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Concise and Highly Stereoselective Synthesis of the C20–C26 Building Block of Halichondrins and Eribulin

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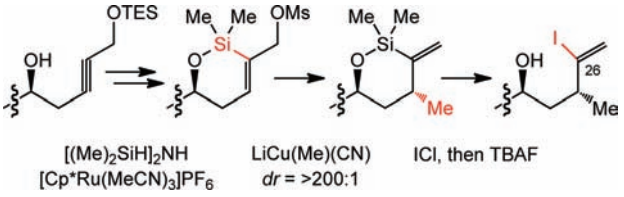
ABSTRACT



A concise, stereoselective, and scalable synthesis of the C20–C26 building block of halichondrins and Eribulin is reported. The synthesis relies on three key transformations: regiospecific Ru-catalyzed intramolecular hydrosilylation, highly stereoselective S_N2' substitution, and selective conversion of a C–Si to C–I bond. It is carried out in a 5-pot/4-workup operation without chromatographic purification, except for filtration through a silica-gel plug, to give the C20–C26 building block (*dr* > 200:1; *ee* > 99%) in ca. 60% overall yield from epoxide 1.

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.[1,2] On completion of the total synthesis of halichondrin B (Figure 1),[3,4] 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,[5] which have served as *the* foundation for the successful development of the antitumor drug Halaven (Eribulin, E7389; Figure 1).[6] This was 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 the best of our knowledge, the structural complexity of the right half of halichondrin B, or Eribulin, exceeds 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 Eribulin will play *the* key role

(1) (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.

(2) For isolation of the halichondrins from different species of sponges, see: (a) 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 and references cited therein. (b) Hickford, S. J. H.; Blunt, J. W.; Munro, M. H. G. *Bioorg. Med. Chem.* **2009**, *17*, 2199 and references cited therein.

(3) 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 and references cited therein.

(4) For synthetic work by Phillips, Salomon, Burke, and Yonemitsu, see: (a) 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. (b) Cooper, A. J.; Pan, W.; Salomon, R. G. *Tetrahedron Lett.* **1993**, *34*, 8193 and references cited therein. (c) Lambert, W. T.; Hanson, G. H.; Benayoud, F.; Burke, S. D. *J. Org. Chem.* **2005**, *70*, 9382 and references cited therein. (d) Horita, K.; Hachiya, S.; Nagasawa, M.; Hikota, M.; Yonemitsu, O. *Synlett* **1994**, 38.

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

(6) (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) 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; p 41.

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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.

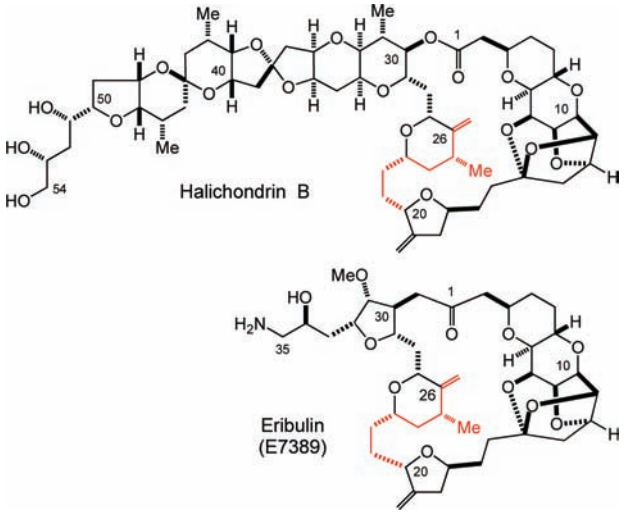
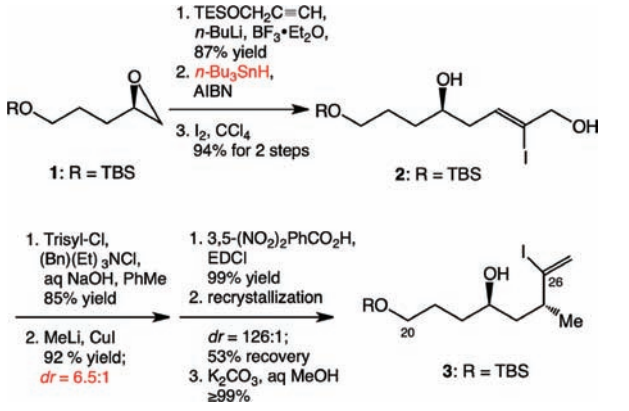


Figure 1. Structure of Halichondrin B and Eribulin (E7389), with the C20−C26 moiety highlighted in red.

With this analysis in mind, we have continued our synthetic work on the halichondrins with two major focuses: (1) design and synthesis of building blocks and (2) catalytic asymmetric Cr-mediated coupling reactions.[7,8] In this letter, we report a concise, highly stereoselective, and scalable synthesis of the C20−C26 building block.

In 2002, we reported a short synthesis of the C20−C26 building block (Scheme 1).[9] This synthesis has served us well for the ongoing work in this laboratory. Nonetheless, we wished to improve two particular steps: (1) eliminate the use of potentially toxic chemicals such as *n*-Bu_3SnH and (2) improve the stereoselectivity of the S_N2' process with lithium dimethylcuprate. With this goal in mind, we studied several synthetic routes, leading to the discovery of some interesting chemistry. However, these studies resulted in only marginal improvements in the overall efficiency of the synthesis.

Scheme 1. First Generation Synthesis of the C20−C26 Building Block



In an attempt to avoid the use of *n*-Bu_3SnH, we initially studied various hydrometalation of the acetylenic bond in the diol obtained at the first step, but without much success. One of the problems encountered was the site selectivity of hydrometalation. To overcome this difficulty, we shifted our focus to the selectively protected homopropargyl alcohol, cf., **4** in Scheme 2, with the hope that the secondary alcohol could be used as a directing group to achieve the desired regioselective hydrometalation. In particular, the recent Trost work[10] encouraged us to explore an intramolecular hydrosilylation.

With this background, we began the synthesis (Scheme 2). The method of Yamaguchi[11] was employed to couple optically active epoxide **1**, obtained by the Jacobsen kinetic resolution,[12] with triethylsilyl (TES) protected propargyl alcohol, to give homopropargyl alcohol **4** (Scheme 2). Following the Trost protocol,[10] **4** was first treated with 2.5 equiv of 1,1,3,3-tetramethyldisilazane at 50 °C (neat) and, after the removal of excess reagent under vacuum, treated with the ruthenium complex (2 mol %) in methylene chloride at rt, to give a single product. Upon brief treatment of the product with K_2CO_3 in methanol, the TES group was selectively removed to furnish cyclic vinylsilane **5** in excellent overall yield. The structure of the product was established via

(7) For syntheses of building blocks from this laboratory, see: (a) C1−C13: Duan, J. J.-W.; Kishi, Y. *Tetrahedron Lett.* **1993**, *34*, 7541. Stamos, D. P.; Kishi, Y. *Tetrahedron Lett.* **1996**, *37*, 8643. Choi, H.; Demeke, D.; Kang, F.-A.; Kishi, Y.; Nakajima, K.; Nowak, P.; Wan, Z.-K.; Xie, C. *Pure Appl. Chem.* **2003**, *75*, 1 and references cited therein. (b) C14−C19: Kurosu, M.; Lin, M.-H.; Kishi, Y. *J. Am. Chem. Soc.* **2004**, *126*, 12248. Liu, S.; Kim, J. T.; Dong, C.-G.; Kishi, Y. *Org. Lett.* **2009**, *11*, 4520 and references cited therein. (c) C20−C26: See ref 9. (d) C14−C26: see refs 3 and 7. Kim, D.-S.; Dong, C.-G.; Kim, J. T.; Guo, H.; Huang, J.; Tiseni, P. S.; Kishi, Y. *J. Am. Chem. Soc.* **2009**, *131*, 15636. 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*, 15642 and references cited therein. (e) C27−C38 building block of halichondrins: Aicher, T. D.; Buszek, K. R.; Fang, F. G.; Forsyth, C. J.; Jung, S. H.; Kishi, Y.; Scola, P. M. *Tetrahedron Lett.* **1992**, *33*, 1549. Chen, C.-L.; Namba, K.; Kishi, Y. *Org. Lett.* **2009**, *11*, 409. (f) C27−C35 building block of Eribulin: ref 8a. Yang, Y.-R.; Kim, D.-S.; Kishi, Y. *Org. Lett.* **2009**, *11*, 4516. (g) C14−C38 building block of halichondrins: refs 3, 7, and 8b,c. Stamos, D. P.; Chen, S. S.; Kishi, Y. *J. Org. Chem.* **1997**, *62*, 7552. Wan, Z.-K.; Choi, H.-w.; Kang, F.-A.; Nakajima, K.; Demeke, D.; Kishi, Y. *Org. Lett.* **2002**, *4*, 4431 and references cited therein. (h) C1−C38 of halichondrins and C1−C35 of eribulin: Namba, K.; Jun, H.-S.; Kishi, Y. *J. Am. Chem. Soc.* **2004**, *126*, 7770. Namba, K.; Kishi, Y. *J. Am. Chem. Soc.* **2005**, *127*, 15382. Kaburagi, Y.; Kishi, Y. *Org. Lett.* **2007**, *9*, 723 and references cited therein.

(8) For Cr-mediated coupling reactions from this laboratory, see: (a) Jin, H.; Uenishi, J.-I.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644. (b) 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*, 15387. (c) Liu, X.; Henderson, J. A.; Sasaki, T.; Kishi, Y *J. Am. Chem. Soc.* **2009**, *131*, 16678 and references cited therein.

(9) Xie, C.; Nowak, P.; Kishi, Y. *Org. Lett.* **2002**, *4*, 4427.

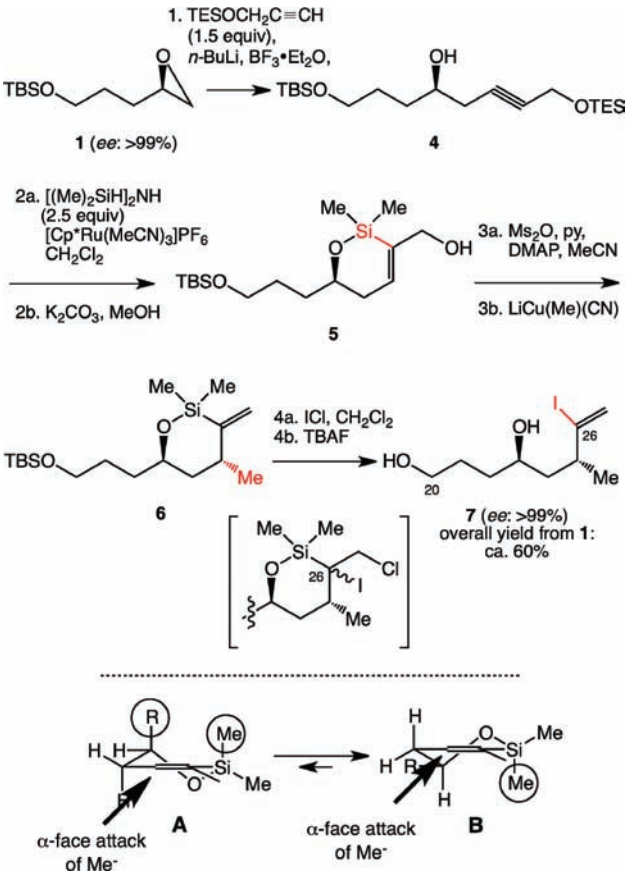
(10) (a) Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc* **2003**, *125*, 30. (b) Trost, B. M.; Ball, Z. T.; Laemmerhold, K. M. *J. Am. Chem. Soc.* **2005**, *127*, 10028.

(11) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391.

(12) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936.

spectroscopic analyses; in particular, the ^{1}H NMR established the site of the intramolecular hydrosilylation.

Scheme 2. Second Generation Synthesis of the C20−C26 Building Block



We planned to incorporate the C5 methyl group via the addition of a "Me" anion to an activated form of **5** in an S_N2' process. In practice, the primary alcohol **5** was converted to its methanesulfonate (Ms) and then treated with lithium cyano(methyl)cuprate to furnish the desired S_N2' product **6** in an excellent overall yield.[13] This transformation deserves several comments. First, ^{1}H NMR analysis of the crude product showed that there was no detectable amount of S_N2 product formed.[14] Second, the S_N2' substitution yielded one major diastereomer, along with a very minor diastereomer; the stereoselectivity estimated from ^{1}H NMR spectrum was ca. 150:1, which was later confirmed via HPLC analysis of bis-*p*-nitrobenzoate of **7** (*vide infra*). Interestingly, treatment of the corresponding *p*-toluenesulfonate (*p*Ts) with lithium cyano(methyl)cuprate gave **6** as the major product, but with a lower stereoselectivity (*dr* = ca. 80:1). Third, the methanesulfonate was stable in solution but exhibited a tendency of decomposition upon evaporation. For this reason, the reaction mixture of methanesulfonylation was used directly in the S_N2' substitution with lithium cyano(methyl)cuprate.

The stereochemistry of the major product was established via correlation of **7** with the diol derived from **3** synthesized by the previous route (*vide infra*). It is worthwhile to make a few additional comments on the S_N2' process. First, the preferential facial selectivity observed for the S_N2' substitution matches that reported for the dimethyldioxirane oxidation of a similar six-member vinylsilane by Trost.[10] Second, we would assume that the S_N2' substitution took place through a transition state resemblant to conformer **A** or **B**, but it is not immediately apparent why the α-face attack is much preferred to the *β*-face attack. This surprisingly dominant α-face attack warrants, in our view, further studies on the stereochemical course of this process.

The next stage of the synthesis was to convert the C−Si bond at C26 into a C−I bond. In the ophiobolin C synthesis,[15] we required a similar transformation, which was achieved with iodine monochloride, followed by tetra-*n*-butylammonium fluoride (TBAF) treatment. Based on this precedent, **6** was treated with iodine monochloride, to yield a ca. 4:1 diastereomeric mixture of the intermediate, cf., the partial structure shown in brackets under the arrow in Scheme 2. Upon treatment with TBAF or HF-pyridine,[16] this intermediate cleanly furnished the desired product **7** (oil). The diastereomeric ratio of **7** (> 200:1) was estimated from a HPLC analysis of its bis-*p*-nitrobenzoate, whereas the optical purity (> 99%) was from a ^{1}H NMR analysis of its bis-(*R*)- and (*S*)-Mosher esters. The structure of **7** was established via its correlation with the diol derived from **3** and, in addition, an X-ray analysis of its bis-*p*-nitrobenzoate.

For preparative purposes, the synthesis was carried out in a 5-pot/4-workup operation without chromatographic purification, except for filtration through a silica-gel plug at each step and an ion-exchange resin based workup for the TBAF step.[17] The overall yield of **7** from **1** is ca. 60%, and the purity of **7** thus obtained is pure enough for our work. If further purification is required, bis-*p*-nitrobenzoate of **7** is crystalline and suitable for recrystallization from aqueous isopropanol.

In conclusion, we have reported a concise, highly stereoselective, and scalable synthesis of the C20−C26 building block of halichondrins and Eribulin. The synthesis relies on three key transformations: regiospecific Ru-catalyzed intramolecular hydrosilylation, stereoselective S_N2' substitution, and selective conversion of a C−Si to C−I bond. The synthesis is carried out in a 5-pot/4-workup operation without chromatographic purification, except for filtration through a silica-gel plug at each

(13) For a recent review on organocopper(I) reactions, see: Yoshikai, N.; Nakamura, E. *Chem. Rev.* ASAP (DOI: 10.1021/cr200241f).

(14) With $LiCu(Me)_2$, a 2:1 mixture of the S_N2' and S_N2 product was obtained.

(15) (a) Rowley, M.; Kishi, Y. *Tetrahedron Lett.* **1988**, *29*, 4909. (b) Rowley, M.; Tsukamoto, M.; Kishi, Y. *J. Am. Chem. Soc.* **1989**, *111*, 2735.

(16) TBAF-deprotection gave a slightly higher yield than HF-deprotection.

(17) Kaburagi, Y.; Kishi, Y. *Org. Lett.* **2007**, *9*, 723.

stage, to give the C20−C26 building block (*dr*: >200:1 and *ee*: >99%) in ca. 60% overall yield from epoxide **1** (*ee*: >99%) in a 10-g scale.

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