

Asymmetric Ni(II)/Cr(II)-Mediated Coupling Reaction: Stoichiometric Process

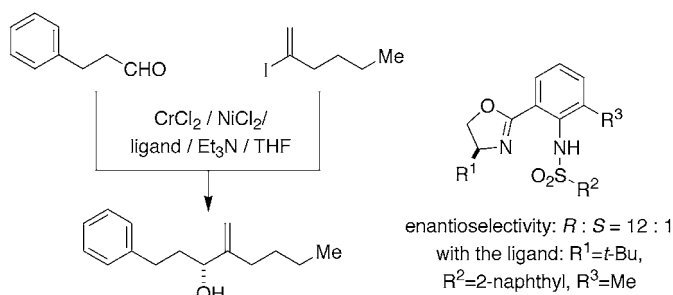
Zhao-Kui Wan, Hyeong-wook Choi, Fu-An Kang, Katsumasa Nakajima, Damtew Demeke, and Yoshito Kishi*

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

kishi@chemistry.harvard.edu

Received September 27, 2002

ABSTRACT



Via an X-ray analysis, the sulfonamide bearing *R*¹ = *i*Pr, *R*² = Me, and *R*³ = Me is shown to be a tridentate ligand to a Cr(III) salt. This class of ligands, represented by *R*¹ = *t*-Bu, *R*² = 2-naphthyl, and *R*³ = Me, is effective to achieve an asymmetric Ni/Cr-mediated coupling reaction and, with the C14-C38 segment of halichondrins, its synthetic potential has been demonstrated. A possible mechanism is suggested for the process.

As demonstrated in a number of examples, the Ni/Cr-mediated coupling reaction has shown its unique potential most when applied to a polyfunctional molecule.^{1,2} Thus, this reaction shows its uniqueness particularly at a late stage in a multiple-step synthesis where scalability and practicability are not necessarily the priority. In connection with the ongoing efforts for development of a practical synthesis of halichondrins (Figure 1) and/or halichondrin analogues,^{3–6} we are specifically interested in the overall transformation depicted in Scheme 1. Obviously, such a transformation can

be applied to a synthesis of the C17-C20 and C23-C27 ring systems present in the halichondrins. However, to use the Ni/Cr-mediated coupling reaction for practical purposes, two specific issues must be addressed. First, since this coupling reaction is typically carried out in the presence of 3~4 equiv

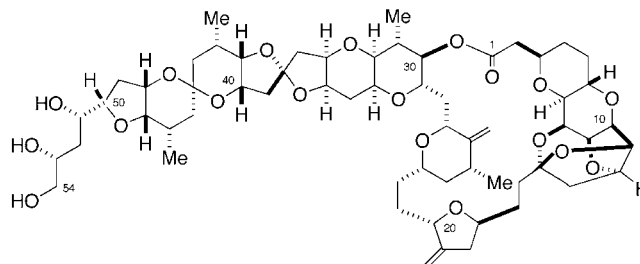


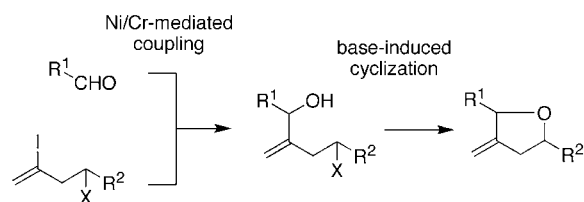
Figure 1. The structure of halichondrin B.

(1) (a) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644. (b) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048.

(2) For recent reviews on Cr-mediated reactions, see: (a) Fürstner, A. *Chem. Rev.* **1999**, *99*, 991. (b) Wessjohann, L. A.; Scheid, G. *Synthesis* **1999**, 1. (c) Saccomano, N. A. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, UK, 1991; Vol. 1, p 173.

(3) (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.

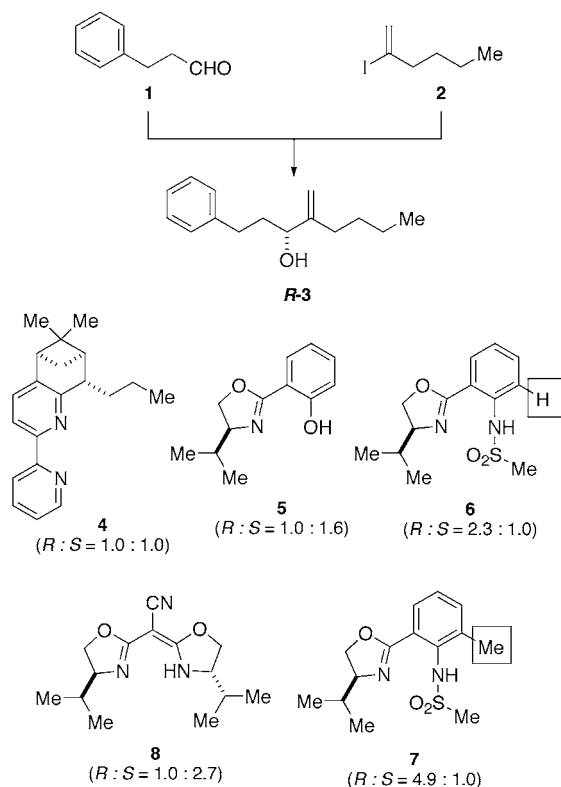
Scheme 1



of CrCl_2 , it is highly desirable to develop a method to reduce the amount of Cr salt. Second, it is also desirable to develop an asymmetric process to control the stereochemical course. This analysis immediately calls for development of a catalytic, asymmetric Ni/Cr-mediated coupling reaction.

Using dihydrocinnamaldehyde (**1**) and 2-iodo-1-hexene (**2**), we searched for a suitable chiral ligand to realize the Ni/Cr-mediated coupling in an enantioselective manner (Scheme 2). In this connection, we first quote the example

Scheme 2



previously studied in this laboratory: the C29–C30 bond of the halichondrins was asymmetrically formed in the presence of chiral dipyrindyl ligand **4**.⁷ Disappointingly, **4** was found not to give an enantiomeric excess for the current system. Among numerous chiral ligands tested, the Kibayashi ligand **5**⁸ gave a modest but definitive asymmetric induction. With consideration of the pK_a similarity between phenolic and sulfonamido groups, the Fujisawa ligand **6**⁹ was then tested, which gave a slightly improved asymmetric induction.

It was soon recognized that replacement of the *o*-hydrogen indicated in **6** with a methyl group resulted in a major impact on the asymmetric induction, cf. **7**.¹⁰

Being encouraged by this preliminary observation, we then made extensive efforts on the optimization of **7**, through which several promising ligands have emerged, including **9**–**11** (Figure 2).^{11,12}

(4) For isolation of the halichondrins from different species of sponges, see: (a) 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. 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. (b) Litaudon, M.; Hart, J. B.; Blunt, J. W.; Lake, R. J.; Munro, M. H. G. *Tetrahedron Lett.* **1994**, *35*, 9435. 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.

(5) For the synthetic work 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 and references therein.

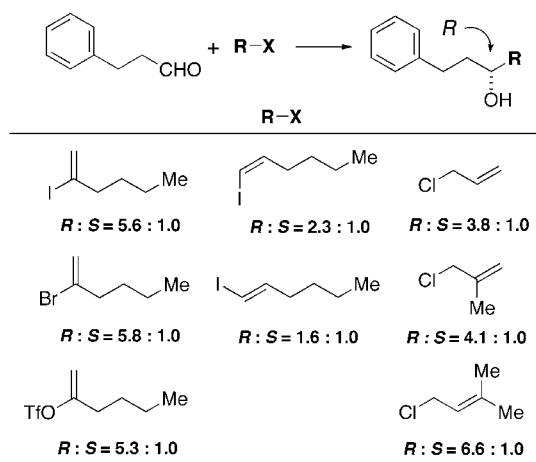
(6) For the synthetic work by Salomon, Burke, and Yonemitsu, see: (a) Kim, S.; Salomon, R. G. *Tetrahedron Lett.* **1989**, *30*, 6279. Cooper, A. J.; Pan, W.; Salomon, R. G. *Tetrahedron Lett.* **1993**, *34*, 8193 and references therein. (b) Burke, S. D.; Lee, K. C.; Santafianos, D. *Tetrahedron Lett.* **1991**, *32*, 3957. Austad, B. C.; Hart, A. C.; Burke, S. D. *Tetrahedron* **2002**, *58*, 2011 and references therein. (c) Horita, K.; Hachiya, S.; Nagasawa, M.; Hikota, M.; Yonemitsu, O. *Synlett.* **1994**, *38*. Horita, K.; Nagasawa, M.; Sakurai, Y.; Yonemitsu, O. *Chem. Pharm. Bull.* **1998**, *46*, 1199 and references therein.

(7) Chen, C.; Tagami, K.; Kishi, Y. *J. Org. Chem.* **1995**, *60*, 5386.

(8) Sugimoto, K.; Aoyagi, S.; Kibayashi, C. *J. Org. Chem.* **1997**, *62*, 2322.

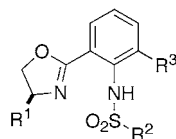
(9) Fujisawa, T.; Ichinaga, T.; Shimizu, M. *Tetrahedron Lett.* **1995**, *36*, 5031.

(10) The ligand **7** was briefly tested with other nucleophiles under the conditions of **7**/ CrCl_2 / NiCl_2 (no NiCl_2 for allyl chlorides)/ Et_3N /THF and some representative examples are listed below.¹²



(11) The sulfonamide ligands were prepared by three different routes: (a) (1) 3-methyl-2-nitrobenzoic acid/ $(\text{COCl})_2$ /DMF (cat.)/ CH_2Cl_2 , (2) L-valinol/ Et_3N / CH_2Cl_2 , (3) H_2 /Pd-on-C/MeOH, (4) MeSO_2Cl /DMAP/py/rt; (b) (1) 3-methylanthranilic acid/triphosgene/toluene-dioxane, (2) L-valinol/DMF/100 °C, (3) MeSO_2Cl /DMAP/py/rt; (c) (1) 3-methylanthranilic acid/L-valinol/EDCI/MeCN, (2) MeSO_2Cl /DMAP/py/rt. Among them, the first route was found to be the most effective and to have a good applicability for preparation of this class of sulfonamide ligands. For the experimental details, see the Supporting Information.

(12) Three conditions, (1) Et_3N /THF, (2) NaH /(Bn)(*n*-Bu) $_3\text{NCl}$ /THF, and (3) NaH /1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) or 1,1,3,3-tetramethylurea (TMU), were routinely used to screen a ligand (see the Supporting Information for the experimental details). The ratios given in Scheme 2 were obtained under condition 3, whereas the ratio given for **8** in Scheme 2 and the ratios given in Figure 2 were obtained under condition 1.



9 : R ¹ = <i>t</i> -Bu, R ² =2-naphthyl, R ³ =Me : <i>R</i> : <i>S</i> = 12 : 1.0	
10 : R ¹ = <i>i</i> -Pr, R ² =4-MeOPh, R ³ =OMe : <i>R</i> : <i>S</i> = 7.6 : 1.0	
11 : R ¹ = <i>i</i> -Pr, R ² =Me, R ³ =OMe : <i>R</i> : <i>S</i> = 6.4 : 1.0	
7 : R ¹ = <i>i</i> -Pr, R ² =Me, R ³ =Me : <i>R</i> : <i>S</i> = 5.6 : 1.0	

Figure 2.

Curiously, the major enantiomer formed in the presence of these sulfonamide ligands was found to be opposite to that formed in the presence of the phenol ligand **5** as well as the C₂-symmetric semicorrin ligand **8** (Scheme 2).^{13,14} These observations led to a speculation that the coordination mode of a sulfonamide ligand is different from that of a phenol or semicorrin ligand. A single crystal of the Cr(III)/

sulfonamide ligand complex **12** [7/Cr(III)(Cl)₂(THF)] was obtained, and its X-ray analysis ultimately demonstrated that the sulfonamide **7** is a tridentate ligand (Figure 3).¹⁵ In addition, the X-ray structure revealed several unique structural features, including the following: (1) **12** possesses an almost perfect octahedral structure, (2) the isopropyl group is *cis* to the sulfonamide chain, (3) one of the sulfonamide oxygens is located above the phenyl ring, and (4) the sulfonamide nitrogen is *trans* to one of the chlorides. Naturally, we attempted to prepare a single crystal of alkenyl-Cr(III)/sulfonamide ligand complexes but without much success. However, a single crystal of the methyl-Cr(III)/sulfonamide ligand complex **13** [7/Cr(III)(Me)(Cl)(THF)] was obtained,¹⁵ whose structure was found to be amazingly similar to that of **12** (Figure 3).¹⁶

These Cr(III)/sulfonamide ligand complexes do not necessarily correspond to the organometallic species actually involved in this chemical transformation. Nonetheless, it is tempting to use the X-ray structures to speculate about possible events (Panel A in Figure 4). At present, it is not

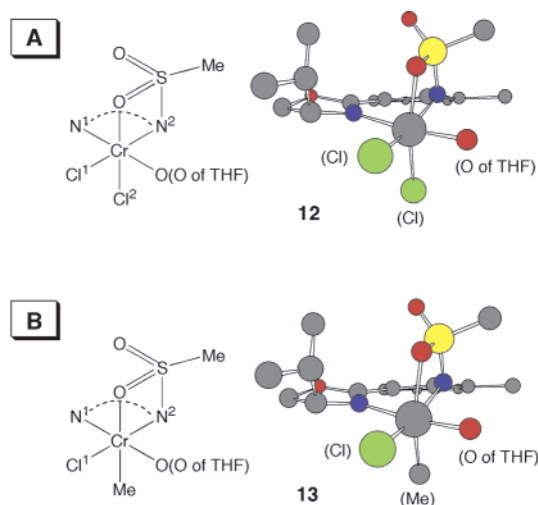


Figure 3. For clarity, only the oxygen of THF is shown. **A** represents the X-ray structure of **12**. Bond lengths: Cr–N¹ = 2.05 Å; Cr–N² = 2.03 Å; Cr–O (O of THF) = 2.04 Å; Cr–Cl¹ = 2.30 Å; Cr–O (O of sulfonamide) = 2.11 Å; Cr–Cl² = 2.27 Å. Bond angles: N¹–Cr–N² = 85.0°; N²–Cr–O (O of THF) = 88.8°; O (O of THF)–Cr–Cl¹ = 91.0°; Cl¹–Cr–N¹ = 94.5°; N¹–Cr–O (O of sulfonamide) = 89.6°; N²–Cr–O (O of sulfonamide) = 69.4°; O (O of THF)–Cr–O (O of sulfonamide) = 85.5°; Cl¹–Cr–O (O of sulfonamide) = 98.6°; N¹–Cr–Cl² = 92.0°; N²–Cr–Cl² = 94.4°; O (O of THF)–Cr–Cl² = 91.3°; Cl¹–Cr–Cl² = 97.7°. **B** represents the X-ray structure of **13**. Bond lengths: Cr–N¹ = 2.06 Å; Cr–N² = 2.05 Å; Cr–O (O of THF) = 2.06 Å; Cr–Cl¹ = 2.32 Å; Cr–O (O of sulfonamide) = 2.28 Å; Cr–Me = 2.05 Å. Bond angles: N¹–Cr–N² = 84.8°; N²–Cr–O (O of THF) = 89.3°; O (O of THF)–Cr–Cl¹ = 91.0°; Cl¹–Cr–N¹ = 94.3°; N¹–Cr–O (O of sulfonamide) = 90.3°; N¹–Cr–O (O of sulfonamide) = 66.5°; O (O of THF)–Cr–O (O of sulfonamide) = 84.6°; Cl¹–Cr–O (O of sulfonamide) = 102.7°; N¹–Cr–Me = 91.5°; N²–Cr–Me = 94.7°; O (O of THF)–Cr–Me = 91.9°; Cl¹–Cr–Me = 96.2°.

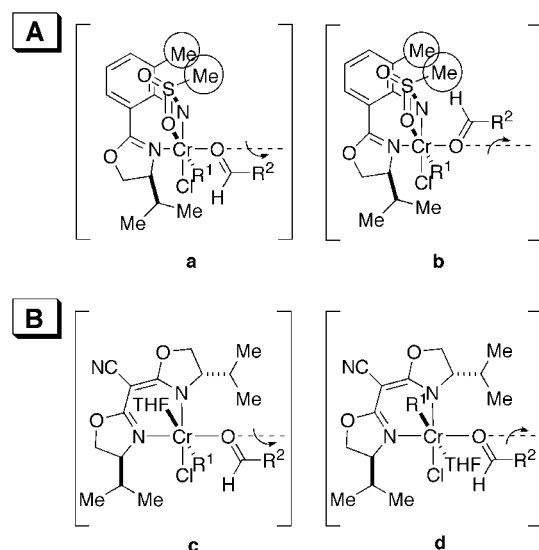


Figure 4. **A** depicts the proposed two modes of coordination of **12** with an aldehyde, whereas **B** depicts the proposed two modes of rotation of a coordinated aldehyde.

established whether the bond-forming step involves a mono- or bimetallic species. However, we assume a four-centered process involving one vinylchromium species.¹⁷ We further

(13) (a) Lowenthal, R. E.; Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1990**, *31*, 6005. (b) Corey, E. J.; Wang, Z. *Tetrahedron Lett.* **1993**, *34*, 4001.

(14) For a recent review, see: Braunstein, P.; Naud, F. *Angew. Chem., Int. Ed.* **2001**, *40*, 681.

(15) The X-ray crystals were obtained as follows: (1) 7/NaH/THF/rt/1 h, (2) CrCl₃·(THF)₃/rt/1 h (THF), (3) pentane dilution for **12** or (3) (Me)₃Al/toluene/–5 °C/1 h, rt/14 h, (4) pentane dilution for **13**. The X-ray analysis of **13** was conducted on the crystal obtained from the antipode of **7**.

(16) Methyl-Cr(III)/sulfonamide complex **13** reacted smoothly with **1** to yield the expected product with the major enantiomer corresponding to (*R*)-**3**.

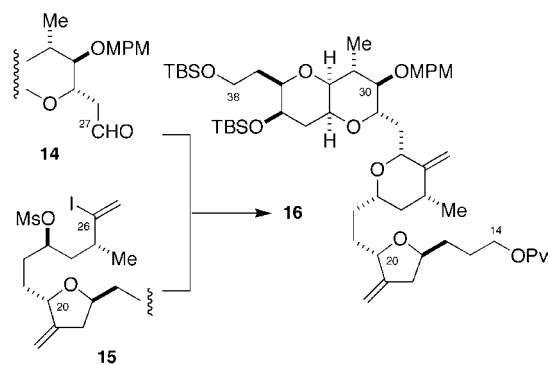
assume the following: (1) the methyl-Cr(III)/sulfonamide ligand complex **13** represents the alkenyl-Cr(III)/sulfonamide ligand complex that participates in the bond-forming process, (2) an aldehyde takes over the THF-ligation site, and (3) the aldehyde coordinates to the metal center with an *s-trans* conformation^{18–20} and, with progress of the reaction, the aldehyde rotates toward the alkenyl group, cf., an arrow. With these assumptions, only two coordination modes **a** and **b** between **1** and **12** need to be considered. Interestingly, the top-right quarter in complex **12** is sterically more congested than the bottom-right quarter, and the **1/12** complex **a**, which leads to the observed major enantiomer, is considered to be favored over the **1/12** complex **b**.

We assume that the bond-forming events in the presence of the semicorrin ligand **8** are parallel to those in the presence of the sulfonamide ligand, including the alkenyl group occupying the axial ligation site. Because of the *C*₂-symmetric nature, the alkenyl-Cr(III)-semicorrin complexes **c** and **d** are identical (Panel B in Figure 4). However, with progress of the reaction, the aldehyde needs to rotate toward the alkenyl group, resulting in desymmetrization of the two complexes; namely, this operation leads to the two transition states in which the isopropyl group in the ligand is either trans or cis to the R² group in the aldehyde moiety. For this steric reason, the latter transition state, which leads to the observed major enantiomer, is considered to be favored over the former.

The explanations given are consistent with the currently available experimental observations. However, with no direct experimental evidence, it should be considered as a working hypothesis. Nevertheless, it should serve us in designing and developing the next generation of chiral ligands for the Cr-mediated reactions.

Having had some success in the development of asymmetric Ni/Cr-mediated coupling under the stoichiometric conditions, we then used the C14–C38 segment⁵ of the right half of halichondrins as well as the C14–C35 segment of ER-086526²¹ and ER-076349²¹ for demonstration of its usefulness. The example shown in Scheme 3 is representative.²²

Scheme 3. Ni/Cr-Mediated Coupling^a



^a The Ni/Cr-mediated coupling was carried out in a glove box as follows: **7** (3 equiv) was treated with NaH (3.3 equiv) in THF at rt for 30 min. To this solution were added CrCl₂ (3 equiv) and (Bn)(*n*-Bu)₃NCl (1 equiv) and the mixture was stirred at rt for 1 h. **14** (1 equiv), **15** (2 equiv), and then NiCl₂ (1 equiv) were added, and the reaction mixture was stirred at rt for 8 h and diluted with THF (ca. 0.01 M). This mixture was cooled down to –15 °C and treated with *t*-BuOK at –15 °C. The overall stereoselectivity was ca. 20:1 in the presence of **7**, whereas ca. 3.5:1 in the absence of **7**. For the details, see the Supporting Information.

In the following paper, we report an extension of this stoichiometric process to the catalytic process.²³

Acknowledgment. We are grateful to the National Institutes of Health (CA 22215) and Eisai Research Institute for generous financial support. D.D. thanks the National Institutes of Health for a postdoctoral fellowship (1 F32 AI50373-01).

Supporting Information Available: Experimental details for Schemes 2 and 3, and for the synthesis of sulfonamide ligand **7**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL0269805

(17) A four-centered transition state involving one vinylchromium species was suggested for an intramolecular Ni(II)/Cr(II)-mediated coupling: MacMillan, D. W. C.; Overman, L. E.; Pennington, L. D. *J. Am. Chem. Soc.* **2001**, *123*, 9033. MacMillan, D. W. C.; Overman, L. E.; Pennington, L. D. *J. Am. Chem. Soc.* **1995**, *117*, 10391.

(18) For the structure of benzaldehyde/boron trifluoride adduct, see: Reetz, M. T.; Hüllmann, M.; Massa, W.; Berger, S.; Rademacher, P.; Heymanns, P. *J. Am. Chem. Soc.* **1986**, *108*, 2405.

(19) For the rotational barriers, see: LePage, T. J.; Wiberg, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 6642.

(20) For a review, see: Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **1990**, *29*, 256.

(21) (a) Towle, M. J.; Salvato, K. A.; Budrow, J.; Wels, B. F.; Kuznetsov, G.; Aalfs, K. K.; Welch, S.; Zheng, W.; Seletsky, B. M.; Palme, M. H.; Habgood, G. J.; Singer, L. A.; DiPietro, L. V.; Wang, Y.; Chen, J. J.; Quincy, D. A.; Davis, A.; Yoshimatsu, K.; Kishi, Y.; Yu, M. J.; Littlefield, B. A. *Cancer Res.* **2001**, *61*, 1013. (b) Wang, Y.; Habgood, G. J.; Christ, W. J.; Kishi, Y.; Littlefield, B. A.; Yu, M. J. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1029. (c) Littlefield, B. A.; Palme, M. H.; Seletsky, B. M.; Towle, M. J.; Yu, M. J.; Zheng, W. U.S. Patents 6214865, 6365759, and S/N 09/843,617.

(22) The C26–C27 bond formation was also demonstrated by using the C20–C26 vinyl iodide, i.e., the mesylate of the vinyl iodide **3** reported in the preceding paper: Xie, C.; Nowak, P.; Kishi, Y. *Org. Lett.* **2002**, *4*, 4427.

(23) Choi, H.; Nakajima, K.; Demeke, D.; Kang, F.-A.; Jun, H.-S.; Wan, Z.-K.; Kishi, Y. *Org. Lett.* **2002**, *4*, 4435.