

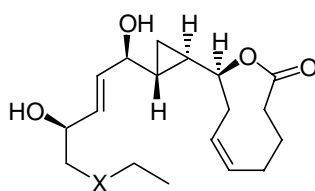
TOTAL SYNTHESIS OF (-)-HALICHOLACTONE

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Abstract - A convergent total synthesis of halicholactone (**1**), 5-lipoxygenase inhibitor, using (1*S*, 5*S*, 6*R*)-5-hydroxybicyclo[4.1.0]heptan-2-one (**7**) as a chiral building block is described. *Z*-Selective RCM reaction was the key step to construct the nine-membered unsaturated lactone linkage of **1**.

Halicholactone (**1**) was isolated from the marine sponge, *Halichondria okadai*, by Yamada *et al.* in 1989 along with neohalicholactone (**2**).¹ Halicholactone (**1**) exhibited inhibitory activity against 5-lipoxygenase of guinea pig polymorphonuclear leukocytes (IC₅₀=630 μ M). These compounds possess a *trans*-disubstituted cyclopropane ring and unsaturated lactone and comprise a linear C₂₀ carbon skeleton characteristic of oxylipin.² Therefore, it is believed that halicholactone (**1**) and neohalicholactone (**2**) are biosynthesized from arachidonic acid and eicosapentaenoic acid, respectively, *via* lipoxygenation and formation of lactone.³ These biologically important and unique structural features have inspired several synthetic studies,⁴ and Wills *et al.* have reported the first total synthesis⁵ followed by several syntheses of **1**.⁶ We show here a novel approach to **1** using our chiral building block, (1*S*, 5*S*, 6*R*)-5-hydroxybicyclo[4.1.0]heptan-2-one (**7**).^{7, 8} We have reported the syntheses of natural products, sporogen-AO **1**, phomenone,⁸ gigantene, phaseolinone⁹, and pironetine¹⁰ and dendryphiellin C¹¹ using this building block (**7**) to date.

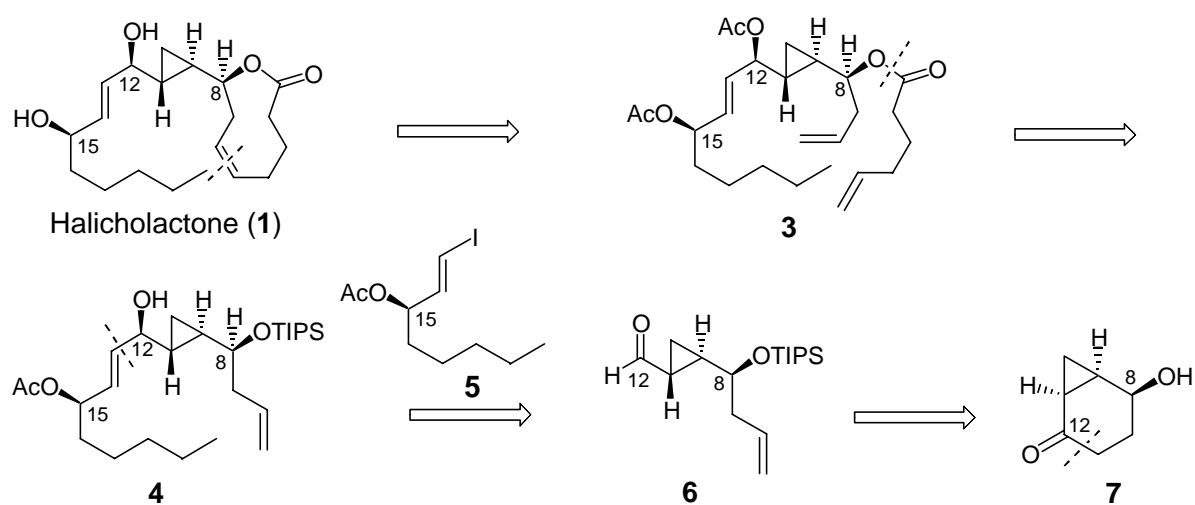


X = -CH₂CH₂- : Halicholactone (**1**)

X = *cis*-CH=CH- : Neohalicholactone (**2**)

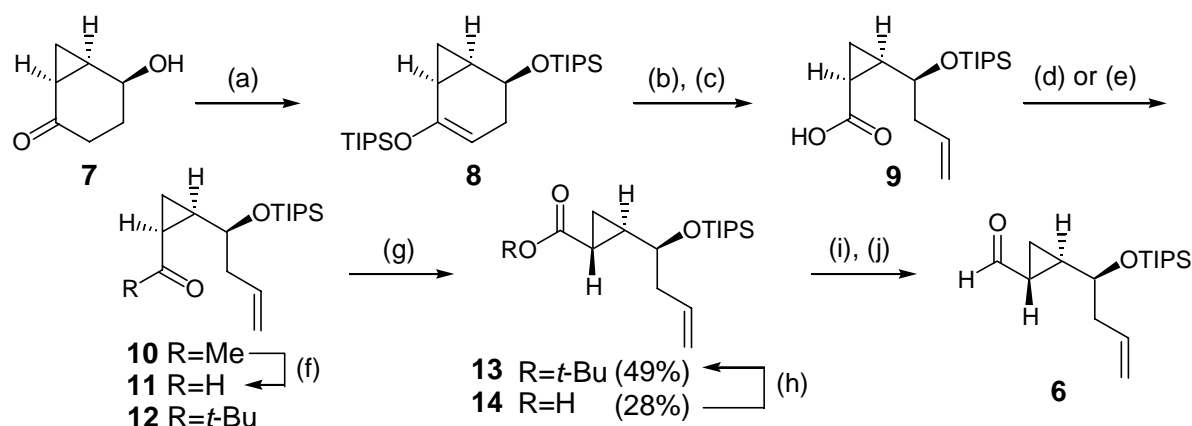
Figure 1.

Our synthetic strategy is illustrated in Scheme 1. As we decided to synthesize a nine-membered unsaturated lactone linkage of **1** using a *Z*-selective RCM reaction,¹² a terminal bisolefin (**3**) was employed as a precursor. This compound would be prepared from **4** by change of the protective groups, entailing esterification with 5-hexenoic acid. The compound (**4**) could be constructed from aldehyde (**6**) by the Nozaki-Hiyama-Kishi reaction (NHK reaction)¹³ with vinyl iodide (**5**), which is obtainable from (*R*)-1-octyn-3-ol. *trans*-Cyclopropyl aldehyde (**6**) should be synthesized from the key building block (**7**) via oxidative ring-cleavage of the corresponding silyl enol ether.



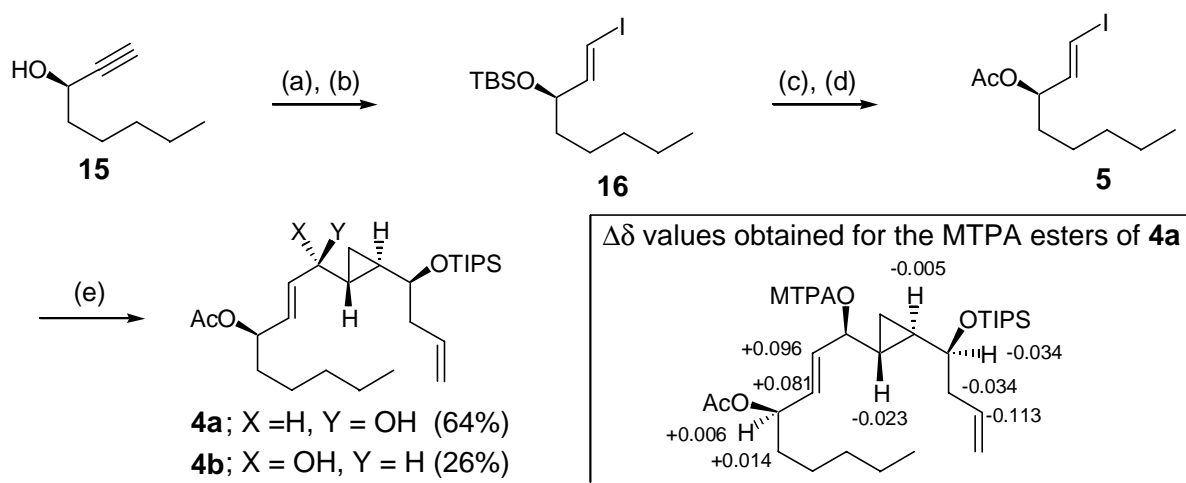
Scheme 1. Synthetic strategy of halicholactone

The ketol (**7**) was converted to protected silyl enol ether (**8**) by treatment with 2.3 equiv. of triisopropylsilyl triflate and triethylamine. Ozonolysis of **8**, followed by the Wittig olefination gave carboxylic acid (**9**) in good yield. In order to obtain the requisite *trans*-cyclopropyl aldehyde (**6**), we prepared the corresponding *cis*-cyclopropyl aldehyde (**11**) from **9**, and examined isomerization to *trans*-derivative under basic conditions. Unfortunately, this attempt failed and gave a complex mixture. Therefore, we tried epimerization under Ohfuné's condition¹⁴ or several basic conditions using a methyl ester (**10**). When potassium *tert*-butoxide was employed as a base in DMSO at room temperature, a rather satisfactory result was obtained, giving 28% of *trans*-fused carboxylic acid (**14**) along with 28% of **9**. This condition gave rise to hydrolyzate. To prevent this, we transformed the carboxylic acid (**9**) to *t*-butyl ester (**12**) using *tert*-butyl trichloroacetimidate and examined isomerization of more bulky *t*-butyl ester (**12**) than the methyl ester (**10**). The best yield was obtained by using a mixture of potassium *tert*-butoxide as a base, 18-crown-6 ether and molecular sieves 4 Å in benzene at 80°C to give the desired *trans*-cyclopropyl *t*-butyl ester (**13**) in 49% yield and *trans*-carboxylic acid (**14**) in 28% yield. The carboxylic acid (**14**) was converted to *tert*-butyl ester (**14**) using the same conditions as above. Reduction of **13** with LiAlH₄ followed by TPAP oxidation gave aldehyde (**6**) in 91% yield.



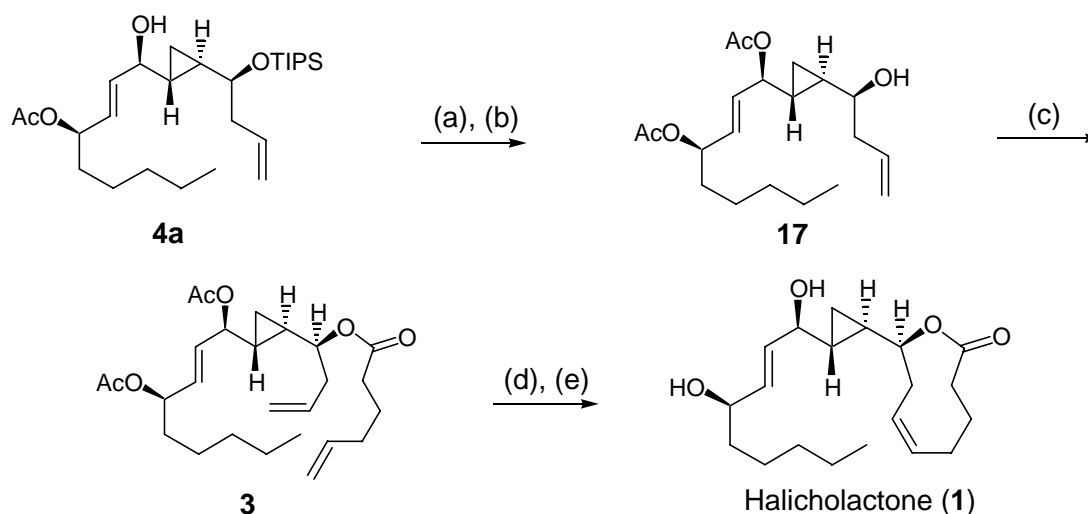
Scheme 2. *Reagents and conditions:* (a) TIPSOTf, Et₃N, CH₂Cl₂, 0°C (98%); (b) O₃, CH₂Cl₂, -78°C then PPh₃; (c) Ph₃PMeBr, *n*-BuLi, DME, 0°C (2 steps 71%); (d) CH₂N₂, Et₂O, 0°C→rt (**10**, 99%); (e) CCl₃C(=NH)Ot-Bu, BF₃·OEt₂, Cyclohexane (**12**, 96%); (f) LiAlH₄, THF, 0°C (99%) then TPAP, NMO, CH₂Cl₂, rt (87%); (g) *t*-BuOK, 18-Crown-6-ether, MS 4Å, Benzene, reflux, for **12**; (h) CCl₃C(=NH)Ot-Bu, BF₃·OEt₂, Cyclohexane, rt (92%); (i) LiAlH₄, THF, 65°C (99%); (j) TPAP, NMO, CH₂Cl₂, rt (92%).

Next, we synthesized vinyl iodide (**5**) from commercially available (*R*)-1-octyn-3-ol (**15**) to examine the NHK reaction. Protection of **15** with TBSCl and successive hydrozirconation-iodination according to Schwartz's method gave vinyl iodide (**16**).¹⁵ Deprotection of the TBS ether followed by acetylation gave the requisite vinyl iodide (**5**). The aldehyde (**6**) and the vinyl iodide (**5**) were treated with 5 wt % of NiCl₂ and CrCl₂ in 1:1 mixture of DMSO/DMF at room temperature to give the desired allylic alcohol (**4**) as a 2.5:1 mixture of diastereomers in 90% yield. The mixture was cleanly separated by silica gel chromatography and the stereochemistry of major product (**4a**) was confirmed by modified Mosher's method¹⁶ and found to be the desired (*R*)-isomer (**Scheme 3**).



Scheme 3. *Reagents and conditions:* (a) TBSCl, imidazole, DMF, 0°C→rt (92%); (b) Cp₂ZrHCl then I₂, THF, rt (72%); (c) TBAF, THF, 0°C→rt (83%); (d) Ac₂O, Et₃N, DMAP, CH₂Cl₂, rt (99%); (e) **6**, CrCl₂, NiCl₂ (0.5 wt%), DMF-DMSO(1:1), rt (**4a**: **4b** = 64%: 26%).

Initial protection of the secondary hydroxyl group of **4a** as acetate and subsequent removal of the triisopropylsilyl group using TBAF-HF gave **17** in 88% yield, which was converted to **3** by esterification with 5-hexenoic acid. RCM reaction of **3** with Grubbs' reagent¹⁷ in the presence of a catalytic amount of $\text{Ti}(\text{O}-i\text{Pr})_4$, reported by Takemoto,^{6b, 6c} gave *Z*-olefin,^{12a} nine-membered lactone derivative, in 93% yield along with 3% of a dimer. Finally, methanolysis of two acetates afforded halicholactone (**1**), the ^1H and ^{13}C NMR, IR, MS spectra and specific optical rotation of which were identical with those of the authentic sample.¹⁸



Scheme 4. *Reagents and conditions:* (a) Ac_2O , Et_3N , DMAP, CH_2Cl_2 , rt; (b) TBAF-HF, aq. THF, rt (2 steps 88%); (c) 5-Hexenoic acid, DCC, DMAP, CH_2Cl_2 , rt (95%); (d) $(\text{Cy}_3\text{P})_2\text{RuCl}_2=\text{CHPh}$, $\text{Ti}(\text{O}i\text{-Pr})_4$, CH_2Cl_2 , 40°C , 0.1 mM (93%); (e) K_2CO_3 , MeOH, rt (55%).

In conclusion, we have succeeded in total synthesis of halicholactone *via* a convergent route in overall 12.5% yield through 14 steps from **7**. This method is applicable to the synthesis of similar oxylipins, and our chiral building block (**7**) was again proved to be extremely versatile for the synthesis of bioactive natural products.

ACKNOWLEDGEMENTS

The authors thanks Professor Y. Takemoto, University of Kyoto, for a kind gift of ^1H and ^{13}C -NMR spectra of halicholactone. This work was supported by a Grant-in-Aid for Scientific Research from the Japanese Ministry of Education, Culture, Sports, Science, and Technology.

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18. Data for synthetic compound (1): $[\alpha]_D^{25}$ -85.4° (c = 0.24, CHCl₃); ¹H NMR (500 MHz, C₆D₆): δ (ppm) 0.27 (1H, ddd, *J* = 5.0, 5.0, 8.0 Hz), 0.45 (1H, ddd, *J* = 4.0, 5.0, 9.0 Hz), 0.86 (1H, m), 0.88 (3H, t, *J* = 7.5 Hz), 1.05 (1H, m), 1.19-1.45 (6H, m), 1.49 (2H, m), 1.54

(2H, m), 1.74 (1H, m), 1.90 (1H, ddd, $J = 1.5, 6.0, 13.0$ Hz), 2.08 (2H, m), 2.34 (1H, m), 2.37 (1H, m), 3.55 (1H, dd, $J = 4.0, 7.0$ Hz), 3.94 (1H, m), 4.33 (1H, ddd, $J = 1.5, 8.5, 12.0$ Hz), 5.34-5.44(2H, m), 5.66-5.73 (2H, m); ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) 8.2 (CH_2), 14.0 (CH_3), 19.4 (CH), 22.6 (CH_2), 23.4 (CH), 25.0 (CH_2), 25.2 (CH_2), 26.4 (CH_2), 31.7 (CH_2), 33.5 (CH_2), 33.8 (CH_2), 37.2 (CH_2), 72.3 (CH), 74.1 (CH), 76.1 (CH), 124.6 (CH), 131.6 (CH), 134.0 (CH), 134.6 (CH), 174.1 (C); IR (film) ν_{max} : 3424, 2927, 1738 cm^{-1} ; HRMS (FAB) Calcd for $\text{C}_{20}\text{H}_{31}\text{O}_3$ (M-OH): 319.2273. Found: 319.2278. [*lit.*,^{1a} $[\alpha]_{\text{D}}^{23} -85.4^\circ$ ($c = 1.16$, CHCl_3); ^1H NMR (500 MHz, C_6D_6): δ (ppm) 0.29 (1H, ddd, $J = 5.0, 5.0, 8.0$ Hz), 0.47 (1H, ddd, $J = 5.0, 5.0, 8.0$ Hz), 0.86 (1H, m), 0.89 (3H, t, $J = 7.0$ Hz), 1.03 (1H, m), 1.10-1.40 (6H, m), 1.50 (2H, m), 1.55 (2H, m), 1.77 (1H, m), 1.91 (1H, ddd, $J = 1.5, 7.0, 13.0$ Hz), 2.07 (2H, m), 2.34 (1H, m), 2.37 (1H, m), 3.53 (1H, dd, $J = 4.0, 7.0$ Hz), 3.92 (1H, m), 4.32 (1H, ddd, $J = 1.5, 8.0, 12.0$ Hz), 5.35-5.45(2H, m), 5.65-5.73 (2H, m); ^{13}C NMR (300 MHz, CDCl_3): δ (ppm) 8.2 (CH_2), 14.0 (CH_3), 19.5 (CH), 22.6 (CH_2), 23.5 (CH), 25.1 (CH_2), 25.3 (CH_2), 26.5 (CH_2), 31.8 (CH_2), 33.6 (CH_2), 33.9 (CH_2), 37.3 (CH_2), 72.3 (CH), 74.2 (CH), 76.1 (CH), 124.7 (CH), 131.7 (CH), 134.1 (CH), 134.7 (CH), 174.0 (C); IR (film) ν_{max} : 3640, 3460, 1730 cm^{-1}].