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Asymmetric total synthesis of halicholactone

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Abstract

The total synthesis of halicholactone by using the chirality of (diene)$Fe(CO)_3$ complexes was reported. The key steps of the synthesis include catalytic asymmetric alkylation, regio- and stereoselective phenylsulfenylation, regio- and stereoselective cyclopropanation and formation of a nine-membered lactone by ring-closing metathesis.

Keywords: iron and compounds; cyclopropanation; ring-closing metathesis; total synthesis; halicholactone.

The marine metabolites, halicholactone **1a** and neohalicholactone **1b**, were isolated from the marine sponge *Halichondoria okadai* by the Yamada group as lipoxygenase inhibitors in 1989.[1] The absolute stereochemistry of **1a** and **1b**, (8*S*,9*R*,11*R*,12*R*,15*R*), was established by Wills and co-workers through their first total synthesis.[2] These compounds possess a number of unusual structural features, including a nine-membered lactone, *trans*-disubstituted cyclopropane ring, and bis-allylic alcohol. Although the formal total synthesis of **1a** was also reported by Datta and Mohapatr in 1997,[3] the stereoselective construction of the stereogenic centers of C-9 to C-12 still remained to be solved. Accordingly, we planned a stereoselective asymmetric synthesis of **1a** using the chirality of (diene)$Fe(CO)_3$.[4]

To this end, our synthetic approach was initiated with the chiral $Fe(CO)_3$ complex **6**, prepared from the dialdehyde $Fe(CO)_3$ complex **7** by the catalytic asymmetric alkylation that we had already reported.[5] Stereoselective introduction of the hydroxy and phenylsulfenyl groups using the chirality of a (diene)$Fe(CO)_3$ complex (**6**→**5**) was followed by 1,3-migration of a sulfoxide, giving the triol derivative **4**. Regio- and stereoselective cyclopropanation by the modified Simmons–Smith reaction of **4** and the nine-membered lactone formation by the ring-closing metathesis of **2** produced the aimed natural product **1a** (Scheme 1). We report here the stereoselective total synthesis of halicholactone **1a** using the chiral (diene)$Fe(CO)_3$ complex **6**.

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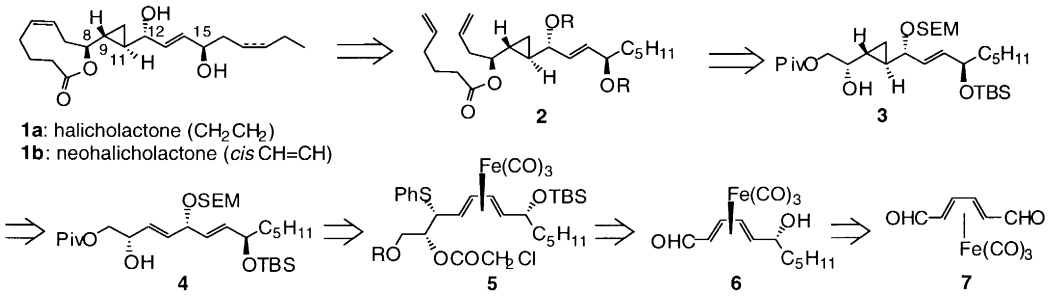
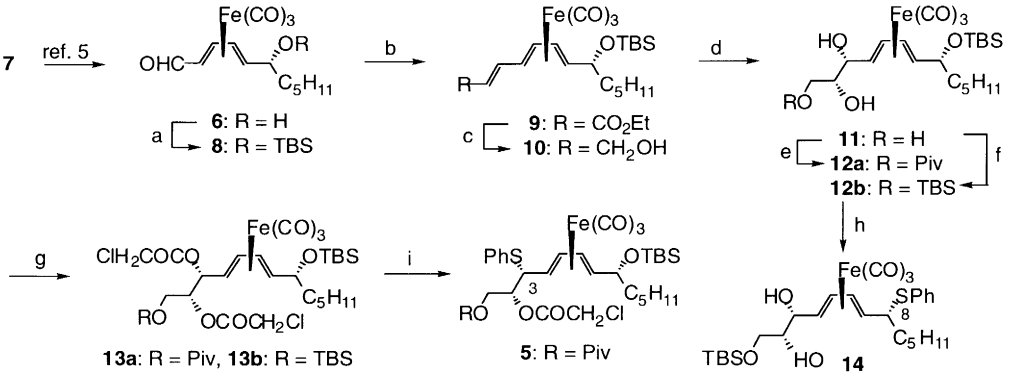


Scheme 1.

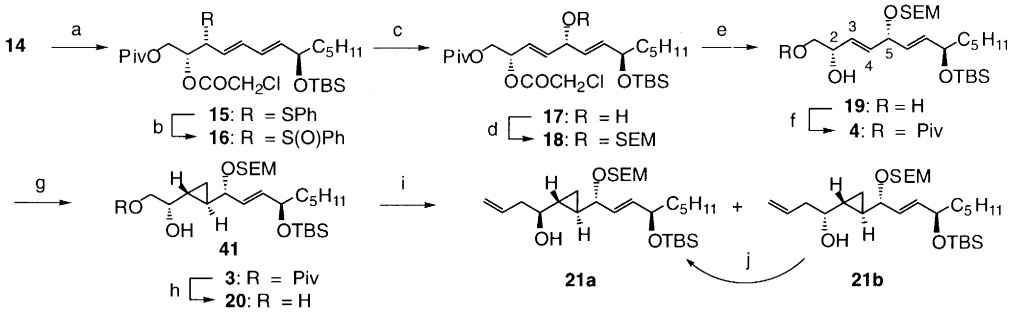
We initiated this study with the elongation and functionalization of the TBS-ether **8**, which was prepared from **6** in the usual manner. Successive subjection of **8** to Horner–Emmons reaction and DIBAL-H reduction gave the allylic alcohol **10** in 97% yield. The dihydroxylation of **10** with OsO_4 proceeded stereoselectively to afford the triol **11** as an inseparable diastereoisomeric mixture in a 9:1 ratio (detected from 500 MHz ^{1}H NMR).[6] The regioselective protection of three hydroxyl groups of **11** with PivCl and TBSOTf gave **12a** and **12b**, respectively. Furthermore, the diols **12a** and **12b** were converted into the bis-chloroacetoxy compounds **13a** and **13b**, respectively. At this stage, the diastereoisomers contaminated in **13a** and **13b** were separated by silica gel column chromatography (Scheme 2). The stereochemistry of **13b** was unambiguously determined by X-ray crystallographic analysis. We next examined the first key step, that is, stereoselective introduction of a phenylsulfanyl group by nucleophilic substitution.[7] Treatment of the diol **12b** with TMSSPh and $Sc(OTf)_3$ in CH_2Cl_2 at room temperature provided the undesired product **14** as the sole product. However, the reaction of **13a**, bearing a more reactive leaving group, with Me_2AlSPh[8] gave the desired phenylsulfide **5** regio- and stereoselectively.



Scheme 2. Conditions: (a) TBSOTf, pyridine, 0°C, 100%; (b) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0°C, 99%; (c) DIBAL-H, CH_2Cl_2, −78°C, 97%; (d) (i) OsO_4, Py, −20°C; (ii) sat. aq. $NaHSO_3$, 94%; (e) PivCl, Py, CH_2Cl_2, 0°C to rt, 97%; (f) TBSOTf, pyridine, 0°C, 56% (89% based on the consumed **11**); (g) $(ClCH_2CO)_2O$, DMAP, CH_2Cl_2, **13a**: 89%, **13b**: 81%; (h) TMSSPh, $Sc(OTf)_3$, CH_2Cl_2, −78°C to rt (62%); (i) Me_2AlSPh, CH_2Cl_2, −78°C, 69%

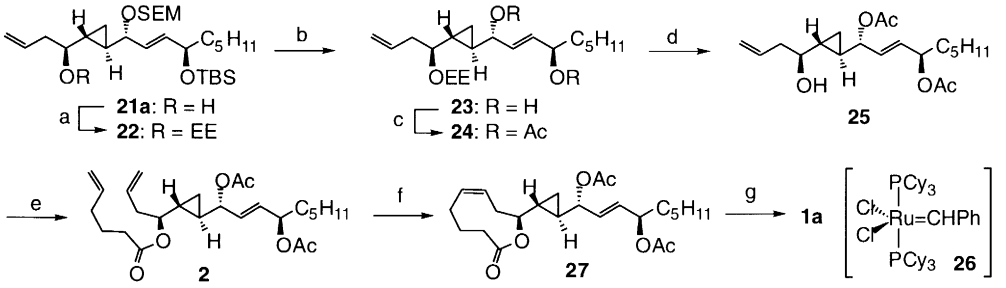
To next investigate the second key step, that is, the regio- and stereoselective Simmons–Smith reaction, **14** was transformed into the alcohol **4** (Scheme 3). After decomplexation of **14** with CAN (ceric(IV) ammonium nitrate), successive treatment of the resulting sulfide **15** with *m*-CPBA and $P(OMe)_3$ in refluxing MeOH furnished the allylic alcohol **17** in good yield. We presumed that the group-selectivity of the two olefins in **17** and diastereomeric face-selectivity of the C3–C4 double bond could be controlled by the hydroxyl group of C2.[9] After **17** was converted into the requisite product **4** by the usual protection–deprotection protocol, the reaction of **4** with 2.5 equiv. of Et_2Zn and 3.0 equiv. of CH_2I_2

in CH_2Cl_2 at −20°C, as expected, provided the desired mono-cyclopropanated product **3** in 68% yield as a single product (11% recovered of **4**). The homoallylic alcohol **21a** was synthesized from **3** by the following sequence: removal of the pivaloyl group with MeLi, cleavage of a 1,2-diol with $Pb(OAc)_4$, and introduction of an allyl group.[10] Although this manipulation gave the undesired product **21b** along with **21a**, **21b** was easily converted into **21a** via the standard Mitsunobu protocol.



Scheme 3. Conditions: (a) CAN, K_2CO_3, MeCN, −30°C, 97%; (b) *m*-CPBA, CH_2Cl_2, −78°C, 95%; (c) $P(OMe)_3$, MeOH, 75°C, 88%; (d) SEMCl, *i*-Pr_2NEt, *n*-Bu_4NI, CH_2Cl_2, 100%; (e) DIBAL-H, CH_2Cl_2, −78°C, 91%; (f) PivCl, Py-CH_2Cl_2, 0°C to rt, 64% (85% based on the consumed **19**); (g) Et_2Zn, CH_2I_2, CH_2Cl_2, −20°C, 69% (77% based on the consumed **4**); (h) MeLi, Et_2O, 0°C, 90%; (i) (i) $Pb(OAc)_4$, Na_2CO_3, CH_2Cl_2, −40°C (68%); (ii) tetraallyltin, $Sc(OTf)_3$, CH_3CN; (j) (i) DIAD, AcOH, PPh_3, THF; (ii) NaH, MeOH, 60% (70% based on the consumed **21b**)

The final task was formation of a nine-membered lactone possessing a (*Z*)-olefin. Although the esterification of **21a** with 5-hexenoic acid and the ring-closing metathesis (RCM) of the resulting product with Grubbs' catalyst **26**[11] gave the desired lactone, removal of the protecting group resulted in only decomposed products due to the instability of the cyclopropane and lactone units to the reaction conditions (Scheme 4). The problem was finally overcome by the replacement of the protecting group of **21a** from the TBS and SEM group to an acetyl group. Namely, the diacetate **2**, prepared from **21a** in five steps, was exposed to the RCM conditions with **26** in the presence of $Ti(O\textit{i}\text{-}Pr)_4$[12], giving rise to the desired *Z*-isomer **27** in 72% yield along with the corresponding dimer (11%). The total synthesis of halicholactone **1a** was completed by methanolysis of two acetyl groups, and the obtained product **1a** was identical (^1H NMR, ^{13}C NMR, IR, MASS and $[\alpha]_D$) in all respects to the reported data of the natural halicholactone **1a**.



Scheme 4. Conditions: (a) Ethyl vinyl ether, PPTS, CH_2Cl_2, 90%; (b) TBAF, MS 4 Å, 85°C, DMPU, 64%; (c) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 88%; (d) PPTS, *t*-BuOH, 69% (71% based on the consumed **24**); (e) 5-hexenoic acid, DCC, DMAP, CH_2Cl_2, 82%; (f) **26**, $Ti(O\textit{i}\text{-}Pr)_4$, CH_2Cl_2 (0.1 mM), reflux, 72%; (g) K_2CO_3, MeOH, 61%

In summary, we have achieved the asymmetric total synthesis of halicholactone **1a** from the chiral (diene)$Fe(CO)_3$ complex **6** via regio- and stereoselective phenylsulfenylation and cyclopropanation as well as formation of a nine-membered lactone by the ring-closing metathesis.

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References

1. Niwa, H.; Wakamatsu, K.; Yamada, K. *Tetrahedron Lett*. **1989**, *30*, 4543–4546; Kigoshi, H.; Niwa, H.; Yamada, K.; Stouk, T. J.; Clardy, J. *Tetrahedron Lett*. **1991**, *32*, 2427–2430.
2. Critcher, D. J.; Connolly, S.; Wills, M. *J. Chem. Soc., Chem. Commun*. **1995**, 139–140; Critcher, D. J.; Connolly, S.; Wills, M. *Tetrahedron Lett*. **1995**, *36*, 3763–3766; Critcher, D. J.; Connolly, S.; Wills, M. *J. Org. Chem*. **1997**, *62*, 6638–6657.
3. Mohapatr, D. K.; Datta, A. *J. Org. Chem*. **1998**, *63*, 642–646.
4. Reviews: Grée, R. *Synthesis* **1989**, 341–355; *Transition Metals in Total Synthesis*; Harrington, P. J., Ed.; John Wiley & Sons: New York, 1990; Pearson, A. J. *Iron Compounds in Organic Synthesis*; Academic Press: London, 1994; Iwata, C.; Takemoto, Y. *Chem. Commun*. **1996**, 2497–2504; Donaldson, W. A. *Aldrich. Acta* **1997**, *30*, 17–24; Cox, L. R.; Ley, S. V. *Chem. Soc. Rev*. **1998**, *27*, 301–314; Knölker, H.-J. *Chem. Soc. Rev*. **1999**, *28*, 151–157.
5. Takemoto, Y.; Baba, Y.; Noguchi, I.; Iwata, C. *Tetrahedron Lett*. **1996**, *37*, 3345–3346; Takemoto, Y.; Baba, Y.; Honda, A.; Nakao, S.; Noguchi, I.; Iwata, C.; Tanaka, T.; Ibuka, T. *Tetrahedron* **1998**, *54*, 15567–15580.
6. A similar dihydroxylation of $Fe(CO)_3$ complexes has been reported: Gigou, A.; Lellouche, J.-P.; Beaucourt, J.-P.; Toupet, L.; Grée, R. *Angew. Chem., Int. Ed. Engl*. **1989**, *28*, 755–757.
7. Roush, W. R.; Park, J. C. *Tetrahedron Lett*. **1990**, *31*, 4707–4710.
8. Itoh, A.; Ozawa, S.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn*. **1981**, *54*, 274–278.
9. Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307–1370; Charette, A. B.; Lebel, H. *J. Org. Chem*. **1995**, *60*, 2966–2967; Barrett, A. G. M.; Doubleday, W. W.; Hamprecht, D.; Kasdorf, K.; Tustin, G. J.; White, A. J. P.; Williams, D. J. *Chem. Commun*. **1997**, 1693–1700.
10. Hachiya, I.; Kobayashi S. *J. Org. Chem*. **1993**, *58*, 6958–6960.
11. Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res*. **1995**, *28*, 446–452; Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450; Sukkari, H. E.; Gesson, J.-P.; Renoux, B. *Tetrahedron Lett.* **1998**, *39*, 4043–4046.
12. Fürstner, A.; Langemann, K. *J. Am. Chem. Soc*. **1997**, *119*, 9130–9136.