HETEROCYCLES, Vol. 58, 2002, pp. 99-104, Received, 8th April, 2002

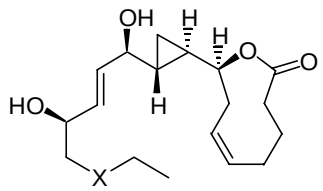
TOTAL SYNTHESIS OF (−)-HALICHOLACTONE

Taichi Takahashi, Hidenori Watanabe, and Takeshi Kitahara*

Department of Applied Biological Chemistry, Graduate School of Agriculturaland Life Sciences, The University of Tokyo, 1-1-1 Yayoi Bunkyo-ku, Tokyo, 113-8657, Japan

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**.

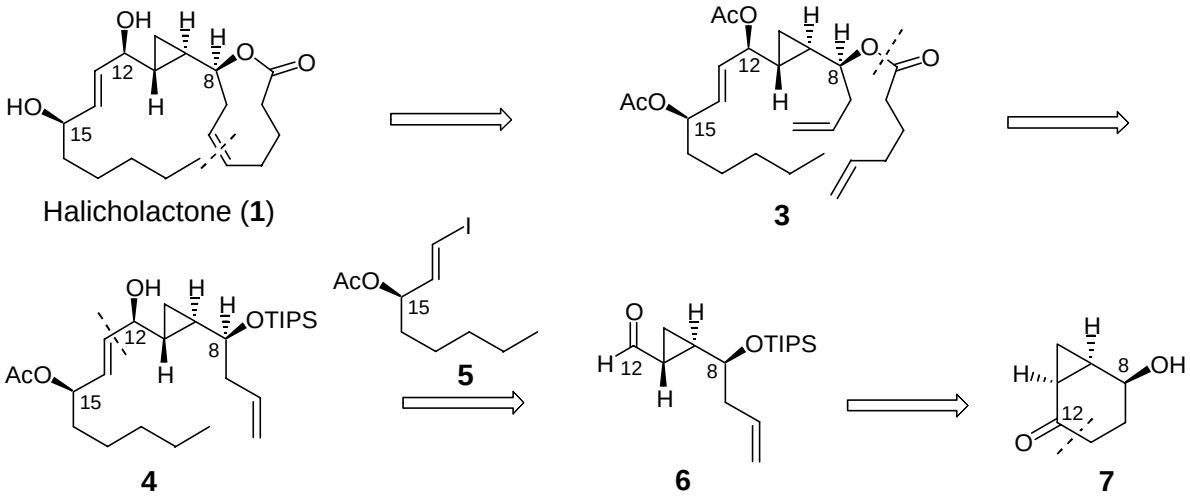
Halicholactone (**1**) was isolated from the marine sponge, *Halichondoria okadai,* by Yamada *et al.* in 1989 along with neohalicholactone (**2**).[1] Halicholactone (**1**) exhibited inhibitory activity against 5-lipoxygenase of guinea pig polymorphonuclear leukocytes (IC_{50}=630 μM). These compounds possess a *trans*-disubstituted cyclopropane ring and unsaturated lactone and comprise a linear C_{20} 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 synthesis[5] 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] gigantenone, phaseolinone[9], and pironetine[10] and dendryphiellin C[11] using this building block (**7**) to date.



X = -CH_2CH_2- : Halicholactone (**1**)
X = *cis*-CH=CH- : Neohalicholactone (**2**)

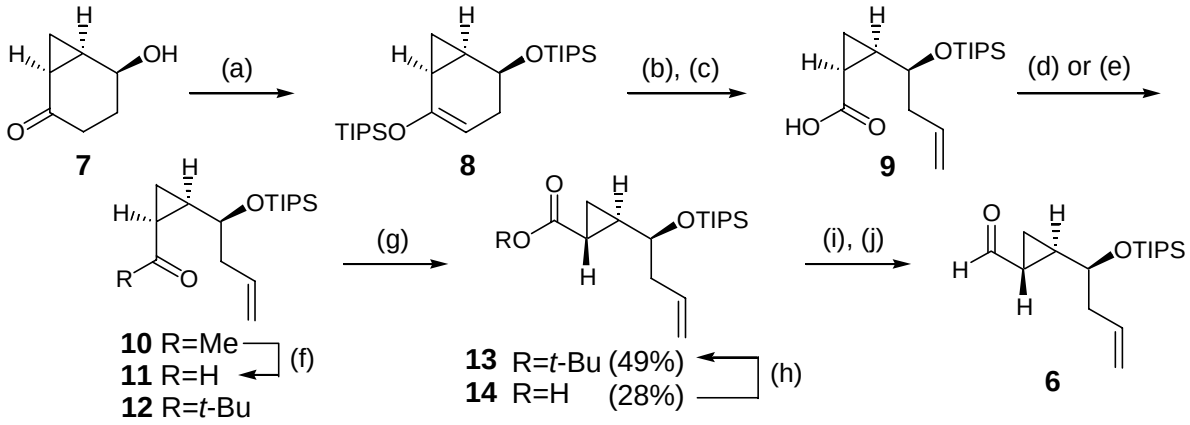
Figure 1.

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.



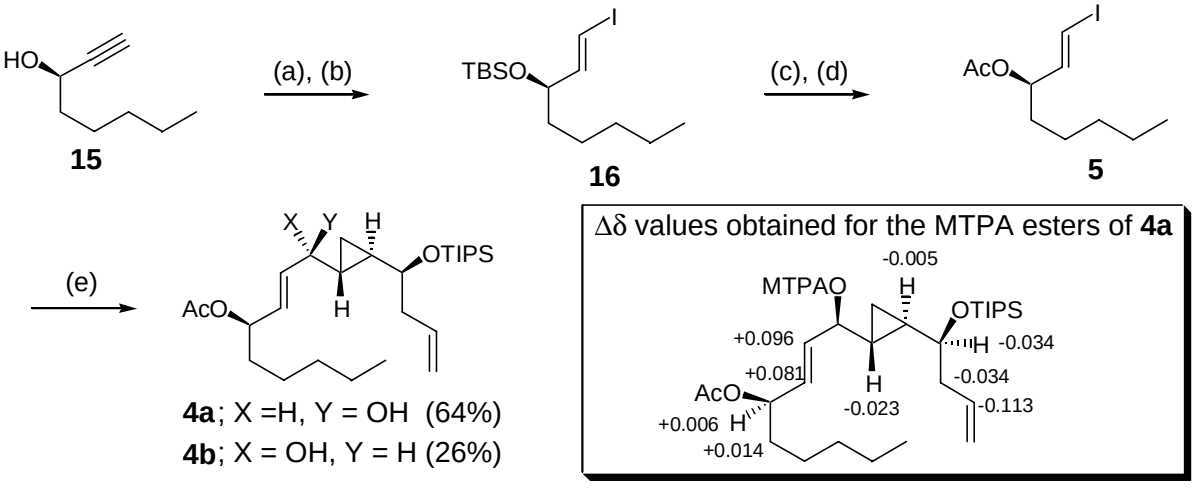
Scheme 1. Synthetic strategy of halicholactone

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*-cycropropyl aldehyde (**11**) from **9**, and examined isomerization to *tras*-derivative under basic conditions. Unfortunately, this attempt failed and gave a complex mixture. Therefore, we tried epimerization under Ohfune's condition[14] 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% yielde and *trans*-carboxylic acid (**14**) in 28% yielde. The carboxylic acid (**14**) was converted to *tert*-butyl ester (**14**) using the same conditions as above. Reduction of **13** with $LiAlH_4$ followed by TPAP oxidation gave aldehyde (**6**) in 91% yield.



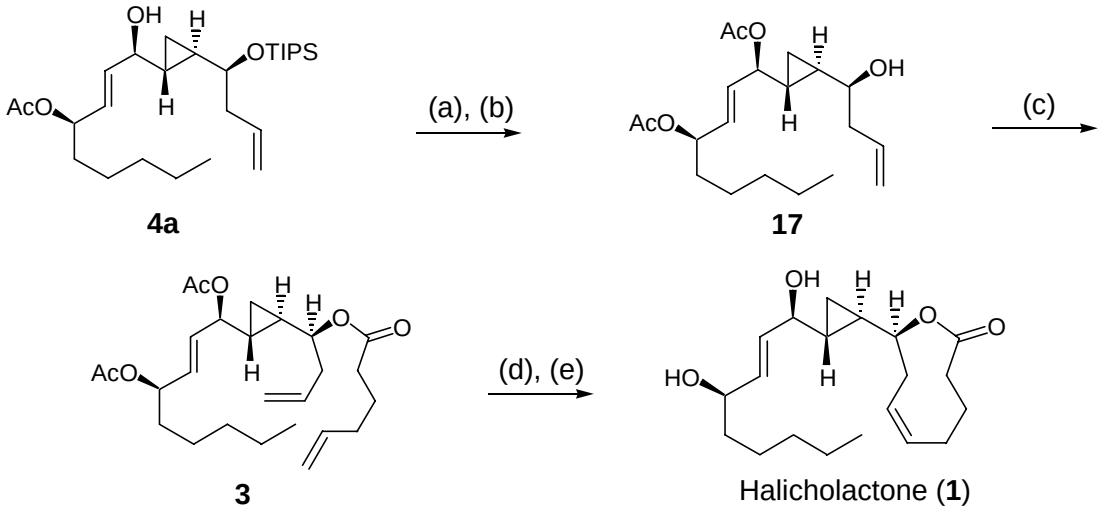
Scheme 2. *Reagents and conditions*: (a) TIPSOTf, Et_3N, CH_2Cl_2, 0ºC (98%); (b) O_3, CH_2Cl_2, -78ºC then PPh_3; (c) Ph_3PMeBr, *n*-BuLi, DME, 0ºC (2 steps 71%); (d) CH_2N_2, Et_2O, 0ºC→rt (**10**, 99%); (e) $CCl_3C(=NH)O$*t*-Bu, $BF_3{\cdot}OEt_2$, Cyclohexane (**12**, 96%); (f) $LiAlH_4$, THF, 0ºC (99%) then TPAP, NMO, CH_2Cl_2, rt (87%); (g) *t*-BuOK, 18-Crown-6-ether, MS 4Å, Benzene, reflux, for **12**; (h) $CCl_3C(=NH)O$*t*-Bu, $BF_3{\cdot}OEt_2$, Cyclohexane, rt (92%); (i) $LiAlH_4$, THF, 65ºC (99%); (h) TPAP, NMO, CH_2Cl_2, 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 $NiCl_2$ and $CrCl_2$ 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 method[16] and found to be the desired (*R*)-isomer (**Scheme 3**).



Scheme 3. *Reagents and conditions*: (a) TBSCl, imidazole, DMF, 0ºC→rt (92%); (b) Cp_2ZrHCl then I_2, THF, rt (72%); (c) TBAF, THF, 0ºC→rt (83%); (d) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt (99%); (e) **6**, $CrCl_2$, $NiCl_2$ (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' reagent[17] in the presence of a catalytic amount of Ti(O-*i*-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 ^{1}H and ^{13}C NMR, IR, MS spectra and specific optical rotation of which were identical with those of the authentic sumple.[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) $(Cy_3P)_2RuCl_2$=CHPh, Ti(O*i*-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 ^{1}H 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.

REFERENCES AND NOTES

1. (a) H. Niwa, K. Wakamatsu, and K. Yamada, *Tetrahedron Lett.*, 1989, **30**, 4543. (b) H. Kigoshi, H. Niwa, K. Yamada, T. J. Stouk, and J. Clardy, *Tetrahedron Lett.*, 1991, **32**, 2427.

2. (a) W. H. Gerwick, *Chem. Rev.*, 1993, **93**, 1807. (b) W. H. Gerwick, *Biochim. Biophys. Acta*, 1994, **1211**, 243.
3. P. J. Proteau, J. V. Rossi, and W. H. Gerwick, *J. Nat. Prod.*, 1994, **57**, 1717.
4. (a) J. D. White and M. S. Jensen, *Synlett*, 1996, **1**, 31.
5. (a) D. J. Critcher, S. Connolly, and M. Wills, *J. Chem. Soc., Chem. Commun.*, 1995, 139. (b) D. J. Critcher, S. Connolly, and M. Wills, *Tetrahedron Lett.*, 1995, **36**, 3763. (c) D. J. Critcher, S. Connolly, and M. Wills, *J. Org. Chem.*, 1997, **62**, 6638.
6. (a) A. Datta and D. K. Mohapatra, *J. Org. Chem.*, 1998, **63**, 642. (b) Y. Takemoto, Y. Baba, G. Saha, S. Nakao, C. Iwata, T. Tanaka, and T. Ibuka, *Tetrahedron Lett.*, 2000, **41**, 3653. (c) Y. Baba, G. Saha, S. Nakao, C. Iwata, T. Tanaka, T. Ibuka, H, Ohishi, and Y. Takemoto, *J. Org. Chem.*, 2001, **66**, 81.
7. T. Kitahara and K. Mori, *Tetrahedron Lett.*, 1985, **26**, 451.
8. T. Kitahara, H. Kurata, and K. Mori, *Tetrahedron*, 1988, **44**, 4339.
9. T. Kitahara, H. Kiyota, H. Kurata, and K. Mori, *Tetrahedron*, 1991, **47**, 1649.
10. H. Watanabe, H. Watanabe, and T. Kitahara, *Tetrahedron Lett.*, 1998, **39**, 8313.
11. H. Akao, and H. Kiyota, T. Nakajima, and T. Kitahara, *Tetrahedron*, 1999, **55**, 7757.
12. For recent reference of RCM reaction: (a) A. Fürstner and K. Langemann, *J. Am. Chem. Soc.*, 1997, **119**, 9130. (b) M. E. Maier, *Angew. Chem., Int. Ed.*, 2000, **39**, 2073. (c) A, K. Chatterjee, J. P. Morgan, M. Scholl, and R. H. Grubss, *J. Am. Chem. Soc.*, 2000, **122**, 3783. (d) J. S. Clark and O. Hamelin, *Angew. Chem., Int. Ed.*, 2000, **39**, 372. (e) D. J. Holt, W. D. Barker, P. R. Jenkins, J. Panda, and S. Ghosh, *J. Org. Chem.*, 2000, **65**, 482. (f) A. Fürstner, O. R. Thiel, L. Ackermann, H. J. Schanz, and S. P. Nolan, *J. Org. Chem.*, 2000, **65**, 2204.
13. (a) K. Takai, K. Kimura, T. Kuroda, T. Hiyama, and H. Nozaki, *Tetrahedron Lett.*, 1983, **24**, 5281. (b) Y. Okude, S. Hirano, T. Hiyama, and H. Nozaki, *J. Am. Chem. Soc.*, 1977, **99**, 3179. (c) H. Jin, J. Uenishi, W. J. Christ, and Y. Kishi, *J. Am. Chem. Soc.*, 1986, **108**, 5644. (d) K. Takai, M. Tagashira, T. Kuroda, T. Oshima, K. Uthimoto, and H. Nozaki, *J. Am. Chem. Soc.*, 1986, **108**, 6048.
14. (a) K. Shimamoto and Y. Ohfune, *Synlett*, 1993, 919. (b) Y. Ohfune, K. Shimamoto, M. Ishida, and H. Shinozaki, *Bioorg. Med. Chem. Lett.*, 1993, **3**, 15.
15. D. W. Hart, T. F. Blackburn, and J. Schwartz, *J. Am. Chem. Soc.*, 1975, **97**, 679.
16. (a) J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.*, 1973, **95**, 512. (b) I. Ohtani, T. Kushumi, Y. Kashman and H. Kakisawa, *J. Am. Chem. Soc.*, 1991, **113**, 4092.
17. (a) G. C. Fu and R. H. Grubbs, *J. Am. Chem. Soc.*, 1992, **114**, 5426. (b) G. C. Fu and R. H. Grubbs, *J. Am. Chem. Soc.*, 1992, **114**, 7324. (c) R. H. Grubbs, J. S. Miller, and G. C. Fu, *Acc. Chem. Res.*, 1995, **28**, 446.
18. Data for synthetic compound (**1**): $[\alpha]_D^{25}$ -85.4° (c = 0.24, $CHCl_3$); ^1H NMR (500 MHz, C_6D_6): 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 $C_{20}H_{31}O_3$ (M-OH): 319.2273. Found: 319.2278. [*lit.*,[1a] $[\alpha]_D^{23}$ -85.4° (c = 1.16, $CHCl_3$); ^{1}H 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); 13C NMR (300 MHz, CDCl3): 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}].