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Synthesis of the tricyclic core of halichlorine

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Synthesis of the tricyclic core of halichlorine, a VCAM-1 expression suppressor, was achieved using ene-yne metathesis cyclization as a key step.

Halichlorine **1** was isolated from a marine sponge in the course of our search for substances that block the induced expression of VCAM-1 (vascular cell adhesion molecule-1).[1] Drugs that inhibit these processes may be useful for treating atherosclerosis, coronary artery diseases, angina, and noncardiovascular inflammatory diseases. The structure of **1** (Fig. 1) is very similar to that of pinnaic acid **2**, which was found in a marine bivalve.[2] We established the absolute stereochemistry of **1** by chemical degradation of **1** and synthesis.[3]

Halichlorine's molecular complexity in conjunction with its potent biological activity have made it an attractive synthetic target. Synthetic approaches to halichlorine/pinnaic acid have been reported by a number of groups;[4] only Danishefsky, however, has accomplished the total synthesis of both **1**[5] and **2**.[6] We have recently reported the second total synthesis of **2**.[7] Most other studies[4] are at the stage of spiro-bicyclic ring construction. Indeed, no other group except Danishefsky *et al.* has reported preparation of the tricyclic core of **1**.[5] We report here synthesis of the C1–C15 tricyclic core of halichlorine *via* an ene-yne metathesis-based strategy.[8]

We envisaged that aldehyde **3** would be a versatile intermediate for halichlorine synthesis (Fig. 2, PMP = 4-methoxyphenyl). The synthesis started with a cyclopentane derivative **4**, which was employed in our recent total synthesis of pinnaic acid (Scheme 1).[7] Oxidative cleavage of the terminal alkene to the aldehyde, followed by a Horner–Wadworth–Emmons reaction gave (*E*)-α,β-unsaturated ketone **5**. Catalytic hydrogenation of **5** in ethanol furnished spiro-piperidine **6**. Saturation of the alkene in **5**, hydrogenolysis of benzyloxycarbonyl (Cbz), and stereoselective reduction of the cyclic imine intermediate could be achieved in one pot. In our previous reports, similar reductive cyclizations were carried out in the presence of acetic acid.[7,9] The cyclization reaction of **5** also proceeded nicely with acetic acid on a small scale; gram-scale preparations of the material, however, often suffered from low reproducibility.

After the survey of catalysts with/without acid, it was concluded that the choice of a palladium catalyst was the most crucial factor. The use of 50 mol% of 5 wt% $Pd(OH)_2$/C (N.E. CHEMCAT Co., Tokyo, Japan) cleanly afforded the desired **6** reproducibly. The addition of acetic acid to the reaction media proved to be unnecessary.

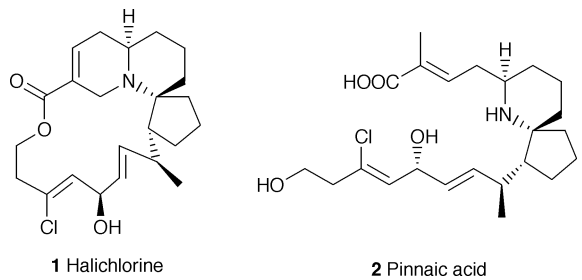


Fig. 1 Halichlorine and pinnaic acid.

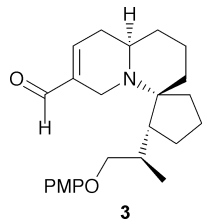
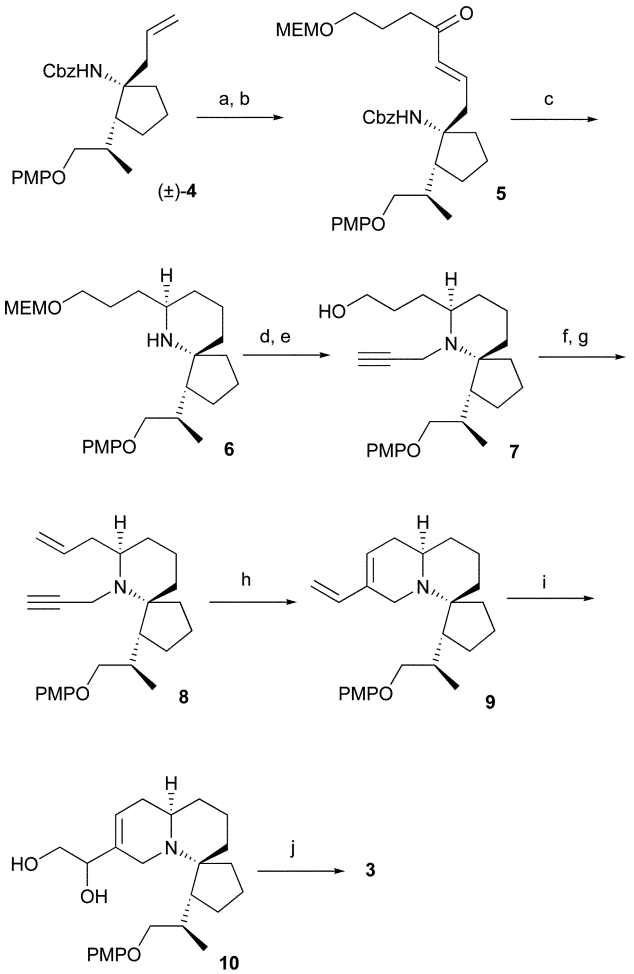


Fig. 2 Tricyclic intermediate **3**.



Scheme 1 a) O_3, MeOH, then Me_2S; b) LiCl, Et_3N, THF, phosphonate **11**,[16] quant.; c) H_2, $Pd(OH)_2$/C, EtOH, 94%; d) propargyl bromide, Proton sponge, MeCN, 60 °C, 60%; e) PPTS, *t*-BuOH, reflux, 77%; f) 2-nitrophenyl selenocyanate, $(n\text{-}Bu)_3P$, THF, room temp., 98%; g) mCPBA, THF, room temp., 87%; h) 2nd generation Grubbs Ru-catalyst (11.7 mol%),[12] ethylene atmosphere, toluene, 80 °C, 72%; i) K_2OsO_4–H_2O, $(DHQD)_2PHAL$, $NaHCO_3$, $K_3[Fe(CN)_6]$, aq. *t*-BuOH, room temp., 52%; j) $NaIO_4$, aq. MeOH, 0 °C to room temp., 81%.

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The introduction of a propargyl substituent to the sterically hindered nitrogen atom in **6** was not as easy as expected. After numerous surveys of bases, the reaction was found to proceed with propargyl bromide and Proton sponge™. Removal of the methoxyethoxymethyl (MEM) group was conducted using pyridinium 4-toluenesulfonate as an acid. The primary alcohol of **7** was converted to the corresponding 2-nitrophenylselenyl group.[10] Upon treatment with 3-chloroperbenzoic acid at 0 °C, the selenoether was oxidized and then eliminated to form a terminal alkene **8**.[11]

Ene-yne **8** was refluxed in toluene with Grubbs' ruthenium catalyst **12**[12] to furnish the desired diene **9** in 72% yield. It was noteworthy that tertiary amine in **8** did not retard the reaction. Regioselective cleavage of the terminal alkene in **9** was then investigated. Ozone oxidation in methanol at −78 °C gave a complex mixture, presumably due to the lack of chemoselectivity over internal alkene and tertiary amine. Thus, bulky Sharpless' chiral osmium reagents were next employed.[13] With the combination of K_2OsO_4, $(DHQD)_2PHAL$, $NaHCO_3$, and $K_3[Fe(CN)_6]$, diol **10** was obtained in 52% yield. Cleavage of the diol proceeded cleanly to afford the desired aldehyde **3**.[14] This two-step procedure was superior to the direct Lemieux–Johnson condition[15] in both yield (32%) and reproducibility.

In conclusion, we succeeded in synthesizing the tricyclic azadecaline core of halichlorine. The synthesis highlights are ene-yne metathesis cyclization and regioselective oxidative cleavage of the conjugated diene. Efforts toward the completion of the total synthesis are currently underway.

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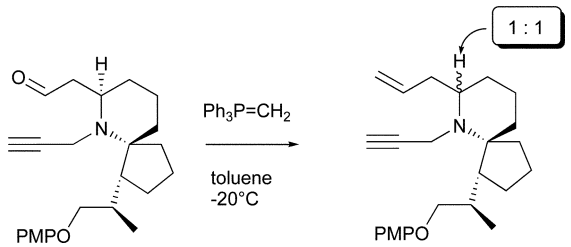

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