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Asymmetric Synthesis of 4,8-Dihydroxyisochroman-1-one Polyketide Metabolites Using Chiral Hypervalent Iodine(III)

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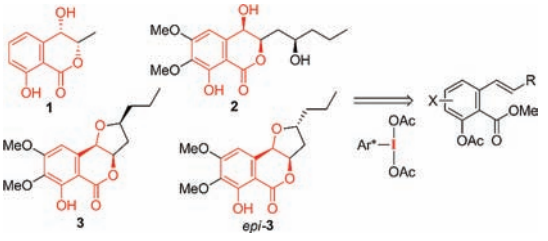
ABSTRACT



Stereoselective oxylactonization of *ortho*-alkenylbenzoate with chiral hypervalent iodine is applied to the asymmetric synthesis of 4-oxyisochroman-1-one polyketide metabolites including 4-hydroxymellein (1), a derivative of fusarentin 2, monocerin (3), and an epimer of monocerin *epi*-3.

The 4-oxyisochroman-1-one motif is present in some types of natural products such as **1**–**8** illustrated in Figure 1, which includes a number of bioactive polyketide metabolites.[1] Owing to their biological and pharmacological potential, these compounds have attracted considerable attention.[1−5] From a synthetic viewpoint, the 4-hydroxyisochroman-1-one structure has been strategically approached in the following two ways: (1) hetero-Diels−Alder cycloaddition of *ortho*-quinone dimethides followed by oxidation;[4] (2) oxidative rearrangement of isobenzofurans followed by reduction.[5] However, enantiomeric control and the total synthesis of this class of natural products are still challenging issues.

Oxidative lactonization of *ortho*-alkenylbenzoates could be an alternative and efficient route toward the 4-hydroxyisochroman-1-one motif, if it proceeds with *endo*-selectivity. Unfortunately, the oxidative lactonization using conventional oxidizing reagents yielded a phthalide product because of *exo* selectivity.[6,7] In contrast, *endo* selective oxylactonization was achieved by using hypervalent

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iodine(III) as an oxidizing reagent.[9] Here, we describe the asymmetric synthesis of 4-oxyisochroman-1-one polyketide metabolites, containing 4-hydroxymellein (**1**), a derivative of fusarentin **2**, monocerin (**3**), and an epimer of monocerin *epi*-**3** by oxylactonization with hypervalent iodine.

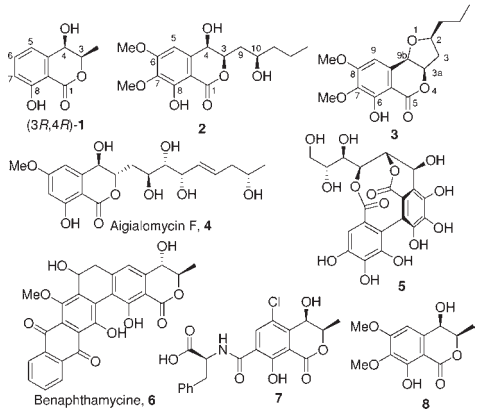


Figure 1. Natural products containing hydroxyisochromanone.

Asymmetric oxidation with chiral hypervalent iodine has attracted considerable attention owing to its high enantioselectivity in metal-free oxidation.[8−12] The chiral hypervalent iodine based on a lactate motif is one of the most attractive reagents for this process because of its short-step access.[9,10c−10g,11e] The lactate-derived reagents **9**−**10** (Figure 2) were used for a key step in the asymmetric synthesis of oxyisochromanones. In particular, the three targets, **2**, *ent*-**3**, and *epi*-**3**, were divergently provided from a single (*R*,*E*)-2-(4-oxyhept-1-enyl)benzoate substrate. Selective formation of one of these targets was achieved through judicious choice of the oxy-functional group in the substrate and the stereochemistry of the chiral hypervalent iodine reagent employed.

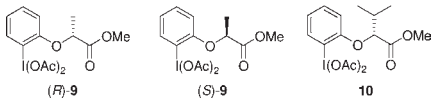
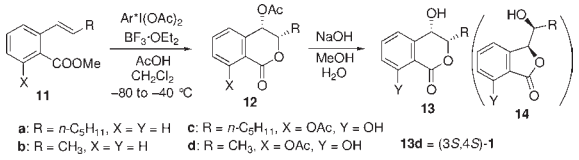


Figure 2. Chiral hypervalent iodine(III).

For the asymmetric synthesis of 4-hydroxymellein (**1**), acetoxy-protected propenylbenzoate **11d** was employed as a substrate of oxylactonization with enantiomerically pure hypervalent iodine (Scheme 1). The enantioselective oxylactonization of **11d** with **10** gave **12d** in 68% isolated yield with 96% ee of the (3*S*,4*S*)-isomer. Hydrolysis of the acetoxy product **12d** successfully yielded the target compound (3*S*,4*S*)-**1** (**13d**) in 61% yield. Details are summarized in Tables S1 and S2 (Supporting Information (SI)), along with the results of model compounds **11a**−**11c**.[13]

Scheme 1. Synthesis of 4-Hydroxymellein and Analogs



In order to identify suitable conditions for the synthesis of **2** and **3**, the simplified model substrates **16Sa** and **16Ha** were subjected to oxylactonization with hypervalent iodine. The yield and selectivity of the model reactions are summarized in Tables 1 and 2. The reaction of the silyl ether substrate **16Sa** yielded dihydrofuran-fused isochromanones **17a** and **18a**, but no acetoxy product (an analog of **19a**), as shown in Table 1. In contrast, the acetoxy

(7) Oxidative lactonization of aryl-substituted substrates such as 2-(2-phenylethenyl)benzoic acid gave isochromanone products. The *endo*- vs *exo*-selectivity may be controlled by an electron-donating aryl group; see: Berti, G. *Tetrahedron* **1958**, *4*, 393. Clive, D. L. J.; Russel, C. G.; Chittattu, G.; Singh, A. *Tetrahedron* **1980**, *36*, 1399. Izumi, T.; Morishita, N. *J. Heterocycl. Chem.* **1994**, *31*, 145. Shahzad, S. A.; Venin, C.; Wirth, T. *Eur. J. Org. Chem.* **2010**, 3465.

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(10) For enantioselective oxidation of alkene with chiral hypervalent iodine(III), see: (a) Hirt, U. H.; Spingler, B.; Wirth, T. *J. Org. Chem.* **1998**, *63*, 7674. (b) Hirt, U. H.; Schuster, M. F. H.; French, A. N.; Wiest, O. G.; Wirth, T. *Eur. J. Org. Chem.* **2001**, 1569. (c) Fujita, M.; Okuno, S.; Lee, H. J.; Sugimura, T.; Okuyama, T. *Tetrahedron Lett.* **2007**, *48*, 8691. (d) Fujita, M.; Ookubo, Y.; Sugimura, T. *Tetrahedron Lett.* **2009**, *50*, 1298. (e) Fujita, M.; Wakita, M.; Sugimura, T. *Chem. Commun.* **2011**, *47*, 3983. (f) Röben, C.; Souto, J. A.; González, Y.; Lishchynskyi, A.; Muñiz, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 9478. (g) After submission of this manuscript a related report on intramolecular oxyamination was published: Farid, U.; Wirth, T. *Angew. Chem., Int. Ed.*, DOI: 10.1002/anie.201107703.

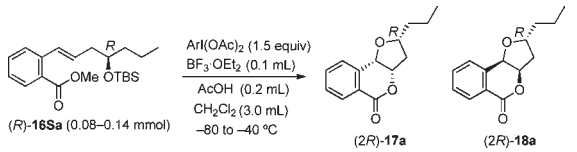
(11) For catalytic use of chiral hypervalent iodine generated in situ, see: (a) Richardson, R. D.; Page, T. K.; Altermann, S.; Paradine, S. M.; French, A. N.; Wirth, T. *Synlett* **2007**, 538. (b) Dohi, T.; Maruyama, A.; Takenaga, N.; Senami, K.; Minamitsuji, Y.; Fujioka, H.; Caemmerer, S. B.; Kita, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 3787. (c) Quideau, S.; Lyvinec, G.; Marguerit, M.; Bathany, K.; Ozanne-Beaudenon, A.; Buffeteau, T.; Cavagnat, D.; Chénedé, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 4605. (d) Farooq, U.; Schäfer, S.; Shah, A. A.; Freudendahl, D. M.; Wirth, T. *Synthesis* **2010**, 1023. (e) Uyanik, M.; Yasui, T.; Ishihara, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 2175.

(12) For reactions featuring metal-free conditions, see: Kang, Y.-B.; Gade, L. H. *J. Am. Chem. Soc.* **2011**, *133*, 3658. Zhdankin, V. V. *J. Org. Chem.* **2011**, *76*, 1185. Duschek, A.; Kirsch, S. F. *Angew. Chem., Int. Ed.* **2011**, *50*, 1524. Silva, L. F., Jr.; Olofsson, B. *Nat. Prod. Rep.* **2011**, *28*, 1722. Miyamoto, K.; Sei, Y.; Yamaguchi, K.; Ochiai, M. *J. Am. Chem. Soc.* **2009**, *131*, 1382. Kita, Y.; Morimoto, K.; Ito, M.; Ogawa, C.; Goto, A.; Dohi, T. *J. Am. Chem. Soc.* **2009**, *131*, 1668.

(13) Rearranged γ-lactone **14** was often obtained in the hydrolysis (Table S2). The rearrangement to thermodynamically stable γ-lactone may take place via hydrolysis of the δ-lactone moiety. The rate for the hydrolysis of the δ-lactone moiety must be affected by the electronic property of a substituent on the benzene ring: the acetoxy group at the 8-position of **12c**,**d** may be hydrolyzed to an electron-donating hydroxy group to decrease the rate for hydrolysis of the lactone moiety. Thus, selectivity in the hydrolysis products **13**/**14** is controlled by the substituent on the benzene moiety as well as basicity of the reaction conditions. Nonsubstituted **13a** was obtained under mild basic conditions with K_2CO_3 (entry 2 in Table S2).

product **19a** was obtained with **17a** and **18a** in the reaction of the hydroxyl substrate **16Ha** (Table 2). These results indicate that the silyloxy group does not act as a protecting group but preferably enhances the electron-donating ability[14] of the oxy-group to promote nucleophilic oxycyclization. The electron donation may be futhermore enahanced by coordination of $BF_3 \cdot OEt_2$ to the silyl group.

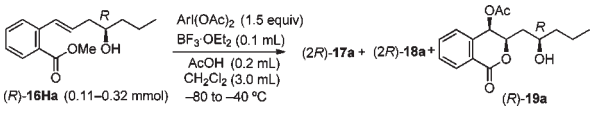
Table 1. Oxylactonization of Silyloxy Substrate



	16Sa		**17/18**	yield (%)[b]		*R*/*S*[c]	
entry	*R*/*S*	$ArI(OAc)_2$	crude[a]	**17**	**18**	**17**	**18**
1	50/50	$PhI(OAc)_2$	50/50	32[d]	42[d]	-	-
2	50/50	(*R*)-**9**	53/47	28	44	92/8	2/98
3	99/1	$PhI(OAc)_2$	50/50	33	41	99/1	99/1
4	99/1	(*R*)-**9**	98/2	75	-	99/1	-
5	99/1	(*S*)-**9**	7/93	-	81	-	99/1

[a] Product ratio determined by ^1H NMR of a crude mixture. [b] Yield for the product purified by column chromatography. [c] Enantiomer ratio ((2*R*)-**17a**/(2*S*)-**17a** or (2*R*)-**18a**/(2*S*)-**18a**) determined by GC analysis on a chiral stationary phase. [d] Products were purified as a diastereomeric mixture (**17**/**18** = 43/57) in 74%.

Table 2. Oxylactonization of Hydroxy Substrate



	16Ha		**17/18/19**	yield (%)[b]		
entry	*R*/*S*	$ArI(OAc)_2$	crude[a]	**17**	**18**	**19**
1	50/50	$PhI(OAc)_2$	7/50/43	-	45	31
2[c]	50/50	$PhI(OAc)_2$	17/75/8	10	50	-
3	50/50	(*R*)-**9**	27/22/51	29 (99/1)	20 (41/59)	39 (26/74)
4	99/1	$PhI(OAc)_2$	0/54/46	-	32 (99/1)	24 (99/1)
5	99/1	(*S*)-**9**	0/30/70	-	31 (99/1)	54 (99/1)
6	99/1	(*R*)-**9**	45/16/27[d]	43[e]	17[e]	19[e]

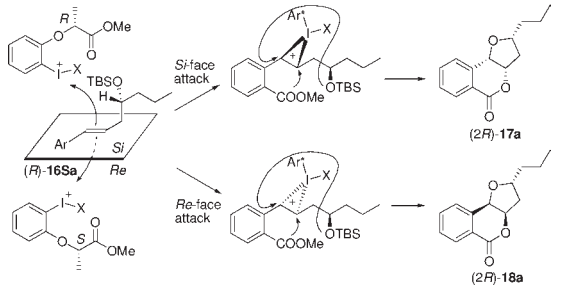
[a] Product ratio determined by ^1H NMR of a crude mixture. [b] Yield for the product purified by column chromatography. The value in parentheses is enantiomer ratio determined by GC analysis on a chiral stationary phase; (2*R*)-**17a**/(2*S*)-**17a**, (2*R*)-**18a**/(2*S*)-**18a**, and (*R*)-**19a**/(*S*)-**19a**. [c] In the absence of AcOH. [d] An unidentified product **X** was included in 12% content. [e] Products were purified as a mixture of **17**/**18**/**19**/**X** = 49/19/22/10 in 88% yield. The enantiomeric ratio was not determined.

In the reaction of the silyl substrate (Table 1), an ~1/1 mixture of **17a**/**18a** was obtained (entries 1–3), unless both substrate **16Sa** and reagent **9** were enantiomerically pure (entries 4 and 5). Selective formation of **17a** and **18a** was achieved in the reaction of (*R*)-**16Sa** with (*R*)-**9** (entry 4) and in that with (*S*)-**9** (entry 5), respectively. The configuration of the (2*R*)-**17a** product corresponds to that of the antipodal enantiomer of monocerin (*ent*-**3**). Thus, a combination of the (*S*)-isomer of the silyloxy substrate and (*S*)-reagent must be suitable conditions for the selective synthesis of **3**.

The structure of target **2** corresponds with that of the acetoxy product (*R*)-**19a**. The reaction of the hydroxyl substrate **16Ha** gave the acetoxy product **19a** (Table 2). The yield of **19a** drastically decreased in the absence of acetic acid (entry 2). The desired enantiomer (*R*)-**19a** was obtained in the reaction of the (*R*)-hydroxyl substrate (entries 4–6). Use of the (*S*)-iodine reagent increased the selectivity of the acetoxy product (entry 5), while reaction with the (*R*)-reagent gave an isomeric mixture (entry 6).

The above-mentioned results provide useful information from mechanistic and synthetic viewpoints. The mechanistic points are discussed as follows. A plausible reaction mechanism for the double oxidative cyclization to give **17** and **18** is proposed in Scheme 2. The oxidative cyclization may be initiated by electrophilic addition of the hypervalent iodine activated by $BF_3 \cdot OEt_2$ toward **16S**. Nucleophilic substitutions with the internal silyloxy and methoxycarbonyl groups follow the electrophilic addition and proceed with inversion of configuration to give **17** and **18**. The product **17a** with a (2*R*,3a*S*,9b*S*)-configuration is formed via the *Si*-face attack, while **18a** is formed via the *Re*-face attack toward the (*R*)-alkene substrate. The 1/1 mixture of **17**/**18** in the reaction with achiral reagent $PhI(OAc)_2$ (entries 1 and 3, Table 1) indicates that the stereogenic center of the silyloxy substrate **16Sa** has little effect on the diastereoface differentiation. The chirality of the hypervalent iodine reagent controls the diastereoface selectivity well: the *R*-reagent preferentially attacks the *Si*-face to give **17a** (entry 4, Table 1), and the *S*-reagent attacks the *Re*-face to give **18a** (entry 5, Table 1). In other words, the reaction of the silyloxy substrate takes place under reagent control.

Scheme 2. Plausible Pathway

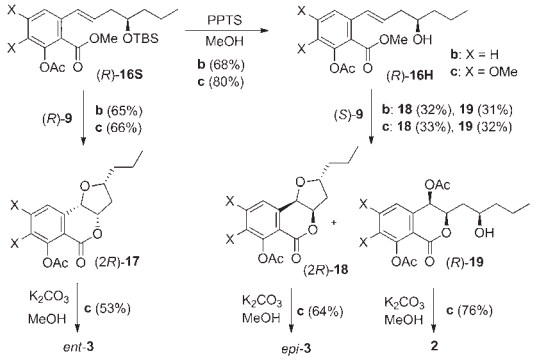


In contrast, the reaction of the hydroxyl substrate **16H** proceeds under substrate control. The reaction of **16H** with the achiral reagent $PhI(OAc)_2$ predominantly gives **18** and **19** (entries 1 and 4, Table 2). The acetoxy product **19** forms through the *Re*-face addition. This indicates that electrophilic addition of the achiral iodine reagent

(14) A silyl group is inductively electon-donating; see: Bassindale, A. R.; Taylor, P. G. In *The Chemistry of Silicon Compounds*; Patai, S., Rappoport, Z., Eds.; John Wiley & Sons: Chichester, 1989; Part 2, Chapter 14, pp 892–963.

preferentially takes place on the *Re*-face.[15] That is, the achiral reagent is able to differentiate the diastereoface of the alkene during the electrophilic addition step. In other words, the stereogenic center of the hydroxyl substrate controls the diastereoface selectivity well.[16] In addition to the substrate control, the stereodifferentiating ability of the chiral hypervalent iodine reagent also affects the product distribution: the (*R*)-**9** reagent favors the *Si*-face attack, which is the reverse of the substrate control and, thus, results in a decrease in diastereoface selectivity to afford isomeric mixtures (entry 6, Table 2). In contrast to the mismatched pair (the reaction of (*R*)-**16Ha** with (*R*)-**9**), the reaction of (*R*)-**16Ha** with (*S*)-**9** yielded only **18** and **19**, both of which were derived from the *Re*-face attack (entry 5, Table 2).[17] These observations of the double asymmetric induction are consistent with the kinetic resolution of racemic **16Ha** with (*R*)-**9**, where (*R*)-enriched **16Ha** remained (SI). This indicates that the reaction of (*S*)-**16Ha** (the matched pair) is faster than that of (*R*)-**16Ha** (the mismatched pair).

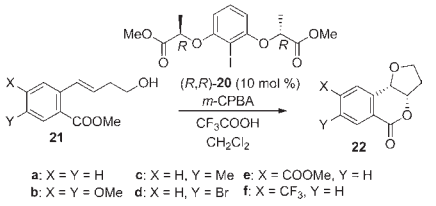
Scheme 3. Synthesis of **2** and **3**



Based on the optimization of reaction conditions presented above, an advanced model substrate **16b** was subjected to oxylactonization (Scheme 3). An analog of monocerin, (2*R*)-**17b**, was obtained in the reaction of the silyl substrate (*R*)-**16Sb** with (*R*)-**9** in 65% yield. The reaction of the hydroxyl substrate (*R*)-**16Hb** with (*S*)-**9** gave the 4-acetoxyisochromanone product **19b** in 31% yield together with **18b**. Thus, the acetoxy group of **16b** does not affect the selectivity of double asymmetric induction. Oxylactonization of the trioxy-substituted benzoate substrate **16c** proceeded with a selectivity similar to that of **16a** and **16b**. Fortunately, the electron-rich aromatic portion of **16c** was tolerated during the oxylactonization. Syntheses of **2**, *ent*-**3**, and *epi*-**3** were completed through hydrolysis under basic conditions. The desired enantiomer of monocerin (**3**) was obtained in the oxylactonization of (*S*)-**16Sc** with (*S*)-**9** (48% yield) and following hydrolysis (41% yield).

A catalytic variant of the oxylactonization is obtained by using chiral iodoarene **20** as an organocatalyst, *m*-CPBA as a terminal oxidant, and trifluoroacetic acid as an activator. Enantioselectivity in the catalytic variant was examined in the reaction of achiral substrates **21a**–**f** (Scheme 4; Table S3, SI). Double oxidative cyclization preferentially took place in the reaction of the hydroxyl substrate **21** to give the dihydrofuran-fused isochromanone **22** with up to 91% ee.

Scheme 4. Catalytic Enantioselective Oxylactonization



Based on the enantioselective catalytic reaction, monocerin (**3**) was synthesized under the catalytic conditions as follows. The substrate (*S*)-**16Sc** was used for the reaction in the presence of (*S*,*S*)-**20** as an organocatalyst to give a mixture of (2*S*)-**17c**/(2*S*)-**18c** in a 9/1 ratio. These isomers were separated by column chromatography with SiO_2, and (2*S*)-**17c** was isolated in 39% yield.

In conclusion, the first asymmetric syntheses of 4-hydroxymellein (**1**) and a derivative of fusarentin **2** were achieved by using enantio- and diastereoselective acetoxylactonization with chiral hypervalent iodine(III). Monocerin (**3**) was also concisely prepared under both the stoichiometric and catalytic conditions. These synthetic applications allow the outstanding selectivity and synthetic capabilities of oxidation mediated by hypervalent iodine to be demonstrated.

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Supporting Information Available. Experimental procedures and data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(15) (a) The product distribution of **18**/**19** is determined by a nucleophilic displacement step at the benzylic position of the iodonium[15b] derived from the *Re*-face electrophilic addition: the internal hydroxy group attacks to give **18**, and intermolecular substitution with AcO^- or AcOH gives **19**. The competition may be affected by the steric effect of the aryliodane moiety. (b) The three-membered ring structure of the iodonium intermediate has previously been proposed judging from the high enantioselectivity in oxylactonization of 2-ethenylbenzoic acid.[9]

(16) Association of hypervalent iodine with a hydroxy group has been suggested; see: (a) Ding, H.; Chen, D. Y.-K. *Angew. Chem., Int. Ed.* **2011**, *50*, 676. (b) Traoré, M.; Maynedier, M.; Souard, F.; Choisnard, L.; Vial, H.; Wong, Y.-S. *J. Org. Chem.* **2011**, *76*, 1409. (c) Pouységu, L.; Chassaing, S.; Dejugnac, D.; Lamidey, A.-M.; Miqueu, K.; Sotiropoulos, J.-M.; Quideau, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 3552. (d) Baldwin, J. E.; Adlington, R. M.; Sham, V. W.-W.; Marquez, R.; Bulger, P. G. *Tetrahedron* **2005**, *61*, 2353.

(17) The results of entry 3 in Table 2 are explained by a combination of those of the matched and mismatched pairs because the substrate is a racemic mixture.

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