New Synthetic Route to the C.14−C.38 Segment of Halichondrins

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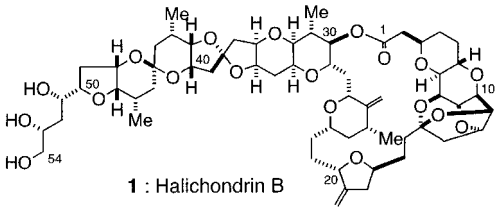
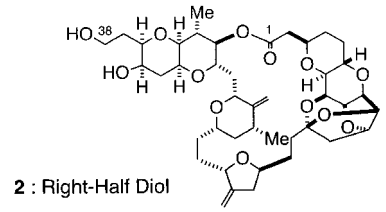
Halichondrin B (**1**), a polyether macrolide isolated from the marine sponge *Halichondria okadai* Kodata, has received much attention due to its extraordinary in vitro and in vivo antitumor activity.[1−6] Selection of halichondrin B by the National Cancer Institute for further development as an anticancer drug indicates a serious need for larger quantities of the material,[7] but the supply from the natural sources is very limited.[1−3] Related to this issue, we should note an exciting discovery that the biological activity of halichondrin B resides in the right half portion of the natural product. For example, the diol **2** not only exhibited the same activity pattern as the parent halichondrin B against over 60 cancer cell lines but also gave IC_{50} values within 1 order of the magnitude of those observed for halichondrin B itself.[8] Encouraged by this discovery, we have recently focused our synthetic efforts on the C.1−C.38 portion of halichondrin B.[5] In this paper we report the development of a new synthetic route to the C.14−C.38 segment of halichondrin B.



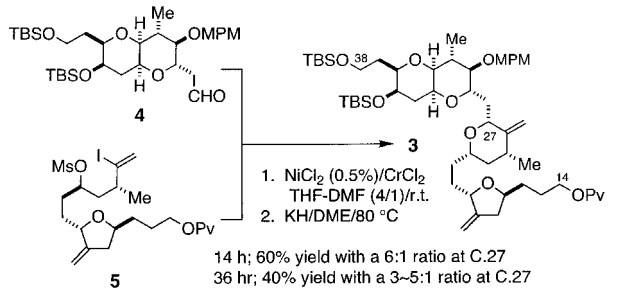
1 : Halichondrin B



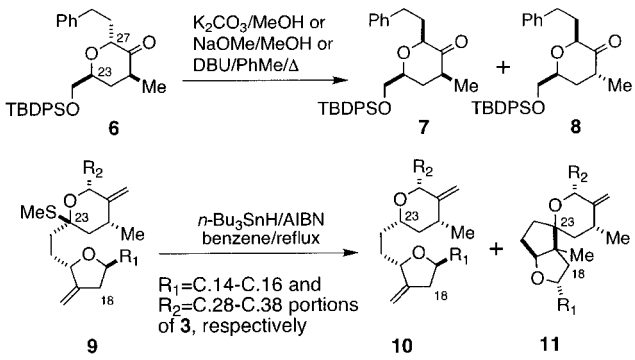
2 : Right-Half Diol

In the first total synthesis of halichondrin B, the C.14−C.38 segment **3** was synthesized via the Ni(II)/Cr(II)-mediated coupling of **4** and **5**, followed by base-induced cyclization of the resultant hydroxy mesylate (Scheme 1).[4] The ability to not only effect the desired coupling with high efficiency but also do so in the presence of sensitive functionality demonstrates the power of this coupling reaction. However, there was one difficulty

Scheme 1



Scheme 2



associated with this step; there seemed to be a narrow window of the reaction time where the yield and diastereoselectivity were satisfactory (cf. Scheme 1).[9]

The plan for a new approach to this segment was developed on the basis of two experimental observations (Scheme 2). First, the base-induced equilibration of the ketone **6** yielded a ca. 4:1 mixture of the C.25 diastereomers **7** and **8**.[5b,10] This experiment suggests that the C.23−C.27 relative stereochemistry could be controlled under equilibration conditions. Second, the reductive cleavage of the cyclic hemithioketal **9** yielded the anticipated product **10**, but it was always accompanied with a significant amount (30−50%) of the byproduct **11**.[11] This result implies that a process involving a radical intermediate would be practical only when the radical is not poised to interact with either the C.19- or C.26-exocyclic olefin. Taking these results into account, we studied a new approach to **3** as outlined in Scheme 3.

Transformation of the alcohol **12**[4] into the phosphono ester **13** was carried out in one pot in 95% yield. A modified Horner−Emmons reaction[12] of **13** with the aldehyde **14**[4] produced the C.14−C.26 fragment **15** in 80% yield as a ca. 3:2 mixture of *E*:*Z* isomers.[13]

(1) For the original isolation and structural elucidation of halichondrins, see: (a) Uemura, D.; Takahashi, K.; Yamamoto, T.; Katayama, C.; Tanaka, J.; Okumura, Y.; Hirata, Y. *J. Am. Chem. Soc.* **1985**, *107*, 4796−4798. (b) Hirata, Y.; Uemura, D. *Pure Appl. Chem.* **1986**, *58*, 701−710.

(2) For isolation of halichondrin B and homohalichondrin B from *Axinella* sponge and mechanistic studies of halichondrin cytotoxicity, 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.; Rutzler, K. C. *J. Med. Chem.* **1991**, *34*, 3339−3340. (b) Bai, R.; Paull, K. D.; Herald, C. L.; Pettit, G. R.; Malspeis, L.; Hamel, E. *J. Biol. Chem.* **1991**, *266*, 15882−15889.

(3) For isolation and structural elucidation of Isohomohalichondrin from *Lissodendoryx* sponge, see: Hart, J. B.; Blunt, J. W.; Munro, M. H. G. *J. Org. Chem.* **1996**, *61*, 2888−2890 and references therein.

(4) For the total synthesis of halichondrin B and norhalichondrin A, see: 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*, 3162−3164 and references therein.

(5) For more recent synthetic efforts on halichondrins from this laboratory, see: (a) Stamos, D. P.; Taylor, A. G.; Kishi, Y. *Tetrahedron Lett.* **1996**, *37*, 8647−8650 and references therein. (b) Stamos, D. P. Harvard Dissertation, Feb, 1997.

(6) For synthetic work from other laboratories, see: (a) Cooper, A. J.; Pan, W.; Salomon, R. G. *Tetrahedron Lett.* **1993**, *34*, 8193−8196 and references therein. (b) Burke, S. D.; Jung, K. W.; Phillips, J. R.; Perri, R. E. *Tetrahedron Lett.* **1994**, *35*, 703−706 and references therein. (c) Horita, K.; Hachiya, S.; Ogihara, K.; Yoshida, Y.; Nagasawa, M.; Yonemitsu, O. *Heterocycles* **1996**, *42*, 99−104 and references therein.

(7) Minutes, NCI Decision Network Committee, Mar 23, 1992.

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

(9) On the basis of the previous observation that the C.23 mesylate of **5** was prone to hydrolysis with retention of configuration,[4] it was suspected that this problem might relate to the slightly Lewis acidic nature of coupling conditions. However, addition of various pyridine bases[15] to the reaction did not solve this problem.

(10) For related subjects, see: Eliel, E. L. *Pure Appl. Chem.* **1971**, *27*, 509−525.

(11) Kobayashi, N.; Jung, S. H.; Kishi, Y. Unpublished results.

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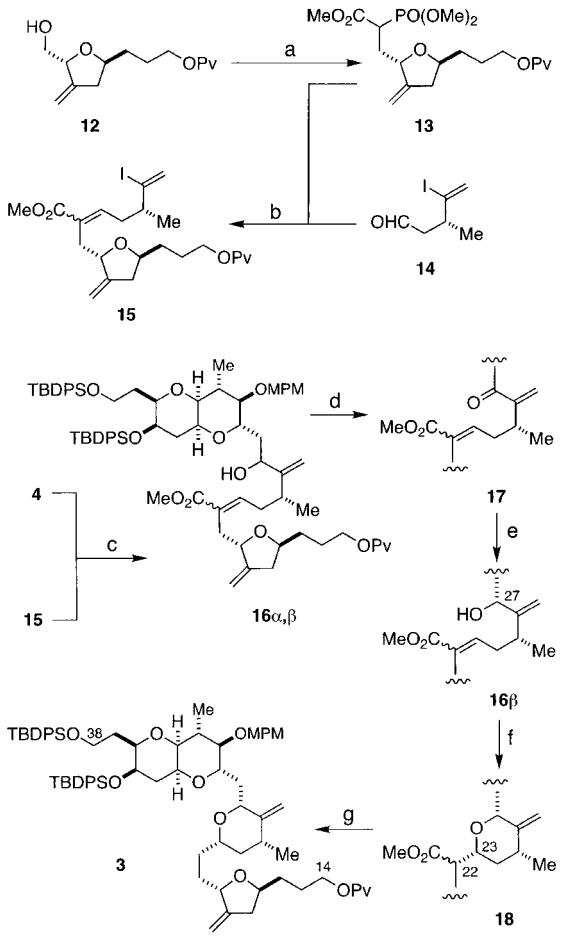
Scheme 3[a]



[a] Reagents and conditions: (a) **12**/Tf_2O/*i*-Pr_2NEt/CH_2Cl_2/−78 °C, then add $MeO_2CCH_2P(O)(OMe)_2$/*n*-BuLi/THF−HMPA (9/1)/−78 °C → rt; (b) **13**/DBU/LiCl/MeCN/rt, then add **14**/MeCN/rt; (c) **4** + **15**/$NiCl_2$ (10%)/$CrCl_2$ (90%)/THF−DMF−4-*t*-BuPy (6/3/1); (d) Dess−Martin reagent/Py/CH_2Cl_2/rt; (e) (*S*)-2-butyl-CBS-oxazaborolidine/catecholborane/PhMe/−25 °C; (f) *t*-BuOK/PhMe/0 °C; (g) (1) LiI/Py/reflux; (2) NaH/Py/$(COCl)_2$/PhH/rt, then sodium mercaptopyridine *N*-oxide/*t*-BuSH/PhH/rt.

Ni(II)/Cr(II)-mediated coupling of **15** with aldehyde **4**[4,14] yielded the desired adduct **16**β,α as a 4:1 diastereomeric mixture at C.27, but the reaction was hampered by variable reaction times and low mass recoveries. This difficulty was overcome by using: (1) 4-*tert*-butylpyridine (4-*t*-BuPy) as an additive for the coupling reaction and (2) the sodium or potassium salt of *d*,*l*-serine as a sequestering agent of chromium ion in the workup. Addition of 4-*t*-BuPy allows for homogeneous reactions, improves reproducibility, and inhibits homocoupling of vinyl iodides or triflates, whereas use of sodium or potassium serinate for the workup provides a better mass recovery.[15] Thus, the coupling of **15** with **4** produced the desired product in 85−90% yield as a 4:1 diastereomeric mixture at C.27 with excellent reproducibility. The major C.27 diastereomer **16**β was confirmed to be the desired product by chemical correlation with the previously synthesized sample.[4] It was also shown that the diastereoselectivity was not affected by the geometry of the C.22 olefinic bond but was delicately affected by the nature of the ester group.[13]

Earlier work from this laboratory demonstrated an asymmetric C−C bond formation via the Ni(II)/Cr(II)-mediated coupling in the presence of chiral dipyridine derivatives.[16] In principle, the use of a proper chiral ligand would improve the diastereoselectivity of this Ni(II)/Cr(II)-mediated coupling of **15** and **4**, but we have not found a satisfactory chiral ligand for this case. Fortunately, the 4:1 mixture could be converted into a 17:1 mixture in 85% overall yield via Dess−Martin oxidation[17] followed by Corey's oxazaborolidine-based asymmetric reduction.[18]

The key Michael reaction of **16**β smoothly proceeded to give the cyclization product **18** in 85% yield. We anticipated that the C.27 stereochemistry should dictate the C.23 stereochemistry in the desired sense (vide supra). The product was found to be a mixture of two diastereomers, but the spectroscopic data suggested that they were epimeric at C.22 but not C.23. This assignment was proven by the decarboxylation experiment.

The final step of this synthesis was a radical decarboxylation to remove the C.22 substituent. We hoped that a radical formed at C.22 would not interact with either the C.19 or C.26 exocyclic olefin. Indeed, this was realized in two steps, (1) hydrolysis of the methyl ester into the corresponding carboxylic acid under S_N2 conditions[14] and (2) decarboxylation under Barton's conditions,[19,20] to furnish the desired product **3** in 75% overall yield. The structure of **3** was established by comparison with an authentic sample[4] previously synthesized.

In conclusion, a highly stereoselective and practical synthesis of the C.14−C.38 segment of halichondrins has been developed. This route involves (1) Ni(II)/Cr(II)-mediated coupling of **15** with **4**, (2) oxazaborolidine-based asymmetric reduction of **17** to set the C.27 stereocenter, (3) oxy-Micahael cyclization of **16**β to control the C.23 stereocenter, and (4) radical decarboxylation to remove the C.22 substituent.

Acknowledgments: Financial support from the National Institutes of Health (CA-22215) and Eisai Company is gratefully acknowledged.

Supporting Information Available: Experimental details for the syntheses and spectroscopic data (13 pages).

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(13) *E*- and *Z*-unsaturated methyl esters **15** were separated by preparative thin-layer chromatography, and each isomer was separately brought up to **3** to determine the stereoselectivity of the Ni(II)/Cr(II)-mediated coupling. No difference in the diastereoselectivity was observed between the *E*- and *Z*-unsaturated methyl esters. Similarly, the Ni(II)/Cr(II)-mediated coupling of **4** with the vinyl iodides corresponding to **15** but with different ester groups was tested. The observed ratio of the desired and undesired diastereomers at C.27 was >8:1 for the *trans*-9-hydroxy-10-(1-phenylthio)-9,10-dihydrophenanthrene ester, 6:1 for the trityl ester, and 5:1 for the dibenzosuberyl ester.

(14) For this synthesis, the C.35 and C.38 alcohols were protected as TBDPS ethers to prevent any complication at the step of LiI-induced methyl ester hydrolysis. Comparison of the products in this work with the authentic samples in the previous work[4,5] was carried out by converting the TBDPS groups into the corresponding TBS groups.

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(20) Decarboxylation using a *trans*-9-hydroxy-10-(1-phenylthio)-9,10-dihydrophenanthrene auxilliary[21] was also effective.[5b] With this auxilliary, the diastereoselectivity of the Ni(II)/Cr(II)-mediated coupling was >8:1, but its overall yield from **12** to **3** was lower than the methyl ester series.

(21) Barton, D. H. R.; Dowlatshahi, H. A.; Motherwell, W. B.; Villemin, D. *J. Chem. Soc., Chem. Commun.* **1980**, 732−733.