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Synthetic Studies on Halichondrins: A New Practical Synthesis of the C.1-C.12 Segment

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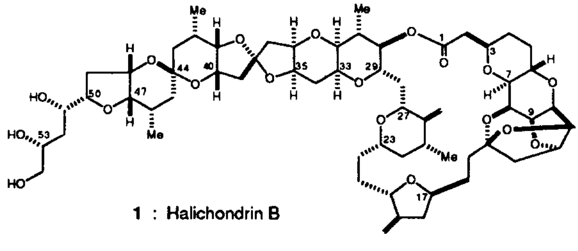
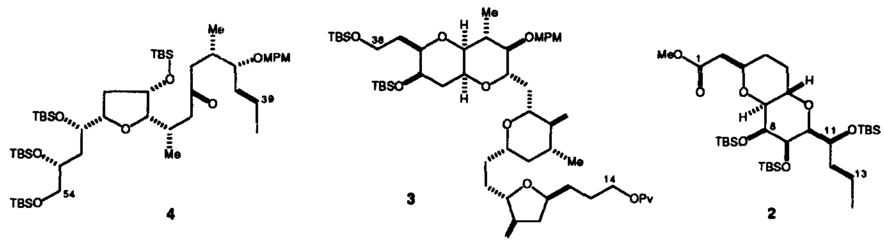
Abstract: *A new practical synthesis of the C.1-C.12 halichondrin segment was achieved from L-mannonic γ-lactone (5), using osmylation, C-allylation and Michael reaction as key steps.*

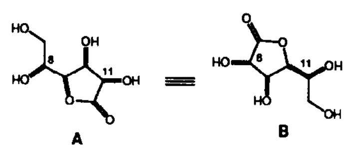
Halichondrins are a class of polyether macrolides isolated originally from the marine sponge *Halichondria okadai* Kadota.[1,2] Halichondrins, especially halichondrin B and homohalichondrin B, exhibit extraordinary *in vitro* and *in vivo* antitumor activity. However, the limited supply of halichondrins from natural sources has prevented further evaluation of their clinical applications thus far. Coupled with this fact, their intriguing and challenging structural features encouraged our synthetic efforts towards this class of natural products, which resulted in the first total synthesis of halichondrin B (1) and norhalichondrin B.[3,4] The *in vitro* and *in vivo* experiments using the synthetic halichondrins have confirmed their outstanding biological activity.[5] Consequently, we began to address the question of how to improve the overall efficiency of our original synthesis of halichondrin B, which utilized the three major building blocks **2-4**. We consider that the couplings of these building blocks to obtain halichondrin B are efficient in terms of the number of synthetic steps and overall yield. However, improvements on the synthesis of the building blocks, in particular **2** and **3**, would secure a greater supply of material for further clinical evaluations. In this communication, we would like to report a practical synthesis of the C.1-C.12 halichondrin segment **13**.



1 : Halichondrin B

The overall yield for the original 30-step synthesis of **2** from D-glucose diacetonide was approximately 4%.[3] This synthesis was scalable, and the efficiency of each step was satisfactory. However, we were interested in reducing the number of synthetic steps, and noticed that inexpensive L-mannonic γ-lactone (**5**) to be an appealing starting material for this purpose. Interestingly, there are two possibilities to match all the four stereocenters of **5** with the C.8-C.11 stereocenters in halichondrin B, cf. **A** and **B**. In this communication, we disclose our results on the synthetic route belonging to the **B**-type structural matching.

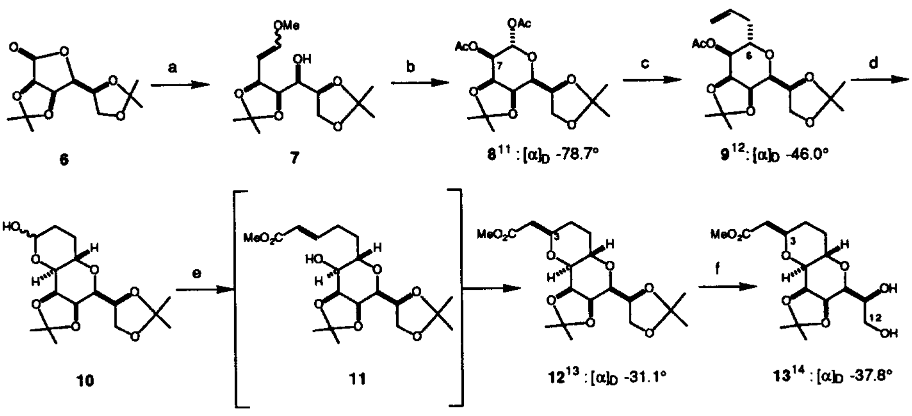




5 : L-mannonic γ-lactone

Scheme 1 summarizes the new synthetic route to **13**. It is worthwhile to comment on the steps incorporating the C.3, C.6 and C.7 stereocenters. First, on the basis of our empirical rule,[6] we predicted that osmylation of **7**[7] should yield the desired stereoisomer at the C.7 position; the stereoselectivity observed for this case was approximately 16:1 favoring the desired diastereomer under the conditions specified. Second, based on our palytoxin work,[8] we anticipated that *C*-allylation such as **8**→**9** should preferentially yield the axial product, and indeed observed the exclusive formation of diastereomer **9**. Third, our previous work in halichondrin area[3] suggested that Michael cyclization of **11** under thermodynamically controlled conditions should stereoselectively yield the product with the desired C.3 stereocenter. In the present case, the initially formed 1:1 mixture of **12** and its C.3 epimer was completely (^{1}H NMR) equilibrated to **12** upon treatment with Triton B(OMe) for 7 hours at room temperature. It is noteworthy that transformation of **10** to **12** was carried out in one pot. The C.3, C.6 and C.7 stereochemistry of **12** was unambiguously established by correlation with one of the synthetic intermediates used in the previous synthesis.[9]

Finally, one of the two acetonide groups in **12** could selectively be hydrolyzed to furnish the C.1-C.12 segment **13**. This product offers a variety of options to functionalize the C.12 position, to intercept the original C.1-C.13 building block **2**,[10] and to explore new synthetic routes to the C.1-C.38 segment. In conclusion, this 9-step synthesis of **13** from **6** is readily scalable in an overall yield of approximately 25% (not optimized).



Scheme 1.

Reagents and conditions: (a) 1. DIBAL/PhMe/-78 °C. 2. *t*-BuOK/$MeOCH_2PPh_3Cl$/THF/reflux.[15] (b) 1. OsO_4/(*i*-$PrNHCH_2)_2$/CH_2Cl_2/-78 °C. 2. Ac_2O/DMAP/Py (58% yield for 4 steps). (c) CH_2=$CHCH_2TMS$/TMSOTf/CH_3CN/-10 °C (62% yield). (d) 1. Catecholborane/$RhCl(PPh_3)_3$/THF (96% yield).[16] 2. PCC/alumina/CH_2Cl_2 (75% yield).[17] (e) Ph_3P=$CHCO_2Me$/PhH/reflux, followed by Triton B(OMe)/RT (99% yield). (f) *p*-TsOH/MeOH (98% yield).

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References and Footnotes

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9. Diol **13** was converted to its tetra-TBS ether in 2 steps, 1. *p*-TsOH/MeOH and 2. TBSOTf/2,6-lutidine/CH_2Cl_2, which was compared with the sample derived from **2** in 2 steps, 1. O_3/MeOH/ -78 °C, followed by Me_2S then $NaBH_4$ work-up and 2. TBSOTf/2,6-lutidine/CH_2Cl_2.

10. For example, **13** has been converted to **2** in 6 steps: 1. $NaIO_4$/pH 7 buffer/THF, 2. *trans-n*-BuCH=CHI/1.1% $NiCl_2$-$CrCl_2$/DMSO, 3. $FeCl_3$/SiO_2/CH_3CN, 4. TBSOTf/2,6-lutidine/CH_2Cl_2, 5. O_3/MeOH/CH_2Cl_2 and 6. CHI_3/$CrCl_2$/THF.

11. ^{1}H NMR ($CDCl_3$) of **8**: δ 1.35 (3H, s), 1.36 (3H, s), 1.42 (3H, s), 1.52 (3H, s), 2.08 (3H, s), 2.15 (3H, s), 3.59 (1H, dd, J = 1.4, 8.2 Hz), 3.87 (1H, dd, J = 3.6, 9.0 Hz), 4.05 (1H, dd, J = 6.2, 8.9 Hz), 4.22-4.26 (1H, m), 4.50 (1H, dd, J = 1.6, 7.9 Hz), 4.65 (1H, dd, J = 2.6, 7.8 Hz), 5.10 (1H, dd, J = 2.6, 7.0 Hz), 6.14 (1H, d, J = 7.0 Hz).

12. ^{1}H NMR ($CDCl_3$) of **9**: δ 1.35 (3H, s), 1.37 (3H, s), 1.41 (3H, s), 1.53 (3H, s), 2.14 (3H, s), 2.26-2.29 (2H, m), 3.41 (1H, dd, J = 1.6, 8.2 Hz), 3.98 (1H, dd, J = 4.0, 8.8 Hz), 4.05 (1H, dd, J = 6.2, 8.8 Hz), 4.07-4.12 (1H, m), 4.17-4.20 (1H, m), 4.46 (1H, dd, J = 1.6, 8.1 Hz), 4.62 (1H, dd, J = 2.6, 8.1 Hz), 4.96 (1H, dd, J = 2.6, 9.8 Hz), 5.08-5.12 (2H, m), 5.78-5.87 (1H, m).

13. ^{1}H NMR ($CDCl_3$) of **12**: δ 1.34 (3H, s), 1.38 (3H, s), 1.40 (3H, s), 1.42-1.46 (1H, m), 1.50-1.59 (1H, m), 1.54 (3H, s), 1.74-1.79 (1H, m), 2.02-2.06 (1H, m), 2.42 (1H, dd, J = 6.0, 16.2 Hz), 2.71 (1H, dd, J = 7.0, 16.2 Hz), 3.49-3.53 (2H, m), 3.67 (3H, s), 3.81-3.86 (2H, m), 4.00 (1H, dd, J = 4.3, 8.8 Hz), 4.05 (1H, dd, J = 6.1, 8.8 Hz), 4.16-4.19 (1H, m), 4.50-4.56 (2H, m).

14. ^{1}H NMR ($CDCl_3$) of **13**: δ 1.37 (3H, s), 1.40-1.46 (1H, m), 1.55 (3H, s), 1.51-1.59 (1H, m), 1.75-1.79 (1H, m), 2.04-2.09 (1H, m), 2.18 (1H, br s), 2.42 (1H, dd, J = 6.0, 16.2 Hz), 2.65 (1H, br s), 2.71 (1H, dd, J = 7.0, 16.2 Hz), 3.51 (1H, dd, J = 2.8, 10.2 Hz), 3.67 (3H, s), 3.68-3.74 (2H, m), 3.79-3.88 (4H, m), 4.55 (1H, dd, J = 2.8, 8.5 Hz), 4.59 (1H, dd, J = 1.6, 8.5 Hz).

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