Tetrahedron Letters, Vol. 33, No. 12, pp. 1553-1556, 1992
Printed in Great Britain

0040-4039/92 $3.00 + .00
Pergamon Press Ltd

Synthetic Studies Towards Halichondrins: Synthesis of the Left Half of Halichondrins

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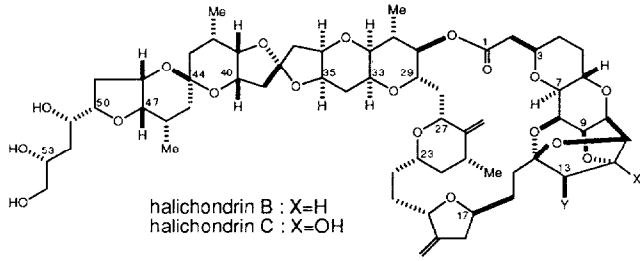
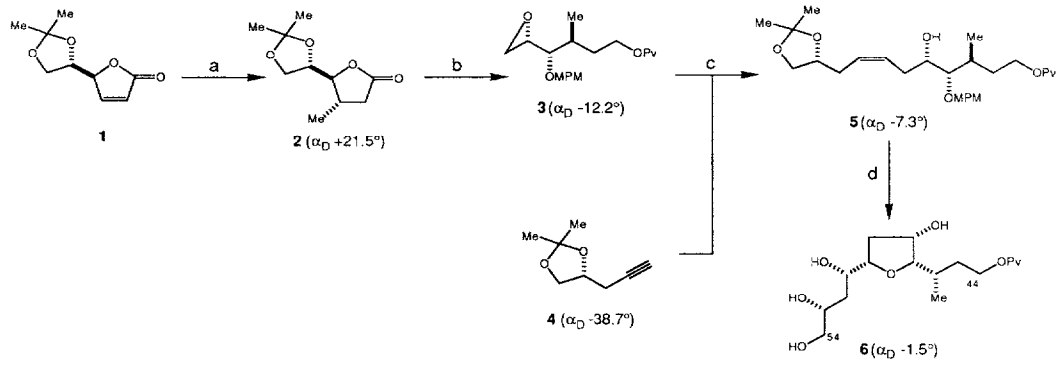
Abstract: *An efficient synthesis of the left half of halichondrins B and C is reported.*

Marine natural products halichondrins B and C share a common structure on the left side.[1] In this letter, we report an efficient synthesis of the left half of these halichondrins.

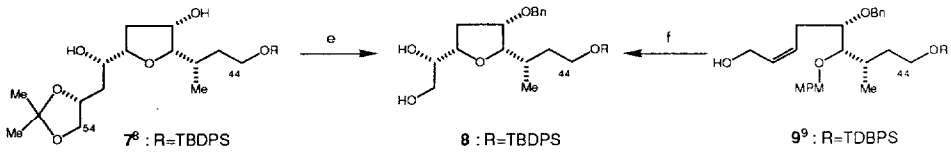


Scheme 1 outlines the synthesis of the C.44-C.54 segment of halichondrin B.[1] The conjugate addition of methylcuprate to the α,β-unsaturated γ-lactone **1**, readily available from L-ascorbic acid,[2] yielded the single stereoisomer **2** in 95% yield.[3] Routine functional group manipulation allowed the transformation of **2** into the epoxide **3**, which was then coupled under Yamaguchi conditions[4] with the acetylene **4**, readily prepared from D-malic acid.[5] Lindlar reduction of the coupled product gave the *cis*-olefin **5** in 86% overall yield from **3**. The *cis*-olefin **5** was then subjected to Sharpless epoxidation[6], followed by acid treatments, to yield the expected tetrahydrofuran **6** in 61% overall yield with a 7~8:1 stereoselectivity. The stereoselectivity of this epoxidation depended sharply on solvents, with a general trend of aromatic solvents giving more satisfactory results.



Scheme 1. Reagents and Reaction Conditions.
(a) 1. Me_2CuLi/TMSCl/THF/-78 °C→RT. (b). 1. LAH/Et_2O/0 °C. 2. PvCl/Py/ CH_2Cl_2/RT. 3. *p*-$MeOC_6H_4CH_2$-Br (MPM-Br)/KH/THF/RT. 4. AcOH-H_2O (4:1)/RT. 5. NaH/THF/RT, followed by treatment with *p*-TsImd/THF/RT. (c) 1. **4**/*n*-BuLi/THF/-78 °C, followed by BF_3•Et_2O at -78 °C then addition of **3** at -78 °C. 2. H_2/Lindlar catalyst/quinoline/hexanes/RT. (d) 1. *t*-BuOOH/VO(acac)$_2$/C_6H_6/RT. 2. TFA/CH_2Cl_2/RT. 3. AcOH-H_2O (4:1)/RT.

The C.50 and C.51 stereochemistry of **6** was assigned on the basis of literature precedents known for the stereochemical outcome of this type of epoxidation.[7] This assignment was further confirmed by degradation of **7**[8] to **8** and correlation of **8** with the authentic sample prepared *via* a different route (Scheme 2).

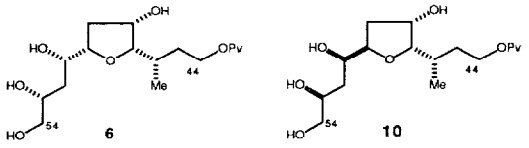


Scheme 2. Reagents and Reaction Conditions.
(c) 1. $C_6H_5CH_2Br$ (1 equiv)/NaH/THF/RT, and chromatographic separation. 2. Ac_2O/Py/RT. 3. AcOH-H_2O (4:1)/RT. 4. $NaIO_4$/H_2O-THF (1:1)/RT, followed by $NaBH_4$/MeOH/0 °C. 5. *o*-$O_2NC_6H_4SeCN$/*n*-Bu_3P/THF/RT, followed by 30% H_2O_2/THF/RT treatment[10]. 6. O_3/MeOH-CH_2Cl_2/-78 °C, followed by $NaBH_4$ reduction. 7. K_2CO_3/MeOH/RT. (f) 1. *t*-BuOOH/(+)-diethyl tartrate/Ti(*i*-PrO)$_4$/CH_2Cl_2/-15 °C[11]. 2. CSA/THF-H_2O (20:1)/RT.

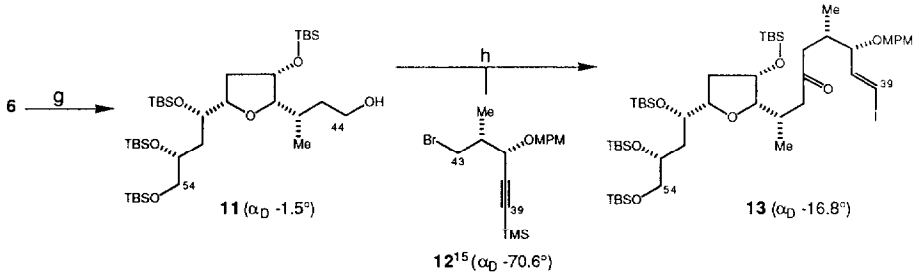
The synthesis outlined in Scheme 1 was designed to specifically address the stereochemical issue of the C.50-C.54 moiety of halichondrin B. The C.50, C.51 and C.53 stereochemistry of halichondrin B was suggested on the basis of vicinal ^1H-^1H coupling constants, as well as biogenetic considerations,[1] yet there remained some ambiguity. This synthetic route allowed the preparation of all the stereoisomers with respect to the C.50, C.51 and C.53 stereocenters, by using Sharpless[6] or MCPBA[12] epoxidation of the *cis*- and *trans*-olefins prepared from the acetylene **4** and its antipode. Examination of the chemical shifts and vicinal

Table 1. ^{1}H NMR data (CD_3OD) of **6**, **10**, and halichondrin B

	6	**10**	halichondrin B[1]
C.50	3.99	4.11	4.00
	(ddd, 9.1, 4.9, 4.2)	(ddd, 9.2, 6.7, 4.5)	(9.0, 4.2. 4.2)
C.51	3.73	3.63	3.78
	(ddd, 8.3, 6.1, 4.9)	(ddd, 8.8, 4.5, 4.1)	(ddd, 8.7, 4.2, 4.2)
C.52	1.70	1.61	1.61
	(ddd, 13.9, 6.1, 4.7)	(ddd, 14, 8.8, 7.8)	(ddd, 14.1, 8.7, 8.3)
C.52	1.75	1.66	1.75
	(ddd, 13.9, 8.3, 8.0)	(ddd, 14, 5.1, 4.1)	(14.1, 4.2, 4.2)
C.53	3.83	3.86	3.87
	(dddd, 8.0, 6.2, 4.7, 4.1)	(dddd, 7.8, 6.0, 5.1, 4.3)	(m)



spin-spin coupling constants in the ^{1}H NMR spectra of stereoisomers thus obtained clearly demonstrated that the ^{1}H NMR data observed for **6** and its diastereomer **10** matched well with the reported values[1] for halichondrin B (Table 1). Therefore, these two stereoisomers were separately brought up to the left half **13**[13] of halichondrins B and C and its corresponding diastereomer (Scheme 3), then to the final products.[14]



Scheme 3. Reagents and Reaction Conditions.
(g) 1. TBSOTf/Et_3N/CH_2Cl_2/RT. 2. same as step b.1. (h) 1. Dess-Martin reagent[16]/CH_2Cl_2/RT. 2. **12**[15]/*t*-BuLi/Et_2O/-78 °C, followed by treatment with the aldehyde at -78 °C. 3. $AgNO_3$ (6 equiv)/HMDS (7 equiv)/H_2O-EtOH (1:4)/RT. 4. *n*-Bu_3SnH/AIBN/toluene/80 °C. 5. I_2/CH_2Cl_2/RT. 6. same as step h.1.

Acknowledgement. Financial support from the National Institutes of Health (CA-22215) is gratefully acknowledged. We thank the National Institutes of Health for Postdoctoral Fellowships to F.G.F. (CA 08515), C.J.F. (CA 08655), and P.M.S. (GM 13631).

References and Footnotes

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.
2. Vekemans, J. A. J. M.; Franken, G. A. M.; Dapperens, C. W. M.; Godefroi, E. F.; Chittenden, G. J. F. *J. Org. Chem.* **1988**, *53*, 627-633.
3. Satisfactory spectroscopic data (^1H and ^{13}C NMR, HRMS, MS, IR, UV, $[\alpha]_D$) were obtained for all new compounds reported in this paper.
4. Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391-394.
5. The acetylene **4** was synthesized from D-(+)-malic acid in 4 steps, 1. BH_3•Me_2S/B(OMe)3/THF/0 °C→RT, 2. acetone/*p*-TsOH/RT, 3. Swern oxidation [Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651-1660; Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480-2482], 4. DAMP/*t*-BuOK/THF/-78 °C [Colvin, E. W.; Hamill, B. J. *J. C. S. Chem. Comm.* **1973**, 151-152 and *J. C. S. Perkin I* **1977**, 869-874; Gilbert, J. C.; Weerasooriya, *J. Org. Chem.* **1979**, *44*, 4997-4998], in 25% overall yield.
6. (a) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136-6137. (b) Tanaka, S.; Yamamoto, H.; Nozaki, H.; Sharpless, K. B.; Michaelson, R. C.; Cutting, J. D. *J. Am. Chem. Soc.* **1974**, *96*, 5254-5255.
7. For example, see: (a) Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63-74. (b) Kishi, Y. *Aldrichimica Acta* **1980**, *13*, 23-30.
8. This correlation was carried out on the substrate with R=TBDPS. The acetonide **7** was the product at the step corresponding to step d.2 in Scheme 1. Then, **7** (R=TBDPS) was converted to **11** to complete the correlation.
9. The *cis*-olefin **9** was synthesized from **3** in 4 steps, 1 and 2: same as steps c.1 and c.2 in Scheme 1 with $TBSOCH_2C{\equiv}CH$ instead of **4**, 3. BnBr/NaH/THF/RT, 4. *p*-TsOH•Py/MeOH-CH_2Cl_2 (1:4)/RT.
10. Sharpless, K. B.; Young, M. W. *J. Org. Chem.* **1975**, *40*, 947-949.
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12. MCPBA epoxidation of these olefins gave the inverse stereoselectivity of $VO(acac)_2$-catalyzed epoxidation; for example, MCPBA oxidation of **5** in CH_2Cl_2 at RT gave a 3:1 mixture of epoxides. For examples similar to this case, see ref 7.
13. ^1H NMR (C_6D_6) of **13**: δ 0.01 (3 H, s), 0.02 (3 H, s), 0.14 (6 H, s), 0.25 (3 H, s), 0.26 (3 H, s), 0.27 (3 H, s), 0.28 (3 H, s), 0.87 (3 H, d, *J* = 6.8 Hz), 0.96 (9 H, s), 0.98 (3 H, d, *J* = 6.8 Hz), 1.02 (9 H, s), 1.07 (9 H, s), 1.08 (9 H, s), 1.35 (1 H, br s), 1.58 (1 H, m), 1.76 (1 H, m), 1.91 (1 H, m), 1.99 (1 H, m), 2.20 (1 H, dd, *J* = 8.7, 16.7 Hz), 2.29 (1 H, dd, *J* = 10.2, 16.7 Hz), 2.39 (1 H, m), 2.53 (1 H, dd, *J* = 4.2, 16.7 Hz), 2.67 (1 H, m), 2.97 (1 H, dd, *J* = 2.2, 16.7 Hz), 3.10 (1 H, m), 3.30 (1 H, m), 3.32 (3 H, s), 3.69 (1 H, dd, *J* = 6.0, 10.3 Hz), 3.76 (1 H, m), 3.80 (1 H, dd, *J* = 3.5, 10.3 Hz), 3.92 (1 H, m), 4.00 (1 H, m), 4.05 (1 H, d, *J* = 11.5 Hz), 4.26 (1 H, m), 4.35 (1 H, d, *J* = 11.5 Hz), 6.01 (1 H, d, *J* = 14.5 Hz), 6.33 (1 H, dd, *J* = 7.8, 14.5 Hz), 6.79 (2 H, d, *J* = 8.6 Hz), 7.13 (2 H, d, *J* = 8.6 Hz).
14. The total synthesis of halichondrin B from the iodoolefin **13** has recently been completed, establishing the complete structure as illustrated.
15. The bromide **12** was synthesized from (S)-(+)-methyl 3-hydroxy-2-methylpropionate (Aldrich) in approximately 40% overall yield, in 8 steps: 1. THP protection, 2. LAH reduction, 3. Swern oxidation, 4. LiC≡C-TMS, followed by chromatographic separation of two diastereomers, 5. MPMO(C=NH)CCl_3/BF_3•Et_2O, 6. CSA/MeOH, 7. MsCl/Et_3N, 8. LiBr.
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(Received in USA 20 December 1991)