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ABSOLUTE STEREOCHEMISTRY OF HALICHLORINE; A POTENT INHIBITOR OF VCAM-1 INDUCTION

Hirokazu Arimoto,* Ichiro Hayakawa, Makoto Kuramoto,† and Daisuke Uemura††

Department of Chemistry, Faculty of Science, Shizuoka University, 836 Ohya Shizuoka 422, Japan

†*Advanced Instrumentation Center for Chemical Analysis, Ehime University, 2-5 Bunkyou-chou, Matsuyama 790-77, Japan*

††*Department of Chemistry, Graduate school of Science, Nagoya University, Chikusa, Nagoya 464-01, Japan*

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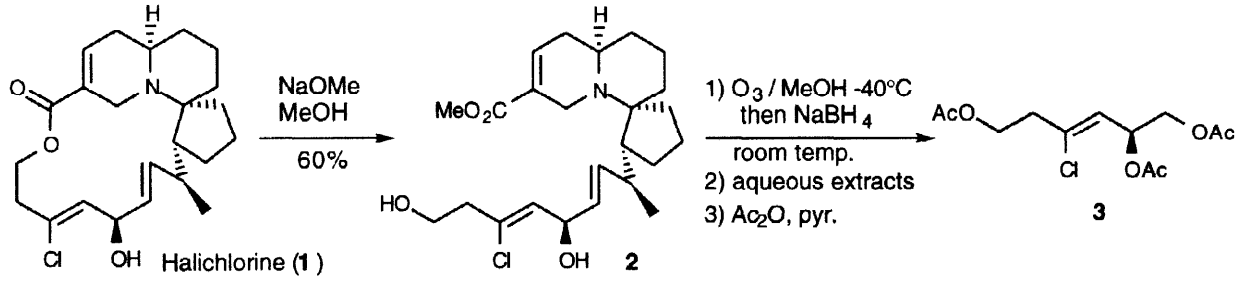
Abstract: *The absolute stereochemistry of a marine alkaloid halichlorine, which significantly inhibits VCAM-1 induction in HUVE cells, was established by synthesis of a degradation product of natural product.*

Inhibitors of induced expression of VCAM-1(vascular cell adhesion molecule-1) are potentially useful for treating atherosclerosis, coronary artery diseases, angina and noncardiovascular inflammatory diseases. In 1996, we reported isolation of halichlorine(**1**) from the marine sponge *Halichondria okadai* Kadota, which inhibits the induction at IC_{50} 7 μg/ml.[1] Although the relative stereochemistry of **1** was clarified by a extensive analysis of coupling constants and the NOESY spectrum, its absolute stereochemistry remained unknown. Our initial attempt to introduce chiral MTPA esters on the secondary hydroxyl at C17 failed due to its low reactivity. We report here oxidative degradation of **1** and asymmetric synthesis of the degradation product, which allows the assignment of the absolute stereochemistry of halichlorine.



Scheme 1. Degradation experiment of halichlorine.

The degradation study began with methanolysis of halichlorine(**1**), which gave ring-opened methyl ester(**2**).[2a] The ester **2** was subsequently oxidized by ozone at -40°C, followed by reductive workup with $NaBH_4$. The reaction was partitioned between chloroform and water. The aqueous layer was collected, and extracted with moist butanol. The butanol solution was concentrated to dryness under reduced pressure, and was acetylated to yield triacetate **3**.[2b] The ^1H NMR spectra of **3** revealed that the chlorinated olefin subunit in halichlorine(**1**) was not affected. Since **3** was obtained only in minute quantity, we decided to synthesize both enantiomers of it to determine the absolute stereochemistry.

Our synthesis of degradation product **3** started from known alcohol **4**,[3,4] readily available from D-(-)-tartaric acid(Scheme 2). The hydroxyl group of **4** was protected as a THP ether. The subsequent C2-

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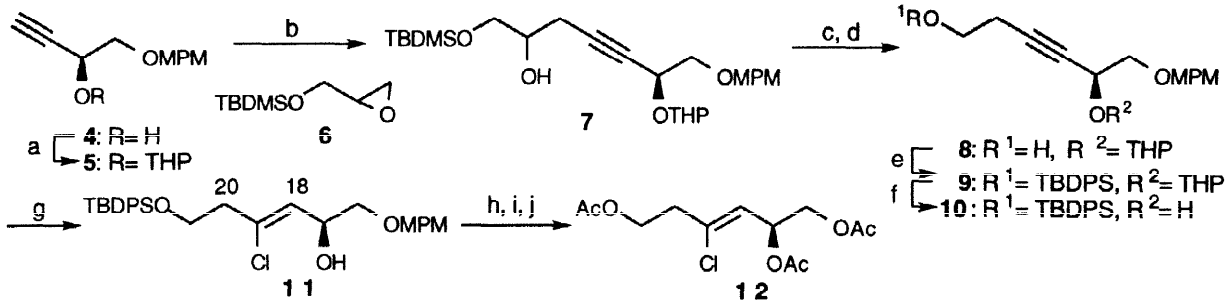

Reagents and conditions: (a) 2,3-dihydropyran, PPTS cat. CH_2Cl_2 (quant.); (b) *n*-BuLi, epoxide **6**, BF_3-Et_2O, THF, -78°C, 30 min(94%); (c) *n*-Bu_4NF, THF, room temp.(74%); (d) $NaIO_4$, 1,4-dioxane-H_2O(2:1), then $NaBH_4$(87%); (e) TBDPSCl, imidazole, DMF (90%); (f)PPTS cat. MeOH, 50°C (87%); (g) Red-Al®, THF -78°C to 0°C, 1 hr, then NCS, 0°C, 30 min(63%); (h) CAN, CH_3CN-H_2O(10:1), room temp.(86%); (i) *n*-Bu_4NF, THF, room temp.; (j)Ac_2O, DMAP, pyr., room temp. (98% in 2steps)

Scheme 2. Synthesis of triacetate.

homologation was done by an indirect 4 step sequence with a glycidyl ether **6**, since ethylene oxide is not easily available in these laboratories for safety reasons. Protection of the primary hydroxyl group of **8** as a *t*-butyl diphenylsilyl ether, followed by the deprotection of THP ether afforded alcohol **10**. A regioselective hydroalumination of the propargylic alcohol and quench with *N*-chlorosuccinimide, furnished the desired (*Z*)-chloroalkene, whose stereochemistry was cofirmed by the observance of a nOe between the C18 olefinic proton and C20 methylene protons. Although attempts to remove the *p*-methoxybenzyl ether with DDQ gave poor yields because of the formation of benzoyl esters, the use of ceric ammonium nitrate provided desired alcohol in 86% yield. Removal of the silyl ether, and subsequent acetylation gave (*S*)-triacetate **12**, whose NMR spectrum agreed with degradation product of natural halichlorine.[5] The enantiomeric (*R*)-triacetate **13** was prepared from L-tartaric acid in a same manner.[5]

With both synthetic enantiomers **12** and **13** in hand, the determination of absolute stereochemistry was performed by comparison of retention time of the degradation product **3** in chiral HPLC(SHISEIDO Ceramospher Chiral RU-2, 4.6x250mm, acetonitrile). The degradation product had the same retention time as synthetic (*S*)-acetate(**12**), evidence which supports the absolute stereochemical assignment of halichlorine depicted in scheme 1.[6]

Acknowledgments.
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2. a) **2**:^{1}H-NMR(400MHz, CD_3OD) δ 0.99(3H, d, *J*= 6.8 Hz), 1.20(1H, m),1.25(1H, m), 1.25(1H, m), 1.40(1H, m), 1.40(1H, m), 1.40(1H, dd, *J*=12.9, 3.9 Hz), 1.45(1H, m), 1.53(1H, m), 1.73(1H, m), 1.77(1H, m), 2.02(1H, m, *J*=19.0 Hz), 2.11(1H, m), 2.24(1H, m), 2.34(1H, m), 2.37(1H, m), 2.93(1H, dddd, *J*= 15.7, 3.9, 3.0, 1.2 Hz), 3.47(1H, br.d, *J*= 15.7 Hz), 3.72(3H, s), 3.73(2H, m), 4.97(1H, *J*= 7.8, 6.3, 0.9 Hz), 5.38(1H, ddd, *J*= 15.6, 6.3, 1.1 Hz), 5.63(1H, dd, 7.8, 0.8 Hz), 5.94(1H, ddd, *J*= 15.6, 7.7, 0.9 Hz), 6.87(1H, br.s): b) Triacetate **3**: ^{1}H-NMR(400MHz, $CDCl_3$) δ 2.04(3H, s), 2.07(3H, s), 2.07(3H, s), 2.67(2H, t, *J*=6.3 Hz), 4.13 (1H, dd, *J*=6.7, 11.8 Hz), 4.2 (3H, complex), 5.57 (1H, *J*=7.6 Hz)
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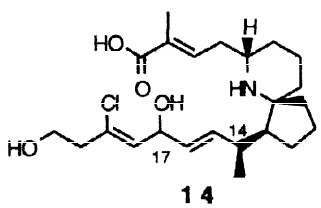
5. **12**: $[\alpha]_D^{27}$ +7.3° (*c* 0.8, $CHCl_3$); ^{13}C NMR(100MHz, $CDCl_3$) 20.62, 20.69, 20.82, 35.8, 61.0 63.5, 69.5, 123.0, 135.5, 169.6, 170.5, 170.7; HRMS(*m/z*, obs.) 233.0575(M^+-OAc), calc. for $C_{10}H_{14}O_4Cl$ 233.0579; **13**: $[\alpha]_D^{27}$ -7.6° (*c* 0.7, $CHCl_3$)
6. These results are of interest in connection with pinnaic acid **14**,[7] another marine natural product isolated in these laboratories. Halichlorine and pinnaic acid share same skeltone, and the stereochemistry of **14** was not fully established. Although we proposed different relative stereochemistries at the C14 for each natural product, the results were not conclusive. A synthetic effort to clarify this point is currently underway.



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