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A Series of Two Oxidation Reactions of *ortho*-Alkenylbenzamide with Hypervalent Iodine(III): A Concise Entry into (3*R*,4*R*)-4-Hydroxymellein and (3*R*,4*R*)-4-Hydroxy-6-methoxymellein

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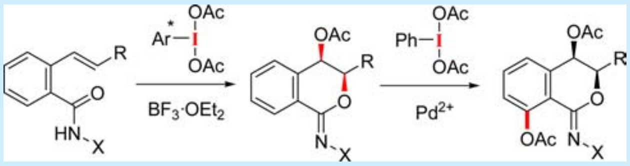
Supporting Information

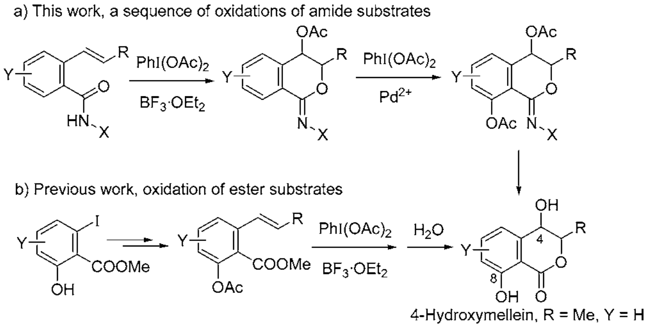
ABSTRACT: A sequence of oxidation reactions of alkenamides with hypervalent iodine is described. Oxidation of *ortho*-alkenylbenzamide substrates selectively gave isochroman-1-imine products. The products underwent further oxidation in the presence of a Pd salt catalyst leading to regioselective C−H acetoxylation at the 8-position. A series of oxidations was applied to the crucial steps of asymmetric synthesis of 4-hydroxymellein derivatives.



Hypervalent iodine compounds have been shown to effect numerous useful chemical oxidations.[1,2] The oxidation is accelerated under acidic conditions in the presence of a Brønsted or Lewis acid.[3] In addition, transition metal salts and complexes catalyze various oxidations with hypervalent iodine.[4] The reactivity of hypervalent iodine reagents is characterized by electrophilicity because of the electron-deficient polyvalent iodine atom and also by the capability for a ligand transfer reaction toward organic substrates. Taking advantage of the diversity of hypervalent-iodine-mediated oxidations, it is possible to achieve a highly oxidized but well controlled product, using a sequence of oxidations that increase the oxidation state of substrates step by step.

To examine the concept of a series of oxidations with hypervalent iodine, we focused on oxidative cyclization of alkenamides[5] and oxidative replacement of the C−H bond catalyzed by a Pd salt.[6,7] The first oxidation is expected to yield an imidate, which will be utilized as a removable directing group[8−10] for the second oxidation catalyzed by Pd salt, as illustrated in Scheme 1a. Although a number of oxidative cyclizations of alkenamides have been investigated, hypervalent iodine(III) reagents mainly gave lactam products via the *N*-attack pathway.[11−13] Thus, we have to find suitable conditions for selective formation of the desired imidate product via the *O*-attack pathway.[5,14]

Scheme 1. Proposed Strategy Leading to 4-Hydroxymellein Derivatives



A sequence of oxidations would be applied for concise synthesis of 4-hydroxymellein and related natural products.[15,16] Most of the isochromanone natural products possess the 8-hydroxy group originating in polyketide biosynthesis.[17] The 8-oxy group is regioselectively introduced in the late stage using the imidate as a scaffold for Pd-catalyzed C−H activation (Scheme 1a). In our previous approach,[18] the oxy group was introduced on the alkenylbenzoate substrate beforehand (Scheme 1b). Dispensing with the oxy group in the early stage (Scheme 1a) would increase the availability of aromatic starting compounds and avoid undesirable side products due to oxidation on the electron-rich aromatic part.

N-Tosyl 2-vinylbenzamide (**1a**) was used as a model substrate in screening tests to determine optimal conditions for obtaining an isochroman-1-imine (Scheme 2 and Table 1). Pleasingly, reaction with (diacetoxyiodo)benzene (DIB) in the presence of $BF_3·OEt_2$ gave imidate products, **2a** and **3a** (entries 1−5). The isomeric structure of these lactone imines was established by X-ray crystal analysis (Figure 1). The imine moiety of **2a** and **3a** had *Z*-geometry, probably owing to the steric repulsion between the tosyl group and the aromatic part. The ratio of **2a** increased with an increase in the equivalent of $BF_3·OEt_2$, and isochroman-1-imine **2a** was isolated in 50% yield in the reaction using 8 equiv of $BF_3·OEt_2$ (entry 5).[19] The yield of a six-membered lactone imine **4a** was not improved when [bis(trifluoroacetoxy)iodo]benzene (BTI) was used instead of DIB (entries 6 and 7). The reaction with BTI accelerated in the presence of trifluoroacetic acid and proceeded at 0 °C (entry

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Scheme 2. Oxidation of *N*-Tosyl 2-Vinylbenzamide (1a)

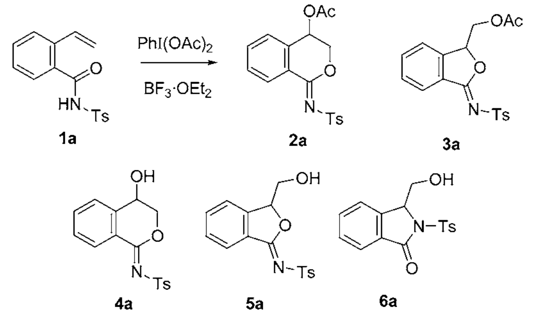
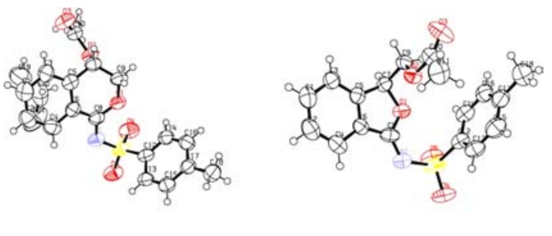


Table 1. Optimization of Oxidative Cyclization of *N*-Tosyl 2-Vinylbenzamide (1a)

entry	conditions[a]	crude 2a/3a	(isolated yield)
1	DIB, BF$_3$·OEt$_2$ (0.5 equiv)[b]	45:55	2a/3a = 44:56 (64%)
2	DIB, BF$_3$·OEt$_2$ (0.8 equiv)	57:43	2a/3a = 50:50 (84%)
3	DIB, BF$_3$·OEt$_2$ (1.5 equiv)	66:34	2a/3a = 67:33 (63%)
4	DIB, BF$_3$·OEt$_2$ (4.0 equiv)	71:29	2a/3a = 72:28 (60%)
5	DIB, BF$_3$·OEt$_2$ (8.0 equiv)[c]	81:19	2a (50%)
6	BTI, reflux, 18 h[d]	62:38[e]	4a (31%), 5a (22%)
7	BTI, TFA, 0 °C, 4 h[d]	[f]	4a (24%), 5a (19%)
8	*m*-CPBA (3 equiv), rt, 28 h	[g]	5a (35%), 6a (46%)

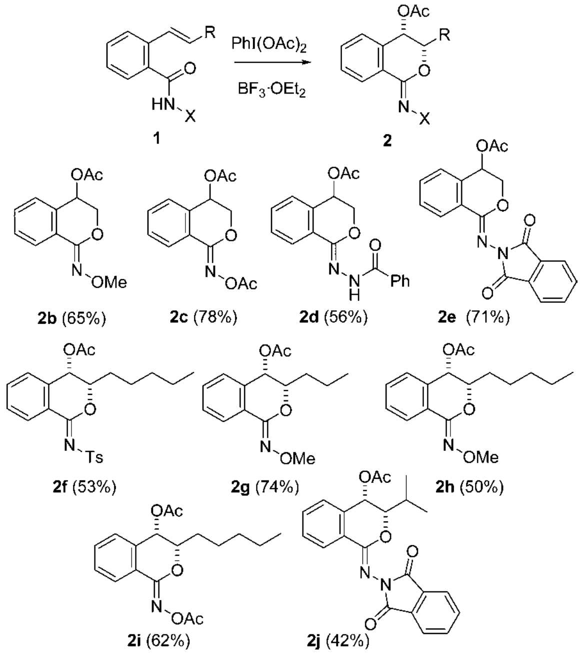
[a] 1a (0.1 mmol), DIB (0.15 mmol), and AcOH (0.2 mL) in CH_2Cl_2 (4 mL) at −40 °C for 3 h, unless otherwise noted. [b] For 14 h. [c] At −80 °C for 1.5 h. [d] BTI (0.15 mmol) was used instead of DIB and AcOH. Crude reaction mixtures were hydrolyzed in aqueous methanol containing K_2CO_3. [e] Ratio of **4a**/**5a**. [f] A five-membered lactone product **5a′** was also observed (**4a**/**5a**/**5a′** = 44/31/25). [g] A mixture of imine **5a** and lactam **6a** was obtained (**5a**/**6a** = 41/59).



2a·1/2cyclohexane **3a**

Figure 1. Structure of **2a** and **3a** in solid state.

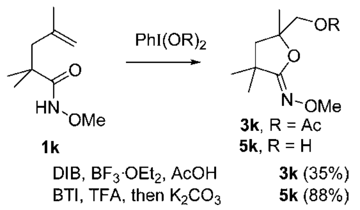
Scheme 3. Oxidative Cyclization of Alkenylbenzamides



7); unfortunately, the ratio of **4a** decreased compared with that obtained in entry 6. Oxidation with *m*-CPBA did not yield **4a**; however, five-membered lactone imine **5a** and lactam **6a** were obtained (entry 8). The structure of lactam **6a** was also established by X-ray crystal analysis (Supporting Information (SI)).

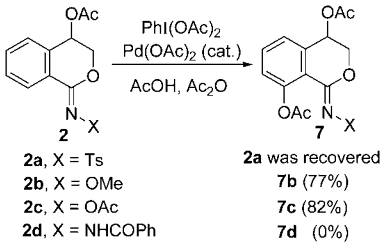
With optimized conditions established for the isochroman-1-imine **2a** (Table 1, entry 5), we examined a range of alkenamides in the oxidative cyclization (Scheme 3). Methoxy, acetoxy, benzamide, and phthalimido *N*-substituted substrates also selectively gave the corresponding isochroman-1-imine product **2**.[20] A relatively good yield was observed in the reaction of the *N*-methoxy (**1b**) and *N*-acetoxy (**1c**) substrates. X-ray crystallographic analysis confirmed the isochroman-1-imine structure of **2b** and **2d** (SI). *Trans*-alkenyl substrates led to *cis*-isochroman-1-imine products. The *cis* configuration was definitively established by X-ray crystal analysis of **2g** and **2j** (SI). Remarkably, an aliphatic alkenamide **1k** also selectively gave the corresponding lactone imine **3k** as a result of exo cyclization, but the yield was low under the conditions in the presence of $BF_3·OEt_2$ (Scheme 4). The yield was improved in the reaction with BTI.

Scheme 4. Oxidative Cyclization of Alkenamide 1k



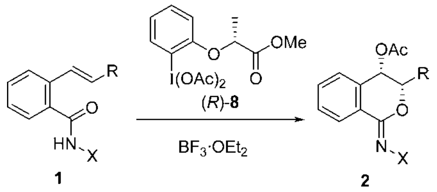
The lactone imines **2a**–**2d** were used for Pd-catalyzed acetoxylation with DIB, as shown in Scheme 5. The *N*-methoxy and *N*-acetoxy imidates, **2b** and **2c**, led to regioselective acetoxylation at the peri-position of the imidates. The position of the acetoxy substitution was determined by NOESY NMR analysis (SI). The regioselectivity can be explained by directing C–H activation using the imidate as a scaffold for the Pd catalyst. The electron-withdrawing tosyl-substituted substrate **2a** resulted in no reaction. In the case of *N*-benzamide **2d**, hydrolysis of the imine moiety proceeded to give the lactone compound of **2d**.

Scheme 5. Regioselective Acetoxylation of 2



An enantioselective variant of the oxidative imino lactonization was examined prior to its application in the synthesis of natural products. We have previously reported the enantioselective oxidation of methyl alkenylbenzoates using a chiral lactate-based hypervalent iodine reagent **8**.[21,22] Based on the results of the ester substrates, the amide substrates **1a**−**1j** were reacted with (*R*)-**8**, as summarized in Table 2.[23] The enantioselectivity of these amide substrates was similar to that of the corresponding methyl ester,[21] and it was not significantly affected by the type of *N*-substituent.

Table 2. Enantioselective Oxidation[a]

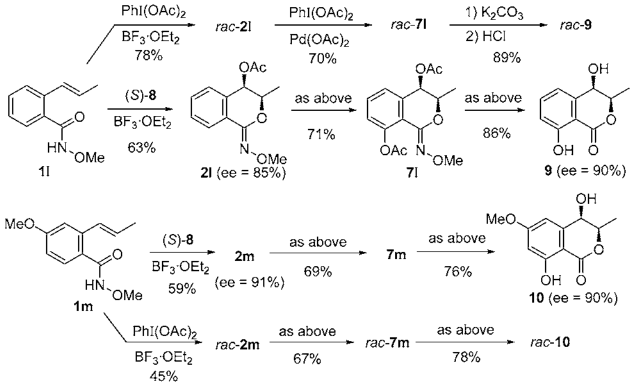


entry	1	2 (yield)	2, ee (%)[b]
1	**1a**	**2a** (66%)	**2a** (81) [83]
2[c]	**1a**	**2a** (24%), **3a** (35%)	**2a** (71), **3a** (31)
3	**1b**	**2b** (62%)	**2b** (78)[d]
4	**1c**	**2c** (79%)	**2c** (84)
5	**1d**	**2d** (70%)	**2d** (83)
6	**1e**	**2e** (53%)	**2e** (74)
7	**1f**	**2f** (73%)	**2f** (82)
8	**1g**	**2g** (71%)	**2g** (90)
9	**1h**	**2h** (50%)	**2h** (88) [98]
10	**1i**	**2i** (61%)	**2i** (82) [97]
11	**1j**	**2j** (42%)	**2j** (80)

[a] In the presence of 8 equiv of $BF_3\cdot OEt_2$ at −80 °C. [b] Determined by HPLC analysis on a chiral stationary phase. The values in brackets correspond to ee after crystallization. [c] In the presence of 0.5 equiv of $BF_3\cdot OEt_2$ at −40 °C. (*S*)-**3a** was the major enantiomer. [d] (*S*)-**2b** was the major enantiomer.

Use of this series of oxidations was demonstrated by its application to the concise entry into (3*R*,4*R*)-4-hydroxymellein (**9**) and (3*R*,4*R*)-4-hydroxy-6-methoxymellein (**10**), as illustrated in Scheme 6. A racemic sample of isochroman-1-imine *rac*-**2l** was synthesized in 78% yield in the oxidation of **1l** with DIB in the presence of $BF_3\cdot OEt_2$, and it was converted to the 8-acetoxy compound *rac*-**7l**. The two acetoxy groups and the *N*-methoxyimidate moiety of **7l** were readily hydrolyzed at rt to yield *rac*-**9** without isomerization to a phthalide compound. The ^1H and ^{13}C NMR data of synthetic *rac*-**9** were consistent with those in the literature.[15] Preparation of *rac*-**9** in a 1 g scale was also performed (SI) as a demonstration of the advantage of this methodology. In order to synthesize the (3*R*,4*R*)-isomer of **9**, we chose the (*S*)-isomer of the lactate-based hypervalent iodine reagent **8** for the imino lactonization. The obtained optically active **2l** was converted to **9** using the same procedures. The enantiomeric sample of **9** was able to be recrystallized from dichloromethane−hexane. The recrystallization resulted in enrichment of ee to 98% ee and provided a single crystal for X-ray analysis (SI). Optical rotation of **9** ($[\alpha]_D^{20}$ = −41 (*c* = 0.17, MeOH)) agreed well with the reported value ($[\alpha]_D^{20}$ = −39.2 (*c* = 0.25, MeOH)).[15c] Moreover, (3*R*,4*R*)-4-hydroxy-6-methoxymellein (**10**) was synthesized according to similar procedures using a methoxy-substituted substrate **1m**. The absolute stereochemistry of **10** was confirmed by comparison with the circular dichroism spectrum[16] (SI).

Scheme 6. Synthesis of 4-Hydroxymellein Derivatives 9 and 10



In conclusion, we found suitable reaction conditions for the regio- and stereoselective synthesis of lactone imines during the oxidation of alkenamides with hypervalent iodine(III). The obtained imidate was utilized as a removable directing group for oxidative C−H acetoxylation catalyzed by a Pd salt in the presence of hypervalent iodine(III). Both oxidations provided appropriate selectivity for the synthesis of 4-hydroxymellein and related natural products.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

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

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Notes

The authors declare no competing financial interest.

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(19) Amount of BF$_3$·OEt$_2$ affected the product ratio of **2a**/**3a**. Selective decomposition of the minor product **3a** might not be a major factor of the product distribution, because ratio **2a**/**3a** was unchanged under treatment of an isolated mixture of **2a**/**3a** (2:1) with BF$_3$·OEt$_2$ (2 equiv) for 1 h at −80 °C.

(20) Although the corresponding regioisomer **3** was not identified, the ratio of **3**/**2** was estimated to be less than 1:9 by ^{1}H NMR of the crude mixture in the reactions of **1b** and **1c**. For the reactions of **1d** and **1e**, it was less than 2:8. In the reactions of **1f**–**1j**, it is difficult to estimate the ratio in the crude mixture.

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(23) Enantioselective oxidation of the aliphatic alkenamide **1k** with (*R*)-**8** in the presence of TFA at 0 °C led to **5k** in 87% yield, but only to an enantiomeric excess of 6%. The enantiomers of **5k** were separated by GLC equipped with DEX-CB column; t_R(major) = 11 min and t_R(minor) = 12 min at column temperature of 130 °C.