CHEMISTRY
A EUROPEAN JOURNAL

ChemPubSoc
Europe

DOI: 10.1002/chem.201200647

C_3-Symmetric Trisimidazoline-Catalyzed Enantioselective Bromolactonization of Internal Alkenoic Acids

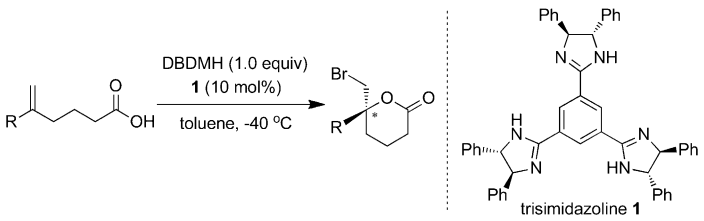
Kenichi Murai, Akira Nakamura, Tomoyo Matsushita, Masato Shimura, and Hiromichi Fujioka*[a]

Abstract: A method for conducting enantioselective bromolactonization reactions of trisubstituted alkenoic acids, using the C_3-symmetric trisimidazoline **1** and 1,3-dibromo-5,5-dimethyl hydantoin as a bromine source, has been developed. The process generates chiral δ-lactones that contain a quaternary carbon. The results of studies probing geometrically different olefins show that (*Z*)-olefins rather than (*E*)-olefins are favorable substrates for the process. The method is not only applicable to acyclic olefin reactants but can also be employed to transform cyclic trisubstituted olefins into chiral spirocyclic lactones. Finally, the synthetic utility of the newly developed process is demonstrated by its application to a concise synthesis of tanikolide, an antifungal marine natural product.

Keywords: alkenes · asymmetric synthesis · lactones · organocatalysis · spiro compounds

Introduction

Halolactonization is an important transformation in synthetic organic chemistry owing to the fact that it is utilized to prepare synthetically useful halolactones,[1] which can be employed as key intermediates in a number of different transformations. Recently, several enantioselective halolactonization reactions using organocatalysts have been described.[2–4] For example, Borhan and co-workers developed an enantioselective chlorolactonization reaction of 4-substituted-4-pentenoic acids that employs hydroquinidine 1,4-phthalazinediyl diether ($(DHQD)_2PHAL$) as the catalyst.[3a,b] A method for enantioselective bromolactonization of conjugated (*Z*)-enynes, using a bifunctional catalyst comprised of a cinchona alkaloid bearing a urea moiety, was also described by Tang and co-workers.[3c] A tertiary amino-urea catalyzed enantioselective iodolactonization reaction and an amino thiocarbamate catalyzed bromolactonization process have also been devised by Jacobsen[3d] and Yeung,[3e,f] respectively. We have also designed an enantioselective bromolactonization method (Scheme 1)[5] that is promoted by the structurally unique, C_3-symmetric trisimidazoline **1**, developed in our earlier efforts.[6] By using this catalyst, asymmetric reactions of 5-substituted-5-hexenoic acids take place to give δ-lactones containing a quaternary carbon center.



Scheme 1. Trisimidazoline **1** catalyzed bromolactonization.

Although several useful methods have been developed previously to carry out enantioselective halolactonization reactions, all of them are limited by the restricted range of reactant olefins. For example, 1,1-disubstituted olefins were commonly employed as substrates to demonstrate the applicability of the developed methods (Figure 1).[3a,d,e,5] Thus

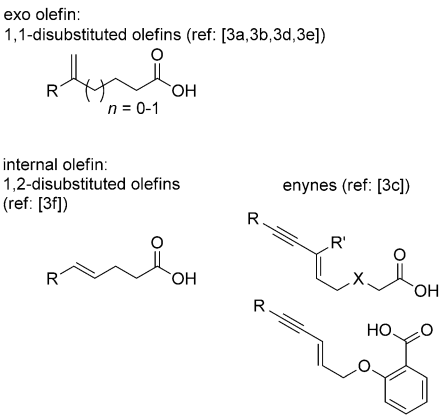


Figure 1. Substrates for asymmetric halolactonization used in previous works.

[a] Dr. K. Murai, A. Nakamura, T. Matsushita, M. Shimura, Prof. Dr. H. Fujioka
Graduate School of Pharmaceutical Sciences
Osaka University
1-6, Yamada-oka, Suita
Osaka, 565-0871 (Japan)
Fax: (+81) 6-6879-8229
E-mail: fujioka@phs.osaka-u.ac.jp

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201200647.

far, among the wide range of other olefins, only conjugated (*Z*)-enynes[3b] and 1,2-disubstituted olefins[3e] have been employed as substrates for enantioselective bromolactonization reactions. In contrast, the reactivity profiles of internal olefins have not been fully investigated, even though an expansion of substrate scope would have a significant impact on the applications of the halolactonization procedures in synthetic organic chemistry.[7]

Here, we describe the results of recent studies carried out to explore asymmetric bromolactonization reactions of 1,1,2-trisubstituted olefins promoted by trisimidazoline **1** (Figure 2). The observations made in this effort demonstrate that acyclic and cyclic olefins in this group undergo this process efficiently to generate bromolactones with high levels of enantioselectivity. We have also demonstrated the utility of this method by its application in a concise synthesis of tanikolide, a natural product that incorporates a δ-lactone ring system with a quaternary carbon.

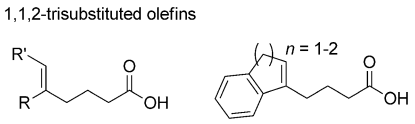
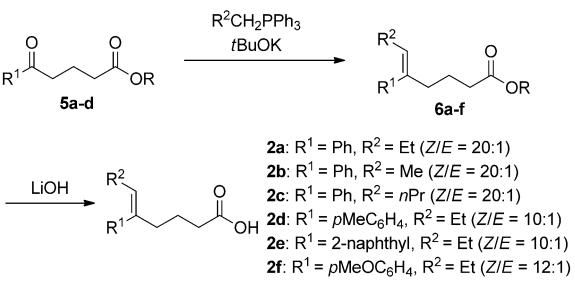


Figure 2. Substrates for asymmetric halolactonization used in this work.

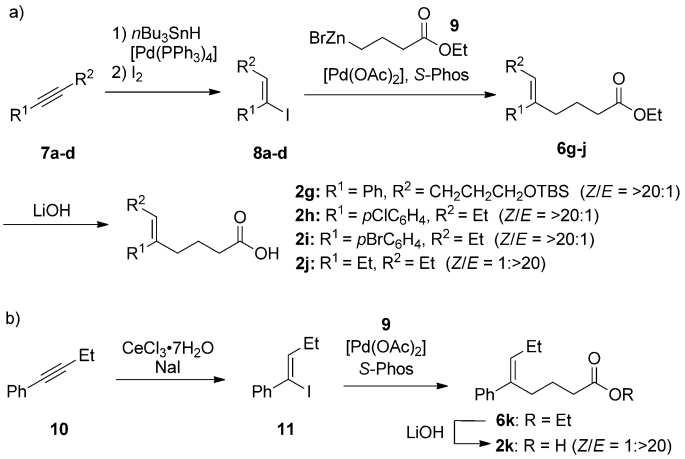
Results and Discussion

Synthesis of substituted ene-carboxylic acids: The scope of the enantioselective bromolactonization reactions was explored by using various substituted alkenoic acids, such as **2a–k** containing tri-substituted alkene moieties, a tetrasubstituted olefin **3**, and substrates **4a–c** bearing cyclic alkene functionality. (*Z*)-Alkenoic acids **2a–f** were readily prepared for this purpose in a stereoselective manner by utilizing low temperature Wittig olefination reactions of the corresponding δ-keto esters **5a–d** followed by hydrolysis of the derived esters **6a–f** (Scheme 2).

Unfortunately, it was not possible to synthesize alkenoic acids **2g–j** using this route because the stereoselectivities of the Wittig olefination reactions were not sufficiently high and chromatographic separation of the resulting stereoisomers was difficult. In another approach to the synthesis of **2g–j** (Scheme 3), the olefinic esters **6g–j** were prepared by a sequence starting with hydrostannation of the corresponding alkynes **7** with nBu$_3$SnH in the presence of a catalytic amount of [Pd(PPh$_3$)$_4$] followed by iodination to form (*E*)-iodo-olefins **8a–d** with high levels of stereoselectivity.[8] Negishi coupling reactions of **8a–d** with the commercially available zinc reagent **9** were found to produce esters **6g–j** in good yields.[9,10] (*E*)-Alkenoic acid **2k** was prepared in a similar manner from (*Z*)-iodo-olefin **11**. Thus, treatment of 1-phenyl-1-butyne (**10**) with NaI and CeCl$_3$ produced (*Z*)-iodo-olefin **11** with a moderate degree of regioselectivity.[11] Purification by using column chromatography gave (*Z*)-iodo-olefin **11** as a single stereoisomer in 50% yield. Negishi coupling reaction with **9** followed by hydrolysis gave the corresponding (*E*)-alkenoic acid **2k**.

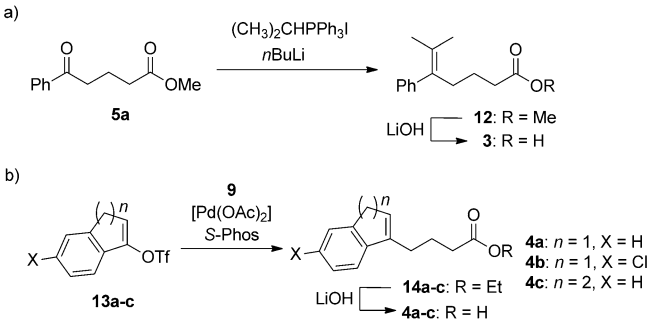


Scheme 2. Preparation of alkenoic acids **2a–f**.



Scheme 3. Preparation of alkenoic acids **2g–k**.

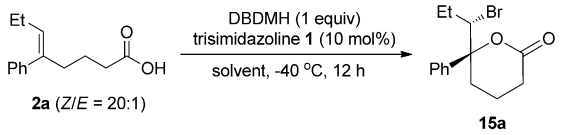
The tetrasubstituted alkenoic acid **3** was prepared by using the Wittig olefination reaction of ketoester **5a** with $(CH_3)_2CHPPh_3I$. Finally, cyclic alkenoic acids **4a–c** were prepared by employing Pd-promoted coupling reactions between **9** and the corresponding triflates **13a–c** (Scheme 4).



Scheme 4. Preparation of alkenoic acids **3** and **4a–c**.

Screening of reaction conditions: Initial studies to explore the new asymmetric bromolactonization reaction of internal olefins were conducted with (*Z*)-alkenoic acid **2a** (Table 1).

Table 1. Solvent effects.[a]



Entry	Solvent	Yield [%]	*ee* [%][b]
1	toluene	92	88
2	toluene/hexane = 2:1	34	75
3	CH_2Cl_2/cyclohexane = 1:2	81	64
4	$CHCl_3$/hexane = 1:3	89	58
5	THF/hexane = 1:3	53	12
6	xylene	99	84
7	TBME	64	44
8	iPr_2O	31	42

[a] Reagents and conditions: **2a** (1 equiv), DBDMH (1 equiv), **1** (10 mol%), solvent (0.05 M), 12 h. [b] Determined by HPLC; the *ee* value of the major diastereomer is shown.

Under the previously developed conditions used for *exo*-olefins, **2a** reacted in the presence of 1,3-dibromo-5,5-dimethyl hydantoin (DBDMH) and a catalytic amount of trisimidazoline **1** in toluene at −40 °C to form the desired bromolactone **15a** in 92% yield with an enantiomeric excess (*ee*) of 88%.[12,13] Various solvent systems were explored in an effort to improve the enantioselectivity of the process. We had previously observed that, among several other solvents, including dichloromethane (CH_2Cl_2), chloroform ($CHCl_3$), and tetrahydrofuran (THF), reactions in the less polar solvent toluene proceeded with the highest efficiencies. Reactions in varying polarity mixed solvent systems comprised of toluene, CH_2Cl_2, $CHCl_3$, and THF along with hexane or cyclohexane were observed to take place with low enantioselectivities, perhaps because of the low solubilities of **1** and DBDMH (Table 1, entries 2–5). The reaction in xylene displayed comparable, but slightly lower, selectivity (Table 1, entry 6), and processes in less polar ethereal solvents, such as *tert*-butyl methyl ether (TBME) or iPr_2O, did not occur with improved levels of asymmetric induction (Table 1, entries 7 and 8).

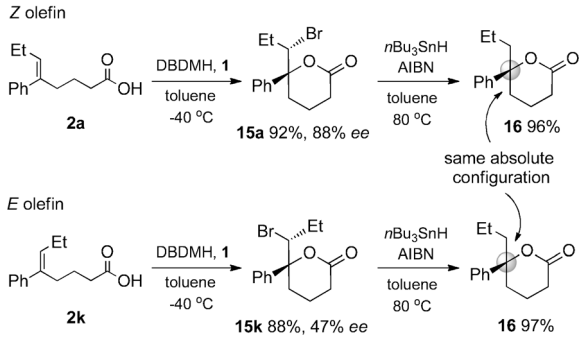
The effect of the bromine source was also investigated by using several commercially available reagents (Table 2, entries 2–5). In our previous study on bromolactonization reactions of exo alkenoic acids, reactions promoted by *N*-bromosuccinimide (NBS) were observed to display comparable efficiencies to those induced by DBDMH. However, NBS was not a suitable reagent for reactions of internal olefins owing to its low reactivity with members of this family of alkenes (Table 2, entry 2). Other bromine sources, such as *N*-bromophthalimide (NBP), *N*-bromoacetamide (NBA), and *N*,*N*′-dibromoisocyanuric acid (DBI)[14] were found to promote the bromolactonization reaction, however, lower levels of enantioselectivity were observed. Although $NsNH_2$[3e] and AcOH[3a] have been used as additives in other asymmetric halolactonizations, these substances had no effect on the current process (Table 2, entries 6 and 7). The combined results show that the conditions used for the reaction described in Table 2, entry 1, which are the same as those employed for exo olefins, are optimal for bromolactonization reactions of internal olefins.

Table 2. Effect of bromine sources and additives.[a]

Entry	Br^+ source	Additive	Yield [%]	*ee* [%][b]
1	DBDMH	none	92	88
2	NBS	none	5	60
3	NBP	none	77	49
4	NBA	none	59	28
5	DBI	none	93	83
6	DBDMH	$NsNH_2$	90	64
7	DBDMH	AcOH	17	31

[a] Reagents and conditions: **2a** (1 equiv), Br^+ source (1 equiv), **1** (10 mol%), additive (1 equiv), toluene (0.05 M), −40 °C, 12 h. [b] Determined by HPLC; the *ee* value of the major diastereomer is shown.

Effect of olefin geometry: The geometry of olefin substrates for the bromolactonization reactions could significantly affect selectivity. Consequently, to probe this issue, bromolactonization reactions of (*Z*)-alkenoic acid **2a** and (*E*)-alkenoic acid **2k** were explored (Scheme 5). As described above,



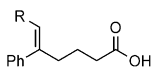
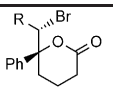
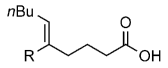
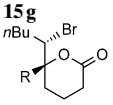
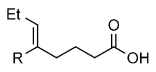
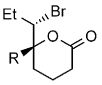
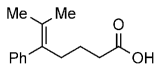
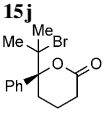
Scheme 5. Effect of geometry.

2a reacted with a high level of enantioselectivity under the optimal reaction conditions. On the other hand, the (*E*)-alkenoic acid **2k** was observed to undergo the bromolactonization reaction to afford the bromolactone **15k** with only 48% *ee* under these conditions.[13] This observation suggests that (*Z*)-olefins are preferable substrates for asymmetric bromolactonization reactions promoted by trisimidazoline **1**.

We were interested in gaining information on the stereochemistry of the quaternary carbon in bromolactones **15a** and **15k**. For this purpose, the bromine atoms in these compounds were removed under radical reduction conditions with nBu_3SnH and AIBN. Reductions of both **15a** and **15k** were observed to afford preferentially the same lactone **16**. The results indicate that bromolactone formation selectively occurs on the same face of the alkene, regardless of its geometry. The absolute facial selectivity of these processes was determined from observations made in the tanikolide synthesis described below.

Generality of asymmetric bromolactonization: The scope of the bromolactonization reaction was investigated by utilizing various (*Z*)-trisubstituted alkenoic acids. The results show that the steric bulk of the alkene substituents does not greatly influence either the reactivity or enantioselectivity (Table 3, entries 1–3). Moreover, olefinic acid **2g**, having an alkyl side chain bearing an OTBS moiety that can be used as a functional handle in further transformations, reacts smoothly to form the corresponding bromolactone, albeit with only a moderate degree of enantioselectivity (Table 3, entry 4). Substrates containing various aromatic rings were found to react smoothly under the optimal conditions, giving bromolactones with moderate to good enantioselectivities (Table 3, entries 5–8). However, substrate **2f**, possessing an electron-rich *p*-methoxybenzene group, reacted to give the corresponding bromolactone **15f** in racemic form (Table 3, entry 9).[15]

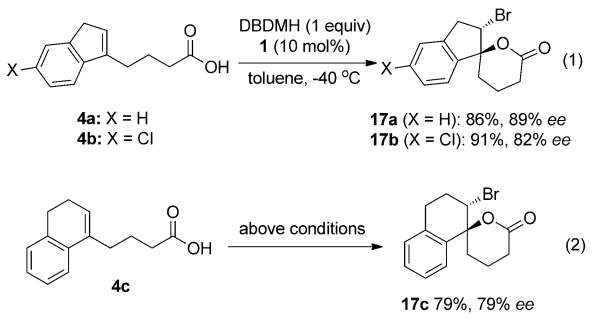
Table 3. Scope of the reaction.[a]

Entry	Substrate (*Z*/*E*)	Product	Yield [%]	*ee* [%][b]
				
1	**2a**: R = Et (20:1)	**15a**	92	88
2	**2b**: R = Me (20:1)	**15b**	89	89
3	**2c**: R = *n*Pr (20:1)	**15c**	93	87
4	**2g**: R = $(CH_2)_3$OTBS (>20:1)	**15g**	70	76
				
5	**2h**: R = *p*ClC_6H_4 (>20:1)	**15h**	99	90
6	**2i**: R = *p*BrC_6H_4 (>20:1)	**15i**	96	88
				
7	**2d**: R = *p*MeC_6H_4 (10:1)	**15d**	80	81
8	**2e**: R = 2-naphthyl (10:1)	**15e**	93	78
9	**2f**: R = *p*$MeOC_6H_4$ (12:1)	**15f**	64	0
10	**2j**: R = Et (1:>20)	**15j**	97	62
				
11	**3**	**15l**	85	65

[a] Reagents and conditions: alkenoic acid (1 equiv), DBDMH (1 equiv), **1** (10 mol%), toluene (0.05 M), −40 °C. [b] Determined by HPLC; the *ee* value of the major diastereomer is shown.

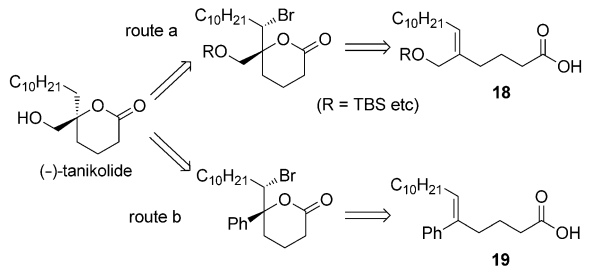
The presence of aromatic moieties on the olefin was found to play an important role in determining the enantioselectivities of the reaction, as shown by the decrease in the levels of enantioselectivity in reactions of nonaromatic ring substituted olefin substrates (Table 3, entry 10). Finally, bromolactonization also took place when the tetrasubstituted alkenoic acid **3** was used as the reactant (Table 3, entry 11), although the enantioselectivity of the process was only moderate. Importantly, to the best of our knowledge, this is the first example of a catalytic asymmetric halolactonization reaction of a tetrasubstituted olefinic acid.

Because they represent interesting synthetic targets,[16] the formation of chiral spirocyclic lactones utilizing the methodology described above was probed. For this effort, bromolactonization reactions of the *endo*-cyclic alkenoic acids **4a–c**, which have similar substitution patterns to (*Z*)-alkenoic acids, were explored. As expected, indene derivatives **4a** and **4b** underwent the reaction to give the respective spirocyclic lactones with high enantioselectivities (Scheme 6, Eq. (1)). Reactions of the *endo*-cyclic olefin within a lager ring system, dihydronaphthalene derivative **4c**, reacted with good enantioselectivity (Scheme 6, Eq. (2)). The results nicely demonstrate the preparative applicability of the bromolactonization process.



Scheme 6. Synthesis of spiro lactones.

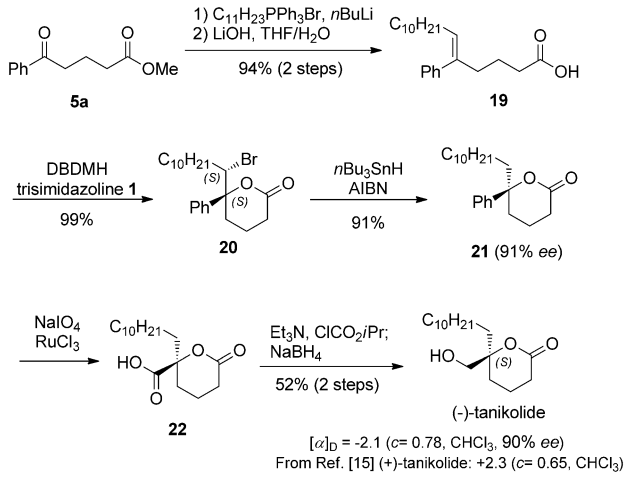
Total synthesis of tanikolide: To further demonstrate its preparative potential, the bromolactonization process was utilized as a key step in a concise route for the synthesis of tanikolide,[17,18] which is a metabolite of the cyanobacterium *Lyngbya majuscule*. In addition, this effort provided information about the absolute configuration of the chiral carbon formed in the bromolactone product. The synthetic strategy used to prepare tanikolide is given in Scheme 7. We envisaged that two asymmetric bromolactonization-based routes could be used to synthesize the quaternary carbon containing target. In one, olefin **18** bearing a protected hydroxymethyl group (CH_2OR with R = protecting group, such as TBS) would be subjected to bromolactonization (Route a)



Scheme 7. Possible synthetic routes.

to produce a bromolactone intermediate. However, because alkyl substituted olefins were found not to be appropriate substrates for the bromolactonization reaction, an alternative route employing the phenyl substituted alkenoic acid **19** as a key intermediate was selected for the synthesis of tanikolide (Route b).

The concise synthetic sequence used to prepare tanikolide is illustrated in Scheme 8. Initially, δ-keto-ester **5a** was transformed into the alkenoic acid **19** by using a Wittig ole-



Scheme 8. Total synthesis of tanikolide.

fination and base-mediated hydrolysis protocol. The mixture of geometric isomers of **19** ($Z/E = 20:1$) was subjected to asymmetric bromolactonization to give the bromolactone **20** in good yield. Radical reduction with nBu$_3$SnH and AIBN was used to remove the bromine to afford the corresponding lactone **21** in 91% yield. At this stage, the enantiomeric excess (*ee*) of lactone **21** was determined to be 90% (HPLC analysis). The final steps in the synthesis of tanikolide involved transformation of the phenyl into a hydoxymethyl group. Thus, the benzene moiety in **21** was oxidized to the corresponding carboxylic acid **22** by using $RuCl_3/NaIO_4$.[19] One-pot mixed anhydride formation with **22** and reduction using $NaBH_4$ led to generation of the alcohol moiety in the target tanikolide in 52% yield from **21**. The enantiomeric purity of tanikolide was determined from its benzoyl ester to be 90% *ee*, an observation that suggests that racemization does not occur in the last two steps of the synthetic route. Although the results of several studies focusing on the synthesis of tanikolide have already been reported, the alternative approach described here features a novel method to generate δ-lactones containing a quaternary carbon. In addition, this is the first strategy developed for synthesis of this natural product that relies on an asymmetric organocatalytic halolactonization reaction.

The optical rotation of natural tanikolide is reported to be positive and the absolute configuration of the quaternary carbon center in the natural product is known to be *R*. In contrast, the optical rotation of tanikolide, prepared by the route described above, is negative. This observation therefore shows that the absolute configuration of the quaternary carbon center in bromolactone **20** is *S*, a configuration that is in accord with those found in products of previously reported asymmetric bromolactonization reactions of exo olefins. Other bromolactones described in this manuscript were assigned the same configuration by analogy.

Conclusion

In the investigation described above, we have expanded trisimidazoline **1** catalyzed asymmetric bromolactonization reactions of alkenoic acids to include internal olefins as substrates. In particular, (*Z*)-olefins were found to be suitable substrates for these processes, giving products in high yields and with high levels of enantioselectivity. The applicability of the asymmetric bromolactonization process to the synthesis of chiral spirocyclic lactones was also demonstrated. Finally, a concise total synthesis of (−)-tanikolide was achieved by using the developed reaction as a key step. This constitutes, to the best of our knowledge, the first example of an organocatalytic asymmetric halolactonization reaction employed in natural product synthesis. We believe the methodology developed in this effort will serve as a valuable tool for the synthesis of a wide range of functionalized chiral lactone derivatives.

Experimental Section

Typical procedure for the bromolactonization; (*S*)-6-[(*S*)-1-Bromoprop-yl]-6-phenyltetrahydro-2*H*-pyran-2-one (15a): A solution of ene-carboxylic acid **2a** (66.6 mg, 0.305 mmol) and trisimidazoline **1** (22.3 mg, 0.0305 mmol) in toluene (6.1 mL) was stirred for 10 min at RT and the resulting solution was cooled to −40 °C. DBDMH (87.3 mg, 0.305 mmol) was then added in one portion to the solution and the reaction mixture was stirred at −40 °C for 12 h. Upon completion, the reaction was quenched with sat. aq. $Na_2S_2O_5$ at −40 °C, and the organic layer was extracted with EtOAc. The extracts were washed with brine, dried with Na_2SO_4, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexane/AcOEt = 2:1) to give **15a** (83.5 mg, 92%) as colorless oil; $[\alpha]_D^{19} = -4.09$ ($c = 0.92$, $CHCl_3$, 88% *ee*); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.49$–7.47 (m, 2H), 7.40–7.31 (m, 3H), 4.08 (dd, $J = 11.6$, 2.0 Hz, 1H), 2.73 (dt, $J = 14.8$, 4.0 Hz, 1H), 2.46–2.30 (m, 2H), 2.20 (ddd, $J = 17.2$, 12.8, 4.8 Hz, 1H), 1.98–1.94 (m, 1H), 1.88–1.80 (m, 1H), 1.65–1.59 (m, 1H), 1.30–1.21 (m, 1H), 0.96 ppm (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 170.4$, 138.3, 128.5, 128.4, 126.8, 87.8, 66.4, 29.4, 29.0, 25.9, 16.2, 12.9 ppm; IR (KBr): $\tilde{\nu} = 2968$, 1736, 1449, 1240, 1043 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{14}H_{17}BrO_2$: 297.0490 $[M+H]^+$; found: 297.0497; HPLC (DAICEL CHIRALCEL OJ; hexane/*i*PrOH = 92:8; flow rate = 1.0 mL min^{-1}; 210 nm): $R_t = 23.8$ (major), 29.7 min (minor).

Acknowledgements

This work was financially supported by Grant-in-Aid for Scientific Research (B) and for Young Scientists (B) from JSPS.

[1] For reviews, see: a) M. D. Dowle, D. I. Davies, *Chem. Soc. Rev.* **1979**, *8*, 171–179; b) S. Ranganathan, K. M. Muraleedharan, N. K. Vaish, N. Jayaraman, *Tetrahedron* **2004**, *60*, 5273–5308.

[2] For reviews, see: a) G. Chen, S. Ma, *Angew. Chem.* **2010**, *122*, 8484–8486; *Angew. Chem. Int. Ed.* **2010**, *49*, 8306–8308; b) A. Castellanos, S. P. Fletcher, *Chem. Eur. J.* **2011**, *17*, 5766–5776; c) C. K. Tan, L. Zhou, Y.-Y. Yeung, *Synlett* **2011**, 1335–1339; d) U. Hennecke, *Chem. Asian. J.* **2012**, *7*, 456–465.

[3] a) D. C. Whitehead, R. Yousefi, A. Jaganathan, B. Borhan, *J. Am. Chem. Soc.* **2010**, *132*, 3298–3300; b) R. Yousefi, D. C. Whitehead, J. M. Mueller, R. J. Staples, B. Borhan, *Org. Lett.* **2011**, *13*, 608–611; c) W. Zhang, S. Zheng, N. Liu, J. B. Werness, I. A. Guzei, W. Tang, *J. Am. Chem. Soc.* **2010**, *132*, 3664–3665; d) G. E. Veitch, E. N. Jacobsen, *Angew. Chem.* **2010**, *122*, 7490–7493; *Angew. Chem. Int. Ed.* **2010**, *49*, 7332–7335; e) L. Zhou, C. K. Tan, X. Jiang, F. Chen, Y.-Y. Yeung, *J. Am. Chem. Soc.* **2010**, *132*, 15474–15476; f) C. K. Tan, L. Zhou, Y.-Y. Yeung, *Org. Lett.* **2011**, *13*, 2738–2741.

[4] For related organocatalytic enantioselective halocyclizations, see: a) S. E. Denmark, M. T. Burk, *Org. Lett.* **2012**, *14*, 256–259; b) U. Hennecke, C. H. Muller, R. Frohlich, *Org. Lett.* **2011**, *13*, 860–863; c) D. Huang, H. Wang, F. Xue, H. Guan, L. Li, X. Peng, Y. Shi, *Org. Lett.* **2011**, *13*, 6350–6353; d) O. Lozano, G. Blessley, D. C. T. Martinez, A. L. Thompson, G. T. Giuffredi, M. Bettati, M. Walker, R. Borman, V. Gouverneur, *Angew. Chem.* **2011**, *123*, 8255–8259; *Angew. Chem. Int. Ed.* **2011**, *50*, 8105–8109; e) L. Zhou, J. Chen, C. K. Tan, Y.-Y. Yeung, *J. Am. Chem. Soc.* **2011**, *133*, 9164–9167; A. Jaganathan, A. Garzan, D. C. Whitehead, R. J. Staples, B. Borhan, *Angew. Chem.* **2011**, *123*, 2641–2644; *Angew. Chem. Int. Ed.* **2011**, *50*, 2593–2596.

[5] K. Murai, T. Matsushita, A. Nakamura, S. Fukushima, M. Shimura, H. Fujioka, *Angew. Chem.* **2010**, *122*, 9360–9363; *Angew. Chem. Int. Ed.* **2010**, *49*, 9174–9177.

[6] a) K. Murai, S. Fukushima, S. Hayashi, Y. Takahara, H. Fujioka, *Org. Lett.* **2010**, *12*, 964–966; b) K. Murai, S. Fukushima, A. Nakamura, M. Shimura, H. Fujioka, *Tetrahedron* **2011**, *67*, 4862–4868.

[7] During the preparation of this manuscript, a report on the asymmetric bromolactonization of styrene type carboxylic acids leading to 3,4-dihydroisocoumarin derivatives was reported, see: J. Chen, L. Zhou, C. K. Tan, Y.-Y. Yeung, *J. Org. Chem.* **2012**, *77*, 999–1009.

[8] G. Xu, T. L. Loftus, H. Wargo, J. A. Turpin, R. W. Buckheit, M. Cushman, *J. Org. Chem.* **2001**, *66*, 5958–5964.

[9] T. Zhang, X. Gao, H. B. Wood, *Tetrahedron Lett.* **2011**, *52*, 311–313.

[10] T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 4685–4696.

[11] G. Bartoli, R. Cipolletti, A. D. Giustino, R. Giovannini, S. Lanari, M. Marcolini, E. Marcantoni, *Org. Biomol. Chem.* **2010**, *8*, 3509–3517.

[12] Although the bromolactone was obtained as inseparable diastereomers when the starting alkenoic acid was an *Z*/*E* mixture, the *ee* value of the major diastereomer was unambiguously determined by HPLC analysis because each peak was separated.

[13] The relative stereochemistry was assigned by analogy to the *anti*-addition mechanism of general halolactonization.

[14] W. Gottardi, *Monatsh. Chem.* **1968**, *99*, 815–822.

[15] We observed ready racemization of the product.

[16] For examples, see: a) T. Dohi, A. Maruyama, N. Takenaga, K. Senami, Y. Minamitsuji, H. Fujioka, S. B. Caemmerer, Y. Kita, *Angew. Chem.* **2008**, *120*, 3847–3850; *Angew. Chem. Int. Ed.* **2008**, *47*, 3787–3790; b) F. Alonso, J. Melendez, M. Yus, *Synlett* **2008**, 1627–1630; c) V. C. Purohit, A. S. Matla, D. Romo, *J. Am. Chem. Soc.* **2008**, *130*, 10478–10479; d) V. Nair, S. Vellalath, M. Poonoth, R. Mohan, E. Suresh, *Org. Lett.* **2006**, *8*, 507–509; e) M.-C. P. Yeh, Y.-C. Lee, T.-C. Young, *Synthesis* **2006**, 3621–3624; f) T. Murakami, Y. Morikawa, M. Hashimoto, T. Okuno, Y. Harada, *Org. Lett.* **2003**, *6*, 157–160; g) M. Eipert, C. Maichle-Mössmer, M. E. Maier, *Tetrahedron* **2003**, *59*, 7949–7960.

[17] I. P. Singh, K. E. Milligan, W. H. Gerwick, *J. Nat. Prod.* **1999**, *62*, 1333–1335.

[18] For previous asymmetric total syntheses of tanikolide, see: a) R. M. Kanada, T. Taniguchi, K. Ogasawara, *Synlett* **2000**, 1019–1021; b) H. Tanaka, Y. Kozuki, K. Ogasawara, *Tetrahedron Lett.* **2002**, *43*, 4175–4178; c) H. Mizutani, M. Wantanake, T. Honda, *Tetrahedron* **2002**, *58*, 8929–8936; d) M. Carda, S. Rodriguez, E. Castillo, A. Bellido, S. D. Oltra, J. A. Marco, *Tetrahedron* **2003**, *59*, 857–864; e) A. E. Koumbis, K. M. Dieti, M. G. Vikentiou, J. K. Gallos, *Tetrahedron Lett.* **2003**, *44*, 2513–2516; f) J. M. Schomaker, B. Borhan, *Org. Biomol. Chem.* **2004**, *2*, 621–624; g) T. Ohgiya, S. Nishiyama, *Tetrahedron Lett.* **2004**, *45*, 8273–8275; h) H. Arasaki, M. Iwata, M. Makida, Y. Masaki, *Chem. Pharm. Bull.* **2004**, *52*, 848–852; i) Y. Kita, S. Matsuda, E. Fujii, M. Horai, K. Hata, H. Fujioka, *Angew. Chem.* **2005**, *117*, 6007–6010; *Angew. Chem. Int. Ed.* **2005**, *44*, 5857–5960; j) T. Ohgiya, K. Nakamura, S. Nishiyama, *Bull. Chem. Soc. Jpn.* **2005**, *78*, 1549–1554; k) F. Wu, R. Hong, J. Khan, X. Liu, L. Deng, *Angew. Chem.* **2006**, *118*, 4407–4411; *Angew. Chem. Int. Ed.* **2006**, *45*, 4301–4305; l) H. Fujioka, S. Matsuda, M. Horai, E. Fujii, M. Morishita, N. Nishiguchi, K. Hata, Y. Kita, *Chem. Eur. J.* **2007**, *13*, 5238–5248; m) P. Vichare, A. Chattopadhyay, *Tetrahedron: Asymmetry* **2008**, *19*, 598–602; n) B. Gourdet, H. W. Lam, *Angew. Chem.* **2010**, *122*, 8915–8919; *Angew. Chem. Int. Ed.* **2010**, *49*, 8733–8737; o) R. Doran, L. Duggan, S. Singh, C. D. Duffy, P. J. Guiry, *Eur. J. Org. Chem.* **2011**, 7097–7106.

[19] M. Date, Y. Tamai, T. Hattori, H. Takayama, Y. Kamikubo, S. Miyano, *J. Chem. Soc. Perkin Trans. 1* **2001**, 645–653.

Received: February 27, 2012
Published online: May 23, 2012

