

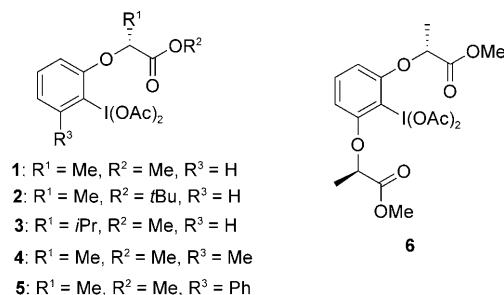
Enantiodifferentiating *endo*-Selective Oxylactonization of *ortho*-Alk-1-enylbenzoate with a Lactate-Derived Aryl- λ^3 -Iodane**

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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 spirocyclization 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 spirocyclization 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-oxisochroman-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).



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]

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

[a] Reaction conditions are given in the Supporting Information. The acetoxylation 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 acetoxylation also preferentially gave δ -lactone **10a**. The enantioselectivity depended on the structure of the

Table 2: Acetoxylation of 2-ethenylbenzoic acid.^[a]

Entry	Ar*I(OAc) ₂	Yield [%] (10a / 11a)	ee [%] ^[b]	
			(<i>S</i>)- 10a	(<i>R</i>)- 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 **7a** also gave acetoxylation 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 **7b–d**

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

Table 3. Methyl ortho-alk-1-enylbenzoate (7) reacts with Ar*I(OAc)₂, AcOH, BF₃*OEt₂ in CH₂Cl₂ at -80 to -40 °C to form lactone 10.

7 **10**

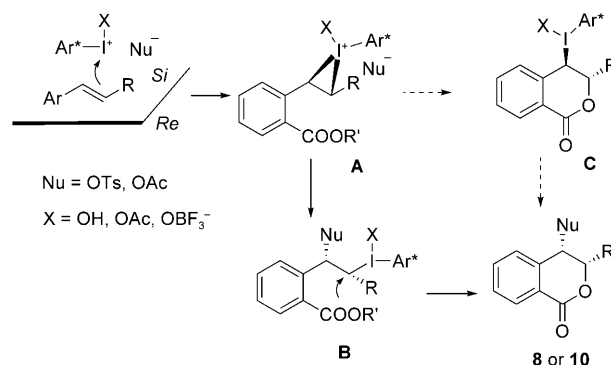
a: R = H, **b:** R = CH₂OMe, **c:** R = CH₂OH, **d:** R = *n*-C₅H₁₁

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 ₂ OMe	7'b	1	80	84
5 ^[c]	CH ₂ OMe	7b	1	84	84
6	CH ₂ OMe	7'b	3	62	97
7	CH ₂ OMe	7'b	6	60	97
8 ^[c]	CH ₂ OMe	7b	6	84	96
9	CH ₂ OH	7'c	1	84	86
10	CH ₂ OH	7'c	3	80	94
11	CH ₂ OH	7'c	6	57	96
12	<i>n</i> -C ₅ H ₁₁	7'd	1	63	90
13	<i>n</i> -C ₅ H 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 (**7b**) and hydroxymethyl (**7c**) 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 ¹H 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 **7b–d** gave higher enantioselectivity than that of the vinyl substrate **7a**.

On the basis of the *syn* selectivity observed, a plausible reaction mechanism is proposed in Scheme 2. (Diacetoxyio-)arene is activated by acid (TsOH or BF₃·OEt₂). 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 arylidonio group. Preferential formation of the δ -lactone is rationalized by the reaction pathway **A** $\rightarrow$ **B** $\rightarrow$ **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 **7b** gave similar regioselectivity independent of the nucleophilicity 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 arylidonio 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

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 tetrahydrofuran-ylation 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*

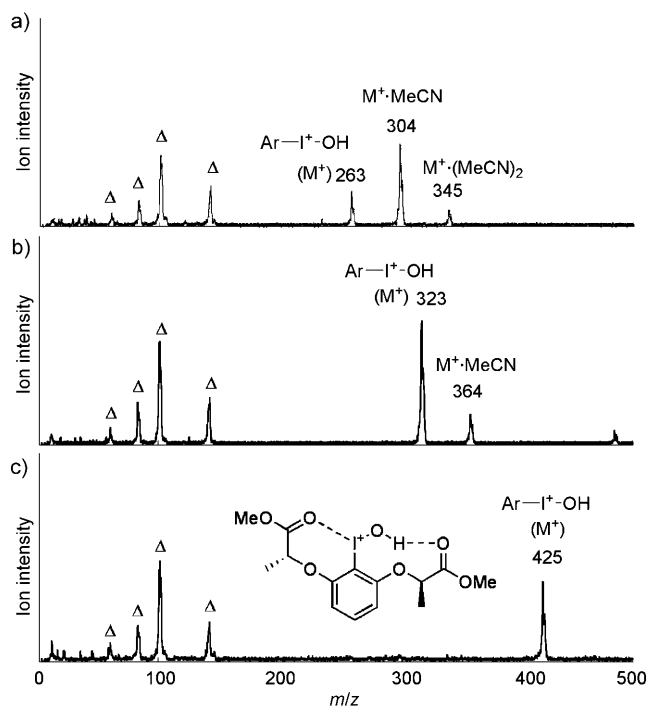
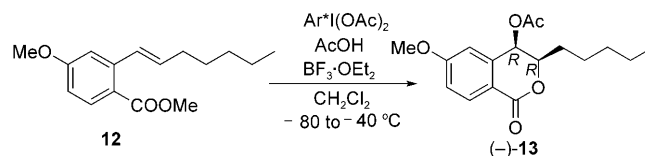


Figure 1. Electrospray ionization mass spectra of a) 1-(diacetoxyiodo)-2,4,6-trimethylbenzene, b) **1**, and c) **6** in 0.5% (v/v) water–99.5% (v/v) acetonitrile solution containing trifluoroacetic acid (16 mM). The peaks marked with Δ represent clusters composed of acetonitrile and water molecules.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

signal corresponding to the aryl(hydroxy)iodonium ion, $\text{M}^+ = \text{ArI}^+(\text{OH})$, was observed together with $\text{H}_3\text{O}^+\cdot(\text{MeCN})_n$ ($n = 1, 2, 3$) in the range *m/z* < 150. The iodonium ion, solvated by acetonitrile, $\text{M}^+\cdot(\text{MeCN})_n$ ($n = 1, 2$), was observed for 1-(diacetoxyiodo)-2,4,6-trimethylbenzene, which has no oxy-substituent on the aryl group (Figure 1a): 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 1c). For the mono-functionalized reagent **1** (Figure 1b), no signal owing to $\text{M}^+\cdot(\text{MeCN})_2$ was detected,

and a small signal owing to $\text{M}^+\cdot\text{MeCN}$ 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 1c. 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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