Oxidation

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Enantiodifferentiating *endo*-Selective Oxylactonization of *ortho*-Alk-1-enylbenzoate with a Lactate-Derived Aryl-λ^3-Iodane**

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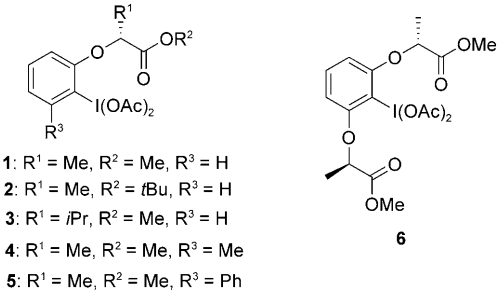
Ongoing efforts have been dedicated to the development of reaction processes controlled by chiral hypervalent iodine reagents with high enantioselectivity.[1–12] The oxidation of sulfides into sulfoxides,[2] the α-oxygenation of ketones,[3,4] the dioxygenation of alkenes,[4,5,12] and the dearomatization of phenols[6–8,9b] have been reported, and most of these reactions resulted in an encouraging level of enantioselectivity. Kita and co-workers reported dearomatizing spirolactonization of naphthols (78–86% *ee*) using a spirocyclic iodine(III) reagent.[6] Ishihara and co-workers recently reported that higher enantioselectivities were obtained for the spirolactonization by using a chiral iodine compound derived from lactic acid.[8]

Our studies with optically active hypervalent iodine compounds have been focused on mechanisms of the reaction concerned[11] as well as synthetic applications.[12] Asymmetric oxidation of 4-acyloxybut-1-ene into 3-acyloxytetrahydrofuran (up to 64% *ee*) was achieved by using chiral hypervalent iodine(III) reagents, **1** and **2**, which have a lactate moiety as a chiral source.[12] During the course of these studies for the asymmetric oxidative cyclization of alkenes, we found that oxidation of *ortho*-alk-1-enylbenzoate with the hypervalent iodine reagent regio- and diastereoselectively gave 3-alkyl-4-oxyisochroman-1-one in a practically useful degree of enantiomeric purity (90—98% *ee*); the isochromanone framework is a biologically relevant building block of natural products.[13,14] Herein, we report the synthetic utility of such enantiodifferentiating *endo*-selective oxylactonizations.

The series of optically active hypervalent iodine (III) reagents **1**–**6** employed in this report is shown in Scheme 1. On the basis of reagents **1** and **2** reported previously,[12] the structures of the iodine reagents were tuned for improved enantioselectivity. The X-ray crystallographic structures of **1**–**4** showed a typical T-shape orientation around the iodine center, where the two acetoxy ligands occupied apical positions (see the Supporting Information).



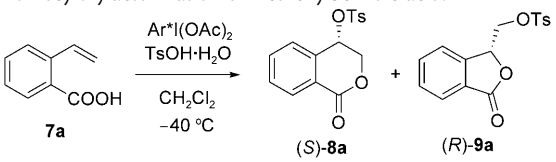
1: R^1 = Me, R^2 = Me, R^3 = H
2: R^1 = Me, R^2 = *t*Bu, R^3 = H
3: R^1 = *i*Pr, R^2 = Me, R^3 = H
4: R^1 = Me, R^2 = Me, R^3 = Me
5: R^1 = Me, R^2 = Me, R^3 = Ph

6

Scheme 1. Optically active hypervalent iodine(III) reagents.

2-Ethenylbenzoic acid (**7a**) was subjected to the reaction conditions with the optically active hypervalent iodine(III) reagent. The reaction was carried out in the presence of *para*-toluenesulfonic acid (TsOH) to activate the iodine reagent, and the tosylate also worked as a nucleophile to give lactones **8a** and **9a** (Table 1). The reaction proceeded regioselectively to give the δ-lactone product **8a** as the major product. The reaction with **6** gave a higher *ee* value of **8a** with high regioselectivity (Table 1, entry 5).

Table 1: Tosyloxylactonization of 2-ethenylbenzoic acid.[a]



7a (*S*)-**8a** (*R*)-**9a**

Entry	$Ar^*I(OAc)_2$	Yield [%] (**8a**/**9a**)	*ee* [%][b] (*S*)-**8a**	**9a**
1	**1**	66 (93:7)	75	18(*R*)
2	**2**	69 (96:4)	90	42(*R*)
3	**4**	70 (96:4)	76	22(*S*)
4	**5**	74 (86:14)	60	28(*S*)
5[c]	**6**	65 (95:5)	97	26(*S*)

[a] Reaction conditions are given in the Supporting Information. The acetoxylactonization product **10a** was detected in less than 10% yield. [b] The *ee* values were determined by HPLC analysis on a chiral stationary phase. [c] In order to estimate a change in *ee* value of the product owing to the crystallization for isolation, the crude mixture was analyzed before crystallization. The *ee* value of **8a** in the crude mixture was 97% and agreed with that in the isolated product.

It is remarkable that the oxylactonization proceeds with *endo* selectivity[15,16] in addition to the high enantioselectivity. For elucidation of the mechanism of the *endo* selectivity and its synthetic applications, we varied the nucleophile and the substrate in the oxylactonization. When boron trifluoride diethyl etherate was employed as an activator in the presence

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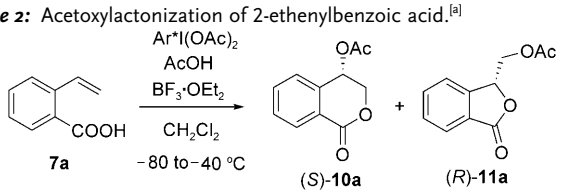
of acetic acid, an acetate group was introduced onto the enantioselective oxylactonization product (Table 2). The acetoxylactonization also preferentially gave δ-lactone **10a**. The enantioselectivity depended on the structure of the

Table 2: Acetoxylactonization of 2-ethenylbenzoic acid.[a]



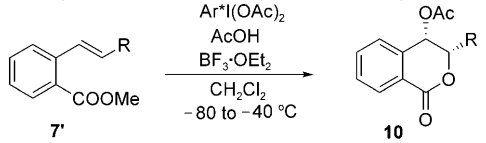
Entry	$Ar^*I(OAc)_2$	Yield [%] (**10a**/**11a**)	*ee* [%][b] (*S*)-**10a**	(*R*)-**11a**
1	**1**	73 (97:3)	82	51
2	**2**	57 (95:5)	83	54
3	**3**	75 (96:4)	86	78
4	**6**	68 (92:8)	88	72

[a] Reaction conditions are given in the Supporting Information. [b] The *ee* value was determined by GC analysis on a chiral stationary phase.

hypervalent iodine(III) reagent, and the trend in enantioselectivity was similar to that observed in the tosyloxylactonization. Although the *ee* value of **10a** was slightly lower than that of tosyloxy lactone **8a**, the *ee* value of the minor product (γ-lactone **11a**) was higher than that of **9a**. The reaction of methyl ester substrate **7′a** also gave acetoxylactonization products **10a** and **11a**, as shown in Table 3, entries 1–3.

Preferential formation of the δ-lactone **10b–d** was also observed for the reaction of the alkenyl substrates **7′b–d**

Table 3: Acetoxylactonization of methyl *ortho*-alk-1-enylbenzoate **7′**.[a]



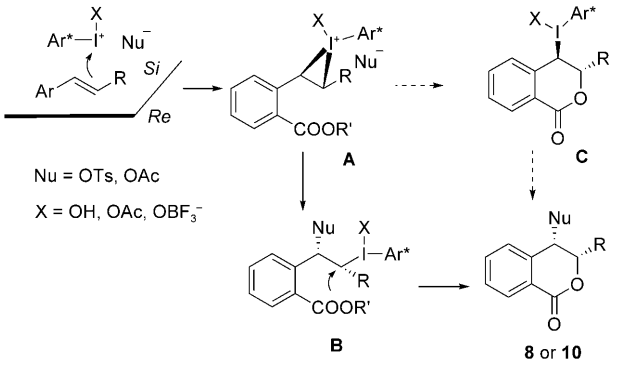
a: R = H, **b**: R = CH_2OMe, **c**: R = CH_2OH, **d**: R = nC_5H_{11}

Entry	R, Substrate		$Ar^*I(OAc)_2$	**10** Yield [%]	*ee* [%]
1	H	**7′a**	**1**	73	75[b]
2	H	**7′a**	**3**	64	84[b]
3	H	**7′a**	**6**	72	90[b]
4	CH_2OMe	**7′b**	**1**	80	84
5[c]	CH_2OMe	**7b**	**1**	84	84
6	CH_2OMe	**7′b**	**3**	62	97
7	CH_2OMe	**7′b**	**6**	60	97
8[c]	CH_2OMe	**7b**	**6**	84	96
9	CH_2OH	**7′c**	**1**	84	86
10	CH_2OH	**7′c**	**3**	80	94
11	CH_2OH	**7′c**	**6**	57	96
12	n-C_5H_{11}	**7′d**	**1**	63	90
13	n-C_5H_{11}	**7′d**	**3**	76	96

[a] Reaction conditions are given in the Supporting Information. Details of the minor isomers are shown in Table S3. [b] The *S* enantiomer was preferentially obtained. [c] 2-((*E*)-3-Methoxyprop-1-enyl)benzoic acid **7b** was used as the substrate.

(Table 3). An oxy functional group, such as methoxymethyl (**7′b**) and hydroxymethyl (**7′c**) groups in the alkenyl moiety hardly affected the yield of the δ-lactone product. The *cis* configuration of the product is consistent with the small coupling constant ($J < 2$ Hz) observed for the ^{1}H NMR signal owing to the benzylic proton, and was confirmed by X-ray crystallographic analysis of **10b** (for further details, see the Supporting Information). The reaction of these alkenyl substrates **7′b–d** gave higher enantioselectivity than that of the vinyl substrate **7′a**.

On the basis of the *syn* selectivity observed, a plausible reaction mechanism is proposed in Scheme 2. (Diacetoxyiodo)arene is activated by acid (TsOH or BF_3·OEt_2). Electro-



Scheme 2. Plausible pathway to explain the stereochemical outcome.

philic addition of the activated iodine(III) reagent to the alkene may be followed by nucleophilic displacement with inversion of configuration. Alkyl-λ^3-iodane **B** or **C** undergoes a second nucleophilic displacement with inversion of configuration. These two consecutive substitution steps proceed with inversion of configuration, and result in the *syn* selectivity. The initial nucleophilic substitution would then take place at the benzylic position, where a positive charge may be localized, and then the intermediate **B** is generated. The counteranion of intermediate **A** may act as the initial nucleophile, judging from the effective formation of tosyloxy product **8a** despite the presence of a highly nucleophilic acetate (Table 1). The ensuing participation of the internal carboxylate (carboxylic acid) leads to the departure of the aryliodonio group. Preferential formation of the δ-lactone is rationalized by the reaction pathway **A**→**B**→**8**/**10**.[17] The δ-lactone could also be generated via intermediate **C**. The reaction pathway via **C** is unlikely because reactions of **7a** and **7′a** gave similar regioselectivity independent of the nucelophilicity of the internal carboxylic acid and carboxylate. If the reaction proceeded via **C**, the stereochemical purity of the product would have decreased owing to facial elimination of aryliodonio group at the benzyl position of the intermediate **C** (S_N1).[18]

The reaction of 2-ethenylbenzoic acid **7a** with **1–6** preferentially gave (*S*)-**8a** and (*S*)-**10a** rather than the (*R*)-isomers. For the reaction of *ortho*-alkenylbenzoate, the (3*S*,4*S*)-isomer was obtained under stereocontrol of these enantiopure hypervalent iodine(III) reagents, as shown in

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synthesis of a natural product **13** (see below). According to the mechanism in Scheme 2, these hypervalent iodine reagents must attack the *si* face of the alkene substrate.[17] Similar facial selectivity was observed for tetrahydrofuranylation of 4-acyloxybutenes.[12] The high facial selectivity of these hypervalent iodine reagents suggests that the iodine atom of reactive site of **1**–**6** may be strongly affected by chirality of the lactate moiety.

To understand structural characteristics of the optically active hypervalent iodine reagent in solution,[19] solvated clusters of cationic iodonium generated from the reagent was analyzed using specially designed mass spectrometry.[20] Electrospray ionization mass spectra of (diacetoxyiodo)arenes were measured in aqueous acetonitrile solution containing trifluoroacetic acid (Figure 1). In all of these cases, an *m*/*z*

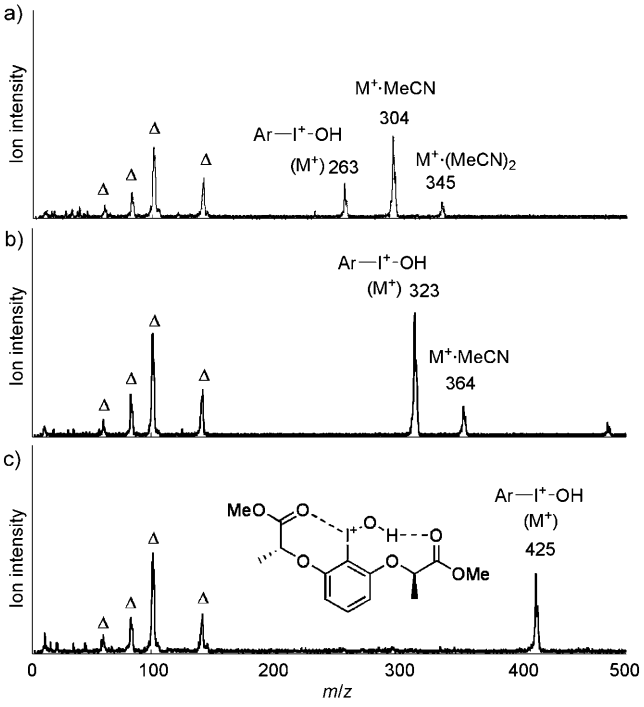
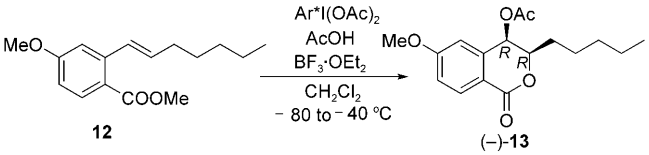


Figure 1. Electrospray ionization mass spectra of a) 1-(diacetoxyiodo)-2,4,6-trimethylbenzene, b) **1**, and c) **6** in 0.5 %(v/v)water-99.5 %(v/v)acetonitrile solution containing trifluoroacetic acid (16 mM). The peaks marked with Δ represent clusters composed of acetonitrile and water molecules. Peaks at *m*/*z* = 60, 83, 101, and 142 correspond to H_3O^+·MeCN, H^+·$(MeCN)_2$, H_3O^+·$(MeCN)_2$, and H_3O^+·$(MeCN)_3$, respectively.

signal corresponding to the aryl(hydroxy)iodonium ion, $M^+ = ArI^+(OH)$, was observed together with H_3O^+·$(MeCN)_n$ (n = 1, 2, 3) in the range $m/z < 150$. The iodonium ion, solvated by acetonitrile, M^+·$(MeCN)_n$ (n = 1, 2), was observed for 1-(diacetoxyiodo)-2,4,6-trimethylbenzene, which has no oxy-substituent on the aryl group (Figure 1 a): one or two molecules of the solvent coordinate to the iodonium. In contrast, the solvation of iodonium by acetonitrile was hardly observed for **6**, which was doubly functionalized by lactate side-chains (Figure 1 c). For the mono-functionalized reagent **1** (Figure 1 b), no signal owing to M^+·$(MeCN)_2$ was detected, and a small signal owing to M^+·MeCN was observed: only one molecule of the solvent coordinates to the iodonium species. That is, the 1-(methoxycarbonyl)ethoxy side-chain of **1** and **6** prevents acetonitrile molecules from interacting with a cationic site of the iodonium.[21] These experimental results strongly suggest that the internal lactate side chain interacts with the hypervalent iodine moiety even in solution: the most reasonable structure is illustrated in Figure 1 c. Such interaction must control the enantiodifferentiating ability of the hypervalent iodine **1**–**6**.

The utility of this enantioselective oxylactonization was demonstrated by its application to the crucial step of a concise asymmetric synthesis of a biologically active compound (−)-**13**, which was recently isolated from *Xyris pterygoblephara* and found to act as a selective inhibitor of aromatase (Scheme 3).[13a,b] The substrate **12** for asymmetric lactoniza-



Scheme 3. Total synthesis of a biologically active natural product **13**.

tion was prepared in 74 % yield by a Suzuki coupling reaction with (*E*)-hept-1-enylboronic acid. The reaction of **12** with **3** gave the antipodal enantiomer of the natural product (−)-**13** ((3*S*,4*S*)-(+)-**13**) in 64 % yield and 98 % *ee*. The desired enantiomer of the natural product, (3*R*,4*R*)-(−)-**13**, was obtained by using the enantiomer of **1** (*ent*-**1**) and isolated in 73 % yield with 95 % *ee*.

In conclusion, we have developed an efficient route to optically active 4-oxyisochroman-1-one through oxidative lactonization of *ortho*-alkenylbenzoate by using lactate-derived aryl-λ^3-iodane **1**–**6**. The oxylactonization proceeds *endo*-selectively to give the δ-lactone. The stereocontrolled transformation was applied to asymmetric synthesis of a biologically active natural product. The easily functionalizable lactate-derived aryl-λ^3-iodane framework and ready availability of its chiral source suggest promising future applications of enantioselective oxidation using hypervalent iodine reagents.

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[17] The absolute stereochemistry of the γ-lactone products **9a** and **11a** depended on the reaction conditions. There are some conceivable reaction pathways for the formation of the minor γ lactone: 1) The internal carboxylic acid participates toward the benzylic position of the intermediate **A**. In this case, the (*S*)-isomer of the γ lactone must form in the reactions with **1**–**6**, judging from the preferential formation of the (*S*)-isomer of the δ lactone. 2) Dioxytosylation of the vinyl group, followed by internal nucleophilic substitution at the benzylic position. The S_N1 route must give a racemic product, and the S_N2 must give the *R* isomer. For the acetoxylactonization, a 1,3-dioxolan-2-yl cation may serve as an intermediate in the double inversion. Results for the enantioselectivity of the minor γ lactone product are rationalized by a combination of these reaction pathways.

[18] T. Okuyama, T. Takino, T. Sueda, M. Ochiai, *J. Am. Chem. Soc.* **1995**, *117*, 3360.

[19] a) Experimental evidence for secondary I···O interactions in solution was obtained in a complex of PhI^+OH and 18-crown-6 by cold-spray ionization mass spectroscopy.[19b] Intramolecular interaction has been discussed in the solid state.[4b,c,10d,e] b) M. Ochiai, K. Miyamoto, M. Shiro, T. Ozawa, K. Yamaguchi, *J. Am. Chem. Soc.* **2003**, *125*, 13006.

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[21] Electrospray ionization mass spectrometry of 1-(diacetoxyiodo)-2-methoxybenzene showed a similar result to that of 1-(diacetoxyiodo)-2,4,6-trimethylbenzene in the relative intensities of $M^+\cdot(MeCN)_n$ ($n = 0$–2). Thus, the oxygen atom bound at the *ortho* position of the aryliodane has little interfering effect on the solvent coordination to the iodonium ion.

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