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Synthetic Studies on Halichondrins: A Practical Synthesis of the C.1-C.13 Segment

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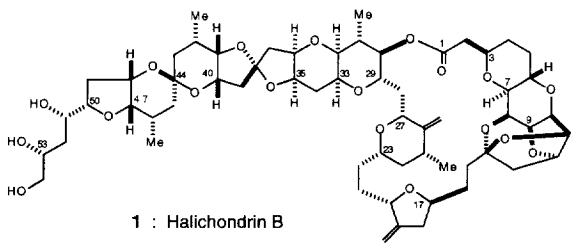
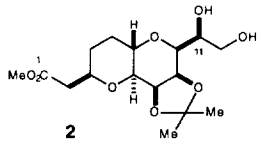
***Abstract**: A practical, scalable synthesis of the C.1-C.13 segment of halichondrin B has been developed starting from L-mannonic-γ-lactone, using C-allylation/oxy-Michael cyclization and Ni(II)/Cr(II)-mediated vinyltrimethylsilane addition to set the C.6/C.3 and C.11 stereocenters, respectively.*

The halichondrin class of polyether macrolides has received much attention due to its extraordinary *in vitro* and *in vivo* antitumor activity.[1] These natural products were originally isolated from the marine sponge *Halichondria okadai* in minute quantities. Due to the scarce availability and intriguing structures of these compounds, a number of synthetic efforts have been aimed towards this family of natural products, culminating in the first total synthesis of halichondrin B and homohalichondrin B.[2,3]



1 : Halichondrin B



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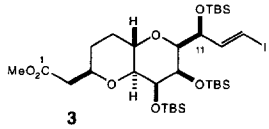


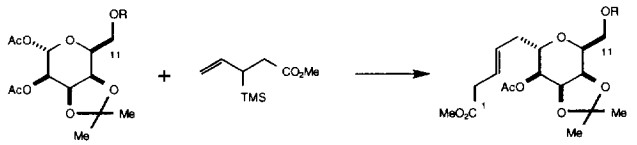
3

In a previous communication from this laboratory, it was demonstrated that the diol **2** could be synthesized in nine steps from L-mannonic-γ-lactone, providing the C.1-C.12 carbon framework with all of the necessary stereocenters.[2] We then envisioned that the requisite vinyliodide **3**, a key intermediate in our synthesis,[2] could be obtained from **2**. In this communication, we report our further efforts towards this goal which ultimately led to a twelve step synthesis of **3** from L-mannonic-γ-lactone.

Since **2** already contains the desired stereocenter at C.11, we first focused on a possible way to achieve an overall transformation of $^{12}CH_2OH \rightarrow {}^{12}CH{=}CHI$ (*trans*) without disturbing this chiral center. Indeed, we reported a six step sequence transforming **2** into **3** which included conversion of the C.12 aldehyde to the vinyliodide using $CrCl_2/CHI_3$.[2,4] However, we met with a great deal of difficulty to perform this reaction in an acceptable efficiency on large scale, which prompted us to examine alternative approaches to solve the problem. Unfortunately, due to complications with C.11 epimerization and protecting group migration,[5] we could not identify an efficient and scalable method to achieve this goal.

In light of all these unsuccessful attempts to preserve the C.11 stereocenter, coupled with the fact that the Ni(II)/Cr(II)-mediated reaction on the C.11 aldehyde gives excellent selectivity,[2] we examined the *C*-allylation of **4**[6] with **5** ($BF_3{\cdot}Et_2O$/MeCN/0 °C). Unlike the previous cases where only the desired diastereomer was obtained using allyltrimethylsilane, **4** gave a 2.5~5:1 ratio of *C*-allylated products, the ratio being inversely proportional to scale (Scheme 1). The difference in stereoselectivity between this system and the previous may be explained by considering stereoelectronic/steric effects.[7] Along this line of analysis, sterically demanding protecting groups including 1-adamantoyl, TBDPS and 9-anthracenylmethyl were tested to improve the stereoselectivity but met with limited success.

Scheme 1



4 **5** **6**

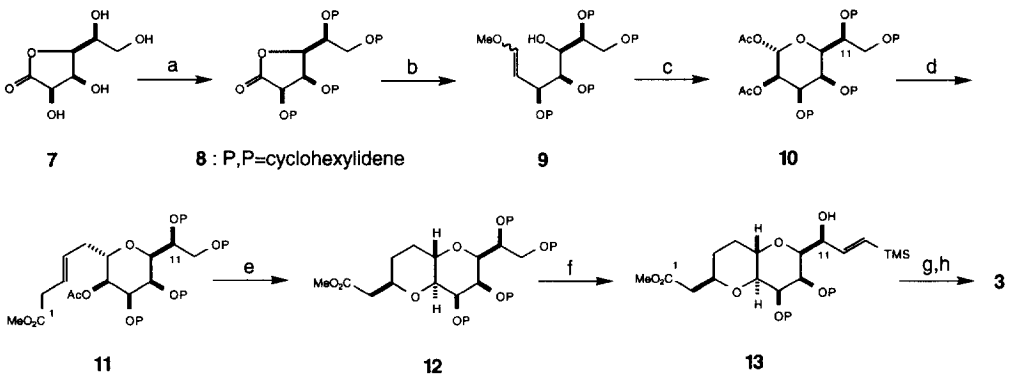
On the basis of these observations, an optimum route was envisioned starting with L-mannonic-γ-lactone (**7**) (Scheme 2). The first three steps follow from earlier work[2] except that cyclohexylidene ketals were used in place of acetonides since the major side product of *C*-allylation was due to participation of the acetonide group in the *C*-allylation.

The conversion of **9** to **10** posed the first scaling problem. Stoichiometric osmylation previously gave the desired diol (75%) with better than 16:1 selectivity on small scale. As stoichiometric osmylation was not practical on large scale, catalytic osmylation was studied; it gave the diols in high yields but with significantly lowered selectivities (1.5~2.0:1), yet the major product was the one predicted according to the empirical rule[8]. To overcome this difficulty, an approach of using double stereodifferentiation[9] was applied; the best results were obtained using dihydroquinidine-4-chlorobenzoate (DHQD) as a chiral ligand under slow addition conditions as described by Sharpless, giving a 4~5:1 ratio at C.7.[10]

Conversion of **10** to **12** was then easily accomplished in two steps using the functionalized allylic silane **5**[11]. This two step sequence represents a major improvement in material throughput. As expected,[7] the *C*-allylation took place to yield exclusively the desired product, which existed as a ca. 1:1 mixture of two chair conformers (^{1}H NMR spectroscopic analysis). Upon treatment with Triton-B(OMe), the adduct **11** underwent a series of transformations, including hydrolysis of the acetate, double-bond isomerization into the conjugated position, oxy-Michael cyclization with trapping of one ring conformer, and equilibration of the C.7 diastereomers exclusively into the desired product.[12] Using the pure diacetate **10**, the overall yield for this transformation was better than 65%. Interestingly, the epimeric diactetate of **10** did not react with **5** under the *C*-allylation conditions. Thus, it was more practical to carry out the transformation of **9** into **12** without isolation of intermediates.

With **12** in hand, the vinyliodide **3** was readily obtained. Selective hydrolysis of the exocyclic cyclohexylidene ketal, oxidative cleavage to generate the C.11 aldehyde, then Ni(II)/Cr(II)-mediated coupling

using *trans*-ICH=CHTMS[13] gave **13** in good overall yield with better than 15:1 selectivity at C.11. It is interesting to note that the workup of the Ni(II)/Cr(II)-reaction significantly affects the yield. Using aqueous NH_4Cl gives ca. 45% isolated yield of **13** from the C.11 aldehyde. However, using a more potent metal sequestering agent such as aqueous ethylenediamine, then conc. HCl gave **13** in 75% yield. Finally, the vinyliodide **3** was obtained by protecting group exchange to the tris-TBS protected vinylsilane, followed by iododesilylation using *N*-iodosuccinimide (NIS)[14] in acetonitrile/ monochloroacetonitrile.



Scheme 2. Reagents and conditions: (a) cyclohexanone/cat. H_2SO_4/toluene (65%). (b) 1. DIBAL/ CH_2Cl_2/ -78 °C. 2. *t*-BuOK/$MeOCH_2PPh_3Cl$/THF/reflux (91% over 2 steps). (c) 1. OsO_4/aq. NMMO/DHQD/acetone/ -5 °C (slow addition). 2. Ac_2O/pyridine/DMAP (90% over 2 steps). (d) **5**/BF_3·Et_2O/MeCN/0 °C→20 °C (65%, single isomer). (e) Triton-B(OMe)/THF/MeOAc/ 0 °C→r.t. (87%, single isomer). (f) 1. HOAc/H_2O/80 °C (80-85%). 2. $NaIO_4$/THF/pH 7 buffer. 3. *trans*-ICH=CHTMS 2.5% $NiCl_2$/$CrCl_2$/DMSO (75% over 2 steps, >15:1 selectivity). (g) i. HOAc/H_2O/TFA/85 °C. ii. TBSOTf/2,6-lutidine/CH_2Cl_2/0 °C→r.t. (73%, one pot sequence). (h) NIS/MeCN/$ClCH_2CN$ (9/1, v/v)/r.t. (80%).

In conclusion, a practical, scalable synthesis of the C.1-C.13 vinyliodide **3**, a key intermediate for our synthesis of halichondrin B, has been achieved in 12 steps starting from L-mannonic-γ-lactone (**8**) in 11% overall yield. This twelve step sequence has been carried out starting with 100 grams of L-mannonic-γ-lactone providing 48 grams of **3** in one batch.

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

References and Notes:

1. (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. (c) Bai, R.; Paull, K. D.; Herald, C. L.; Pettit, G. R.; Malspeis, L.;Hamel, E. *J. Biol. Chem.* **1991**, *266*, 15882-15889. (d) Halichondrin B and homohalichondrin B were also isolated from Acinella sponge: 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. Isohomohalichondrin has been isolated from Lissodendoryx sponge: see Hart, J. B.; Blunt, J. W.; Munro, H. G. *J. Org. Chem.*, **1996**, *61*, 2888-2890 and references cited therein.

2. For synthetic work from this laboratory, see: Duan, J. J.-W.; Kishi, Y. *Tetrahedron Lett.* **1993**, *34*, 7541-7544 and references cited therein. For the stereoselectivity of the Ni(II)/Cr(II)-mediated coupling, see footnote 10 of this reference.

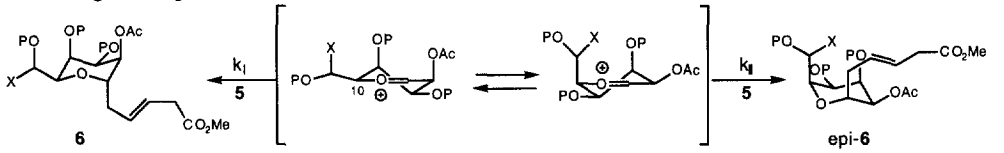
3. For synthetic work from other labs, see: (a) Cooper, A. J.; Pan, A.; Salomon, R. G. *Tetrahedron Lett.* **1993**, *34*, 8193-8196 and references cited therein. (b) Burke, S. D.; Jung, K. W.; Phillips, J. R.; Perri, R. E. *Tetrahedron Lett.* **1994**, *35*, 703-706 and references cited therein. (c) Horita, K.; Sakurai, Y.; Nagasawa, M.; Maeno, K.; Hachiya, S.; Yonemitsu, O. *Synlett* **1994**, 46-48 and references cited therein.

4. Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.*, **1986**, *108*, 7408-7410.

5. Three different approaches were tested. First, **2** was converted to the C.12 aldehyde with a C.11 TBS ether and then subjected to diazomethyldimethylphosphonate (DAMP) homoligation (Triton-B(OMe)/THF/-78→0 °C), leading to the diazoaldol adduct with the TBS group migrated from C.11 to C.12. The homoligation could be driven to completion by using TBAF either in a separate step or in the same pot. But, the overall yield (30~80% with the yield being inversely proportional to scale) was not satisfactory. Second, **2** was converted to the C.12 phenylthio ether with a C.11 THP ether and subjected to Pummerer rearrangement (1. MCPBA/-78 °C. 2. Ac_2O/NaOAc/ 140 °C. 3. aq. $NaHCO_3$/MeOH; 50~65% overall yield), to furnish the required aldehyde but contaminated with the C.11 stereoisomer (~3.5:1 mixture). Third, an attempt of preserving the C.11 stereocenter and generating the enone from the C.12 aldehyde was studied; **2** was first converted into the C.8, 9, 11-tris-TBS aldehyde and then subjected to stabilized ylide coupling ($(Ph)_3PCHCOMe$/PhMe/reflux; 60% yield). However, this reaction was not only very slow, but proceeded with epimerization of the C.3 stereocenter (2.5:1 mixture).

6. The diacetate acetonide **4** with R=benzyl, adamantoyl, TBDPS, and 9-anthracenylmethyl was prepared from D-ribono-γ-lactone in good overall yields. The details of this synthesis will be given elsewhere; Dean P. Stamos, Harvard Dissertation, 1996.

7. The addition of **5** to an oxonium ion generated from **4** is expected to take place in a trans diaxial mode due to a stereoelectronic effect. Between the two possible axial additions, k_I is expected to be greater than k_{II}. The degree of stereoselectivity depends on the degree of the steric interaction between the C.10 substitutent and the incoming nucleophile; see Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976-4978.



8. Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3943-3946.

9. For an excellent review on double stereodifferentiation, see Masamune, S; Choy, W.; Peterson, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Eng.*, **1985**, *24*, 1-76.

10. Lohray, B. B.; Kalantar, T. H.; Kim, B. M.; Park, C. Y.; Shibata, T.; Wai, J. S. M.; Sharpless, K. B. *Tetrahedron Lett.* **1989**, *30*, 2041-2044. For a review on catalytic asymmetric dihydroxylation, see Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.*, **1994**, *94*, 2483-2547.

11. **7** was prepared by orthoester Claisen rearrangement of (E)-3-trimethylsilyl-2-propene-1-ol with $MeC(OMe)_3$ (4 eq.) and $EtCO_2H$ (cat.), in refluxing toluene with removal of the liberated methanol in 90% yield on 55 gram scale (b.p. 47-50 °C, 0.1 mmHg). Similarly, the C.2 methylated allylic silane corresponding to **7** may be prepared using $EtC(OMe)_3$ with equal efficiency (b.p. 51-53 °C , 0.1 mmHg).

12. Earlier work in this group (see reference 2) indicated that the initial oxy-Michael adduct was a 1:1 mixture at C.3. This ratio could be easily raised to 1:0 favoring the desired product upon extended treatment with TRITON-B(OMe).

13. *trans*-ICH=CHTMS was prepared by iodination of *trans*-1-trimethylsilyl-2-tri-*n*-butylstannylethene with I_2 in CH_2Cl_2 in 90% yield (b.p. 90-92 °C, 30 mmHg). For the preparation of the above vinylstannane, see: Colvin, E. W. *Silicon Reagents in Organic Synthesis*, **1988**, p 10, Academic Press.

14. Stamos, D. P.; Taylor, A. G.; Kishi, Y. the accompanying letter.

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