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Synthetic Studies Towards Halichondrins: Synthesis of the Left Halves of Norhalichondrins and Homohalichondrins

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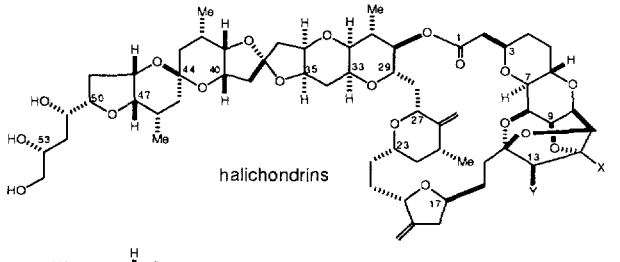
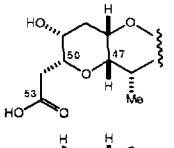
Abstract: *The left halves of norhalichondrins and homohalichondrins were synthesized from γ-lactone* ***1****, readily available from D-galactose glycal via Ireland-Claisen rearrangement then iodolactonization.*

There are eight members known in the halichondrin class of natural products. They are divided into the subclass of A, B and C series or into the subclass of halichondrin, norhalichondrin and homohalichondrin series. The structural variations among the A, B and C series are concerned with the oxidation level at the C.12 and C.13 positions whereas the structural variations among norhalichondrin, halichondrin and homohalichondrin series are concerned with the C.50-and-beyond positions.[1,2] In this paper, we report the syntheses of the left halves of norhalichondrins and homohalichondrins.

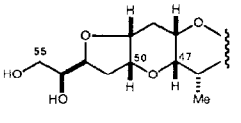




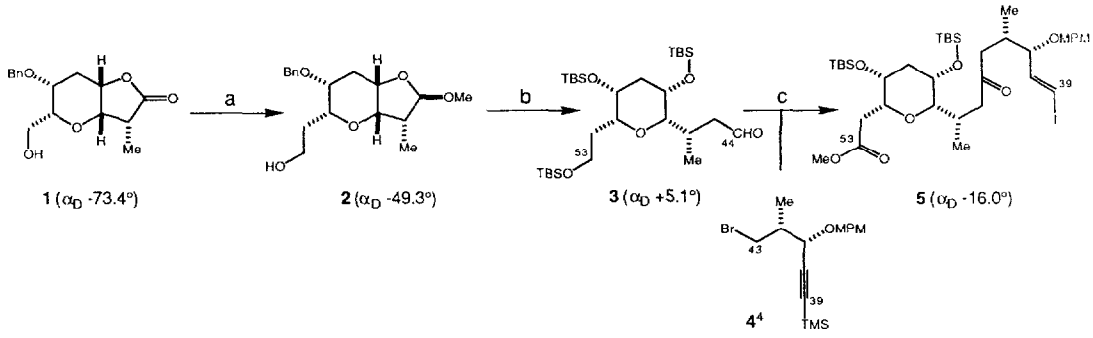
A series : X = Y = OH

B series : X = Y = H

C series : X = OH, Y = H



We noticed that the stereochemistry of γ-lactone **1**, readily available from D-galactose glycal *via* Ireland-Claisen rearrangement and iodolactonization, perfectly matches the stereochemistry at the C.46-and-beyond positions of norhalichondrins.[3] Using virtually the same sequence of reactions used for the synthesis of the left half of halichondrins,[4] the left half **5**[5] of norhalichondrin B was synthesized from **1** in an excellent overall yield (Scheme 1).[6]

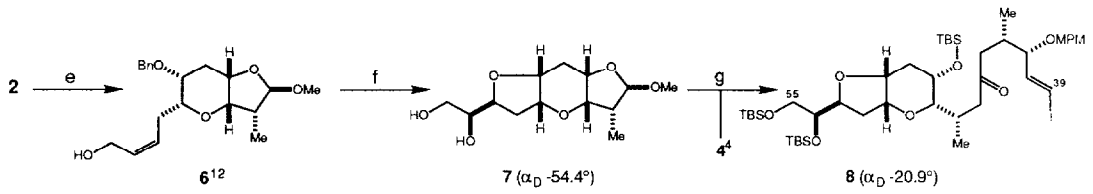


Scheme 1. Reagents and Reaction Conditions.
(a) 1. DIBAL/CH_2Cl_2/-78 °C→0 °C. 2. *p*-TsOH/MeOH/RT. 3. Tf_2O/Py/ CH_2Cl_2/-42 °C, followed by treatment with NaCN/DMF/RT. 4. DIBAL/CH_2Cl_2/-78 °C, followed by reduction with $NaBH_4$/MeOH/0 °C. (b). 1. H_2/Pd(OH)$_2$ on C/MeOH/RT. 2. EtSH/BF_3•Et_2O/CH_2Cl_2/0 °C. 3. TBSOTf/Et_3N/CH_2Cl_2/0 °C. 4. I_2/$NaHCO_3$/acetone-H_2O (12:1)/0 °C, followed by reduction with $NaBH_4$/MeOH/0 °C. 5. MsCl/Et_3N/CH_2Cl_2/0 °C, followed by treatment with NaCN/DMSO/50 °C. 6. DIBAL/CH_2Cl_2/-78 °C. (c) 1. bromide **4**[4]/*t*-BuLi/Et_2O/-78 °C, followed by treatment with **3** at -78 °C. 2. $AgNO_3$ (6 equiv)/HMDS (7 equiv)/H_2O-EtOH (1:4)/RT. 3. *n*-Bu_3SnH/AIBN/toluene/80 °C. 4. I_2/CH_2Cl_2/RT. 5. Dess-Martin reagent[7]/CH_2Cl_2/RT. 6. CSA/THF-*t*-BuOH-*i*-PrOH (1:1:1). 7. same as step c.5. 8. $NaClO_2$/NaH_2PO_4/*t*-BuOH, followed by treatment with CH_2N_2/Et_2O.

Interestingly, the methyl acetal **2** also served as the starting material for the synthesis of the C.44-C.55 segment of homohalichondrins. Although the stereochemistry of the C.50, C.51, C.53 and C.54 positions of homohalichondrins was unknown, we felt safe to assume that the stereochemistry of the C.50 and C.51 positions of homohalichondrins corresponds to that of norhalichondrin A, the structure of which was unambiguously established by X-ray analysis.[1] Therefore, we focused only on the synthesis of all the possible stereoisomers with respect to the C.53 and C.54 positions of homohalichondrin B. This was accomplished by Sharpless asymmetric epoxidation[8] of the *cis*- and *trans*-allylic alcohols, i.e. step f.1, followed by acid-catalyzed cyclization (Scheme 2). Examination of the chemical shifts and vicinal spin-spin coupling constants clearly showed that only the diastereomer **7** among these stereoisomers exhibited ^1H NMR data close to the data reported for homohalichondrin A.[9] As the stereoisomer **7** was derived

from Sharpless asymmetric epoxidation of *cis*-allylic alcohol **6** in the presence of diethyl L-(+)-tartrate, its stereochemistry was concluded as shown. As described for the conversion of **2** to **5**, **7** was converted to the *trans*-iodoolefin **8**[10].

The total synthesis of norhalichondrin B and homohalichondrin B from the iodoolefins **5** and **8**, respectively, has recently been completed, establishing their complete structures.[11]



Scheme 2. Reagents and Reaction Conditions.

(e) 1. Dess-Martin oxidation[7], followed by Horner-Emmons reaction, using $(F_3CCH_2O)_2P(O)CH_2CO_2Me$/KN(TMS)$_2$/18-crown-6/THF/-78 °C[13]. 2. DIBAL/pentane-CH_2Cl_2 (2:1)/-78 °C. (f) 1. *t*-BuOOH/diethyl L-(+)-tartrate/Ti(*i*-PrO)$_4$/CH_2Cl_2/-20 °C. 2. *p*-TsOH/wet $CHCl_3$/RT. (g) 1.-10. same as steps b.2 through c.5.

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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. To the best of our knowledge, halichondrin A has not been isolated.
3. Aicher, T. D.; Buszek, K. R.; Fang, F. G.; Forsyth, C. J.; Jung, S. H.; Kishi, Y.; Scola, P. M. a preceding paper.
4. Buszek, K. R.; Fang, F. G.; Forsyth, C. J.; Jung, S. H.; Kishi, Y.; Scola, P. M.; Yoon, S. K. a preceding paper.
5. ^{1}H NMR ($CDCl_3$) of **5**: δ -0.02 (3 H, s), 0.03 (3 H, s), 0.04 (3 H, s), 0.07 (3 H, s), 0.77 (3 H, d, *J* = 6.6 Hz), 0.81 (3 H, d, *J* = 6.5 Hz), 0.88 (9 H, s), 0.89 (9 H, s), 1.83 (1 H, ddd, *J* = 4.5, 4.6, 14.9 Hz), 1.96 (1 H, ddd, *J* = 2.7, 2.8, 14.8 Hz), 2.10 (1 H, dd, *J* = 9.3, 16.5 Hz), 2.15-2.24 (2 H, m), 2.39-2.44 (2 H, m), 2.50 (1 H, dd, *J* = 3.2, 16.5 Hz), 2.65 (1 H, d, *J* = 8.6, 16.2 Hz), 2.77 (1 H, dd, *J* = 3.7, 16.4 Hz), 2.88 (1 H, dd, *J* = 1.5, 9.1 Hz), 3.51 (1 H, dd, *J* = 7.0, 7.1 Hz), 3.62 (3 H, s), 3.70 (1 H, m), 3.75 (1 H, m), 3.78 (3 H, s), 3.81 (1 H, m), 4.23 (1 H, d, *J* = 11.3 Hz), 4.46 (1 H, d, *J* = 11.2 Hz), 6.24

(1 H, d, J = 14.5 Hz), 6.39 (1 H, dd, J = 7.8, 14.5 Hz), 6.85 (2 H, m), 7.19 (2 H, m).

6. Satisfactory spectroscopic data (^{1}H and ^{13}C NMR, HRMS, MS, IR, UV, $[\alpha]_D$) were obtained for all new compounds reported in this paper.

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8. Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974-5976.

9. ^{1}H NMR data (CD_3OD) of triacetate of **6** and homohalichondrin A triacetate

	triacetate of **6**	homohalichondrin A triacetate[1 b]
C.53	4.31 (m)	4.42 (m)
C.54	5.09 (ddd, J = 7.7, 4.4, 3.5 Hz)	5.31 (ddd, J = 7.3, 4.6, 3.3 Hz)
C.55	4.14 (dd, J = 11.9, 7.7 Hz)	4.18 (dd, J = 12.1, 7.3 Hz)
C.55	4.32 (dd, J = 11.9, 3.5 Hz)	4.41 (dd, J = 12.1, 3.3Hz)

10. ^{1}H NMR ($CDCl_3$) of **8**: δ 0.01 (6 H, s), 0.02 (3 H, s), 0.03 (3 H, s), 0.06 (3 H, s), 0.08 (3 H, s), 0.81 (3 H, d, J = 6.6 Hz), 0.84 (3 H, d, J = 4.2 Hz), 0.85 (9 H, s), 0.86 (9 H, s), 0.88 (9 H, s), 1.60 (H, td, J = 4.2, 15.4 Hz), 1.85 (1 H, dd, J = 6.3, 13.0 Hz), 2.03 (1 H, m), 2.17 (1 H, dd, J = 8.4, 16.1 Hz), 2.19-2.27 (3 H, m), 2.31 (1 H, m), 2.53 (1 H, dd, J = 8.4, 19.6 Hz), 2.67 (1 H, dd, J = 4.9, 16.1 Hz), 2.74 (1 H, d, J = 10.5 Hz), 3.51 (1 H, dd, J = 5.8, 7.6 Hz), 3.54 (1 H, m), 3.61 (1 H, dd, J = 6.3, 10.3 Hz), 3.65 (1 H, dd, J = 4.0, 10.3 Hz), 3.75 (1 H, br t, J = 2.3 Hz), 3.79 (3 H, s), 3.80 (1 H, m), 3.90 (1 H, dd, J = 2.3, 3.5 Hz), 4.22 (1 H, td, J = 2.6, 6.3 Hz), 4.23 (1 H, d, J = 11.5 Hz), 4.47 (1 H, d, J = 11.5 Hz), 6.25 (1 H, d, J = 14.3 Hz), 6.40 (1 H, dd, J = 8.0, 14.3 Hz), 6.85 (2 H, d, J = 8.6 Hz), 7.19 (2 H, d, J = 8.6 Hz).

11. 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.; manuscript in preparation.

12. $[\alpha_D]$ of the corresponding methyl ester: -37.9° (*c* 0.28, MeOH).

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