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### Application of Asymmetric Ylide Cyclopropanation in the Total Synthesis of Halicholactone

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Halicholactone belongs to a family of oxylipins that have important and interesting biological activities, such as inhibiting lipoxygenase and farnesyl protein transferase. These compounds are featured unique molecular structures containing a 1,2-trans-substituted cyclopropane subunit with a 6-, 8- or 9-membered lactone (Figure 1).<sup>[1]</sup> The first total synthesis of halicholactone 1 was accomplished by Wills et al. using (S)-malic acid as the starting material.<sup>[2a]</sup> In their synthesis, the cyclopropane fragment was obtained by the reaction of the unsaturated ester with Corev vlide: the lactone unit was constructed by Yamaguchi's mixed anhydride method. Later, Takemoto, Tanaka,<sup>[2c]</sup> and their co-workers reported an asymmetric total synthesis of halicholactone 1 from chiral [(diene)Fe(CO)<sub>3</sub>], in which the cyclopropane fragment was prepared in moderate yields with excellent diastereoselectivity by the modified Simmons-Smith reaction of a chiral allylic alcohol. Kitahara<sup>[2d]</sup> documented a total synthesis of halicholactone by using (1S,5S,6R)-5hydroxybicyclo[4.1.0]-heptan-2-one as a chiral building block. Datta's group<sup>[2b]</sup> described a 12-step synthesis of compound 29 by employing the cyclopropanation of trans-cinnamyl alcohol through Charette's protocol, finishing the formal synthesis of halicholactone. Mohapatra et al. also reported the total synthesis of halicholactone with (R)-2,3-O-

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isopropylidene glyceraldehyde as a chiral pool building block.<sup>[2e]</sup> In our studies on ylide chemistry in organic synthesis,<sup>[3]</sup> we developed an efficient method for the preparation of vinylcyclopropanes from a readily available D-camphorderived ylide.<sup>[3c,e]</sup> In this cyclopropanation,<sup>[3c,e]</sup> excellent diastereoselectivity (*cis/trans*) and enantioselectivity can be achieved. Very recently, we found that this cyclopropanation could be applied successfully to the preparation of intermediate **13** in five steps to provide a formal synthesis of halicholactone. In this communication, we wish to report our results as well as the total synthesis of halicholactone in detail.



Figure 1. Halicholactone and related compounds (where  $X = CH_2 = CH_2$ the double bond has Z configuration).

Our retrosynthetic approach is shown in Scheme 1. Disconnecting the C12–C13 bond will afford two fragments 13 and 14. Compound 14 is accessible from (R)-(+)-1-octyn-3-ol.<sup>[2a]</sup> Fragment 13 can be obtained by the ring-closing meta-thesis reaction of compound 15, which would be prepared by the reaction of 5-hexenoic acid 16 with cyclopropane

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OTBDPS 14 RCM (-)-halicholactone 1 OtBu 13 16 CO<sub>2</sub>tBu OH 15 CO<sub>2</sub>tBu гмs ButO<sub>2</sub>C сно ButO<sub>2</sub>( 19 18

Scheme 1. Retrosynthetic approach to Halicholactone.

piece **17**. The *trans*-disubstituted cyclopropane **19** should be synthesized by an asymmetric ylide cyclopropanation developed by our group.<sup>[3c]</sup>

The synthesis of fragment **13**<sup>[2a]</sup> started with the enantioselective cyclopropanation of acrylate with the ylide derived from sulfonium salt **20**.<sup>[3c]</sup> Initially, we tried the cyclopropanation of methyl acrylate on a much larger scale at much higher concentration of sulfonium salt than that in our previous reports.<sup>[3c,e]</sup> As shown in Table 1, unfortunately, only a

Table 1. Ylide cyclopropanation.<sup>[a]</sup>

Ĺ	$\begin{array}{c} & & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ $		THF, -78°C	
Entry	<i>c</i> of <b>20</b> [mol]	L <sup>-1</sup> ] ([mmol])	<b>21 a</b> [equiv]	Yield [%]
1	0.21 (4.2)		4	trace <sup>[b]</sup>
2	0.25 (0.5)		4	31
3 <sup>[c]</sup>	0.01 (2)		8	63
4 <sup>[c]</sup>	0.1 (4.8)		8	72
5 <sup>[c]</sup>	0.1 (10)		8	65

[a] Reaction conditions: -78°C, KOtBu (3.0 equiv), THF as a solvent. [b] 2,3-Sigma rearrangement product was isolated. [c] tBuOK was added in 7-10 portions over 2 h.

trace amount of the desired product was obtained (entry 1). In this case, the 2,3-sigma rearrangement of the ylide was obtained as the major product. The probable reason is that the increasing concentration of the sulfonium salt decreased the molar ratio of acrylate **21a** to ylide **22**; this would favor the rearrangement reaction (Scheme 2). On the basis of the aforementioned analysis, we assumed that the addition of base in portions would lower the concentration of the ylide, thus improving the cyclopropanation. As expected, the yield was increased to 63 % when KOtBu was added in 7–10 por-



Scheme 2. Mechanism of cyclopropanation.

tions within 2 h. By employing this method, the yield was improved to 72 % when the scale was increased to 4.8 mmol at a concentration of 0.1 M (entry 4, Table 1). Under the optimal conditions, the desired compound **19b** was synthesized in 76% yield with 97% *ee* and excellent diastereoselectivity (dr > 99:1) (Scheme 3).



Scheme 3. Synthesis of cyclopropane 18.

With the cyclopropane 19b in hand, we first tried its oxidation into the corresponding aldehyde 18 with NaIO<sub>4</sub> in the presence of catalytic OsO<sub>4</sub>. As shown in Scheme 3, the reaction proceeded very smoothly affording the desired aldehyde in up to 97% yield. The allylation of 18 was tested with Roush reagent<sup>[4]</sup> 26, but the reaction proceeded very slowly. Only 25% of 18 was converted even after 18 h at -78°C and a further 47 h at 0°C. In addition, the diastereomeric ratio was 1:1, probably due to the steric hindrance of the cyclopropane moiety. We were very pleased to find that aldehyde 18 reacted smoothly with allyl bromide in the presence of zinc powder in a mixed solvent of saturated aqueous ammonium chloride and THF,<sup>[5]</sup> giving alcohol 17a-b in very high yields. Although the diastereoselectivity remained poor, the two diastereoisomers 17a and 17b were separated readily by flash chromatography on silica gel. In addition, isomer 17b could easily be transformed into the desired isomer 17a in nearly quantitative yield by the Mitsunobu

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protocol.<sup>[6]</sup> Condensation of **17a** with 5-hexenoic acid **16** in  $CH_2Cl_2$  in the presence of dicyclocarbodiimide (DCC) and DMAP afforded compound **15** in 99% yield (Scheme 4).



Scheme 4. Synthesis of 17 and 15.

Using 1st generation Grubbs catalyst  $27^{[7]}$  as the catalyst, ring-closing metathesis of 15 proceeded smoothly in the presence of catalytic amount of  $[Ti(OiPr)_4]^{[2c,d]}$  giving 13 in 63% yield as shown in Scheme 5. Attempts to further improve the yield by employing the second generation Grubbs' catalyst  $28^{[8]}$  failed and only 9% yield was obtained. Thus, the formal synthesis of halicholactone was accomplished in five steps in total up to 44.5% yield, much shorter than the 12 steps reported in the literature.<sup>[2a]</sup> The <sup>13</sup>C and <sup>1</sup>H NMR spectra of 13 were consistent with those reported by Wills et al.<sup>[2a]</sup>



Scheme 5. RCM reaction of 15 to give 13.

Following Wills' protocol, the transformation of **13** to aldehyde **29** was accomplished in a total 61% yield for four steps.<sup>[2a]</sup> This process involved the saponification of **13** into the corresponding carboxylic acid, followed by treatment of the acid with methyl chloroformate in the presence of triethylamine. After removal of triethylamine hydrochloride by filtration, the mixed anhydride was reduced with sodium borohydride affording a primary alcohol. Aldehyde **29** was obtained by oxidation of the alcohol with Dess-Martin periodinane (DMP)<sup>[9]</sup> (Scheme 6).



Scheme 6. Synthesis of aldehyde 29.

Since the diastereoselectivity of the coupling reaction of aldehyde **30** with (3S)-(1E,5Z)-3-O-[(*tert*-butyldiphenylsily])-oxy]-1-iodo-1,5-octadiene was poor (nearly 1:2) in the Wills' synthesis,<sup>[2a]</sup> we tried to improve the selectivity by asymmetric addition of alkyne **14** with aldehyde **29**, followed by reduction reaction of the carbon–carbon triple bond as shown in Scheme 7. Unfortunately, the enantioselective alkynylation of aldehyde **29** catalyzed by a chiral amino alcoholbased ligand,<sup>[10]</sup> developed by Jiang, did not work probably due to the steric hindrance of the cyclopropane moiety. It was found that the coupling reaction of aldehyde **29** with the lithium salt of alkyne **14** proceeded readily, affording alkynol **30** in good yields with a diastereomeric ratio of 2.6 to 1 (Scheme 7), in which the major one is the desired product. The transformation of **30** to **31** was accomplished by a Cr<sup>II</sup>-



Scheme 7. Total synthesis of halicholactone.

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promoted reduction<sup>[11]</sup> and the desired isomer **31a** was isolated easily by column chromatography on silica gel. TBAFmediated deprotection of the TBDPS group afforded halicholactone **1** in 97% yield.

In summary, an enantioselective ylide cyclopropanation has allowed facile access to the main fragment of halicholactone, **13**, with excellent enantioselectivity and diastereoselectivity in five steps, making the synthesis much more practical than those previously reported in the literature. Thus, a total synthesis of halicholactone has been accomplished in 11.2% overall yield, providing the shortest synthetic route thus far.

#### **Experimental Section**

Cyclopropanation of tert-butyl acrylate: To a stirred suspension of sulfonium salt 20 (3.5 g, 9.0 mmol) and tert-butyl acrylate (5.8 g, 45 mmol) in THF (150 mL) at -78°C was added tBuOK (3.0 g, 27 mmol) in seven portions over 2 h. After stirring for 4 h at -78°C, the reaction mixture was passed through a short silica gel column, which was eluted with ethyl acetate. After concentration of the combined elution, the residue was purified by flash column chromatography on silica gel (petroleum ether/ EtOAc 50:1). Yield: 1.5 g (70%); 97% ee. When 0.9 g of salt 20 was used (THF, 100 mL), 0.35 g (76%, 97% ee) of the product was obtained. The ee cannot be determined by chiral HPLC and was determined based on the *ee* of **18**.  $[\alpha]_{D}^{20} = -157.1$  (*c*=1.00, CHCl<sub>3</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>/TMS):  $\delta$  = 5.78 (dd, J=0.4, 18.4 Hz, 1 H), 5.49 (dd, J=8.4, 18.4 Hz, 1H), 2.00-1.94 (m, 1H), 1.60-1.56 (m, 1H), 1.44 (s, 9H), 1.32-1.27 (m, 1H), 0.94-0.87 (m, 1H), 0.03 ppm (s, 9H); 13C NMR (100 MHz,  $CDCl_3$ :  $\delta = 172.4, 146.1, 129.7, 80.3, 28.1, 27.5, 23.2, 15.6, -1.3 ppm; IR$ (film):  $\tilde{\nu} = 3452$  (w), 3074 (w), 2955 (m), 2911(s), 1723 (s), 1634 (m), 1461 (w), 1353 (m), 1246 (w), 910 (m), 792 cm<sup>-1</sup> (s); MS (EI): *m/z* (%): 240 (1.35)  $[M^+]$ , 75 (100.00); HRMS (EI): m/z: calcd for C<sub>13</sub>H<sub>24</sub>O<sub>2</sub>Si: 240.1546, found: 240.1556 [M<sup>+</sup>].

RCM reaction for the synthesis of compound 13: A solution of 15 (154 mg, 0.5 mmol) and freshly distilled [Ti(OiPr)4] (43 mg, 0.15 mol) in dry CH<sub>2</sub>Cl<sub>2</sub> (500 mL) was refluxed for 1.5 h under an nitrogen atmosphere. After the addition of first generation Grubbs' catalyst (123 mg, 0.15 mol), the resulting solution was refluxed for 60 h. The mixture was cooled to room temperature and then exposed to air with stirring for 4 h. Silica gel (ca. 2 g) was added and the resulting mixture was stirred at room temperature for 1 h, passed through a short silica gel column, which was eluted with ethyl acetate. After concentration of the elution, the residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc 15:1). Yield: 88 mg (63%);  $[a]_{D}^{20} = -87.7$  (c = 1.20, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>/TMS):  $\delta = 5.49-5.45$  (m, 2 H), 4.27 (ddd, J=1.6, 7.2, 10.8 Hz, 1 H), 2.55-2.46 (m, 2 H), 2.37-2.29 (m, 1H), 2.27-2.23 (m, 1H), 2.18-2.13 (m, 1H), 2.09-2.04 (m, 2H), 1.82-1.72 (m, 1H), 1.67-1.60 (m, 2H), 1.45 (s, 9H), 1.18-1.13 (m, 1H), 0.86-0.81 ppm (m, 1 H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta = 174.0, 172.6, 134.8,$ 124.3, 80.4, 74.6, 33.7, 33.5, 28.1, 26.4, 25.2, 24.5, 19.5, 12.5 ppm; IR (film):  $\tilde{\nu} = 3081$  (w), 2978 (m), 2919 (m),1719 (s), 1638 (w), 1457 (w), 1368 (m), 1151 (s), 1087 (w), 999 (w), 917 (m), 803 cm<sup>-1</sup> (m); MS (ESI): m/z (%): 303.1 [M<sup>+</sup>+Na]; HRMS (EI): m/z: calcd for C<sub>16</sub>H<sub>24</sub>O<sub>4</sub>: 280.1675, found: 280.1674 [M<sup>+</sup>].

Halicholactone (1): To a solution of 31a (40 mg, 0.07 mmol) in THF (2 mL) was added TBAF (66 mg, 0.21 mmol). The solution was refluxed for 3 h, concentrated and the residue was purified by chromatography on silica gel (petroleum ether/EtOAc 10:3) to give the product 1 as colorless oil (22 mg, 97%).  $[\alpha]_D^{20} = -94.7$  (c=0.61, CHCl<sub>3</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>/TMS):  $\delta$ =5.80-5.71 (m, 2H), 5.51-5.43 (m, 2H), 4.22 (ddd, J= 1.6, 8.4, 10.8 Hz, 1H), 4.11 (q, J=6.4 Hz, 1H), 3.69 (dd, J=4.0, 7.6 Hz, 1H), 2.53-2.43 (m, 2H), 2.33-2.22 (m, 2H), 2.17-2.12 (m, 1H), 2.10-2.02 (m, 2H), 1.83-1.72 (m, 3H), 1.56-1.46 (m, 2H), 1.43-1.30 (m, 6H), 1.13-

1.08 (m, 1H), 1.06–1.00 (m, 1H), 0.89 (t, J=7.2 Hz, 3H), 0.71 (ddd, J= 5.6, 5.6, 8.8 Hz, 1H), 0.60 ppm (ddd J=5.2, 5.2, 8.4 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 174.1, 134.6, 133.9, 131.6, 124.6, 76.2, 74.1, 72.2, 37.2, 33.8, 33.5, 31.7, 26.4, 25.2, 25.0, 23.4, 22.5, 19.4, 14.0, 8.2 ppm; IR (film):  $\tilde{\nu}$  = 3410 (br), 2928 (s), 2857 (s), 1738 (s), 1712 cm<sup>-1</sup> (s); MS (ESI): m/z: 359.1 [M+Na<sup>+</sup>]; HRMS (ESI): m/z: calcd for C<sub>20</sub>H<sub>32</sub>O<sub>4</sub>Na: 359.2206, found: 359.2193 [M+Na<sup>+</sup>].

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- a) H. Niwa, K. Wakamatsu, K. Yamada, *Tetrahedron Lett.* **1989**, *30*, 4543–4546; b) D. G. Nagle, W. H. Gerwick, *Tetrahedron Lett.* **1990**, *31*, 2995–2998; c) D. G. Nagle, W. H. Gerwick, *J. Org. Chem.* **1994**, *59*, 7227–7237; d) Y. Seo, K. W. Cho, J.-R. Rho, J. Shin, B.-M. Kwon, S.-H. Bok, J.-I. Song, *Tetrahedron* **1996**, *52*, 10583–10596. For structure revision of solandelactone E, F: J. E. Davoren, S. F. Martin, *J. Am. Chem. Soc.* **2007**, *129*, 510–511.
- [2] a) D. J. Critcher, S. Connolly, M. Wills, J. Org. Chem. 1997, 62, 6638–6657; b) D. K. Mohapatra, A. Datta, J. Org. Chem. 1998, 63, 642–646; c) Y. Baba, G. Saha, S. Nakao, C. Iwata, T. Tanaka, T. Ibuka, H. Ohishi, Y. Takemoto, J. Org. Chem. 2001, 66, 81–88; d) T. Takahashi, H. Watanabe, T. Kitahara, *Heterocycles* 2002, 58, 99–104; e) D. K. Mohapatra, K. A. Durugkar, ARKIVOC 2004, 146–155.
- [3] For reviews: a) Y. Tang, S. Ye, X.-L. Sun, Synlett 2005, 2720–2730;
  b) X.-L. Sun, Y. Tang, Acc. Chem. Res. 2008, 41, 937–948. For recent examples: c) S. Ye, Z.-Z. Huang, C.-A. Xia, Y. Tang, L.-X. Dai, J. Am. Chem. Soc. 2002, 124, 2432–2433; d) W.-W. Liao, K. Li, Y. Tang, J. Am. Chem. Soc. 2003, 125, 13030–13031; e) X.-M. Deng, P. Cai, S. Ye, X.-L. Sun, W.-W. Liao, K. Li, Y. Tang, Y.-D. Wu, L.-X. Dai, J. Am. Chem. Soc. 2006, 128, 9730–9740; f) L.-W. Ye, X.-L. Sun, Q.-G. Wang, Y. Tang, Angew. Chem. 2007, 119, 6055–6058; Angew. Chem. Int. Ed. 2007, 46, 5951–5954; g) Q.-G. Wang, X.-M. Deng, B.-H. Zhu, L.-W. Ye, X.-L. Sun, Y. Tang, J. Am. Chem. Soc. 2008, 130, 5408–5409.
- [4] W. R. Roush, K. Ando, L. K. Hoong, J. Am. Chem. Soc. 1985, 107, 8186–8190.
- [5] P. Barbier, C. R. Acad. Sci. 1899, 110.
- [6] O. Mitsunobu, M. Yamada, Bull. Chem. Soc. Jpn. 1967, 40, 2380– 2382.
- [7] a) G. C. Fu, R. H. Grubbs, J. Am. Chem. Soc. 1992, 114, 5426-5427;
   b) G. C. Fu, R. H. Grubbs, J. Am. Chem. Soc. 1992, 114, 7324-7325;
   c) R. H. Grubbs, J. S. Miller, G. C. Fu, Acc. Chem. Res. 1995, 28, 446-452.
- [8] M. Scholl, S. Ding, C. W. Lee, R. H. Grubbs, Org. Lett. 1999, 1, 953– 956.
- [9] a) D. B. Dess, J. C. Martin, J. Org. Chem. 1983, 48, 4155-4156.
- [10] B. Jiang, Z. Chen, W. Xiong, Chem. Commun. 2002, 1524-1525.
- [11] a) C. E. Castro, R. D. Stephen, J. Am. Chem. Soc. 1964, 86, 4358– 4363; b) D. Brillon, D. Deslongchamps, Can. J. Chem. 1987, 65, 56– 68.

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