**, *9*, 723.
(23) Namba, K.; Jun, H.-S.; Kishi, Y. *J. Am. Chem. Soc.* **2004**, *126*, 7770.
(24) Kaburagi, Y.; Kishi, Y. *Tetrahedron Lett.* **2007**, *48*, 8967.