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Asymmetric Total Synthesis of (−)-Maldoxin, a Common Biosynthetic Ancestor of the Chloropupukeananin Family

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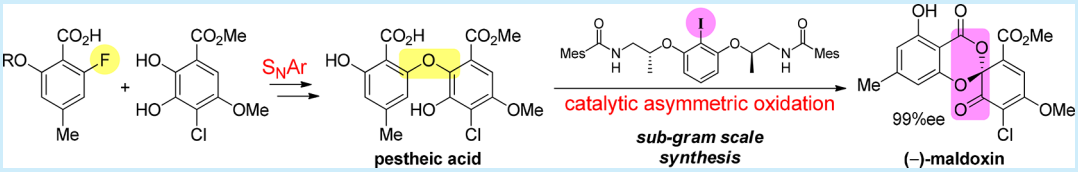
Supporting Information



ABSTRACT: The total synthesis of pestheic acid based on an intramolecular S_NAr reaction without a nitro group and the asymmetric synthesis of (−)-maldoxin by a catalytic enantioselective oxidative dearomatization of pestheic acid are described. The reactivity of (−)-maldoxin as a diene in the Diels−Alder reaction is also investigated.

Maldoxin (**1**, Figure 1) was originally isolated from the *Xylaria* species collected in the Malaysian rain forest,[1] along with dihydromaldoxin (**2**, also known as pestheic acid[2a] and RES-1214-2[2b]) and maldoxone (**3**). Since the optical rotation of **1** was not reported, its absolute stereochemistry has remained ambiguous. During the past decade, Che and colleagues have reported the subsequent isolation of members of the chloropupukeananin (**4**) family, including chloropestolides A−G and chloropupukeanolides A−E from *Pestalotiopsis fici*.[3,4] These natural compounds contain the maldoxin unit as a part of the bicyclo[2.2.2]octane skeleton that arises from an intermolecular Diels−Alder reaction with various natural products possessing alkenes. Since the stereocenter of the acetal carbon of all these compounds has an (*R*)-configuration, (*R*)-**1** is presumed to be a biosynthetic intermediate for the chloropupukeananin family.

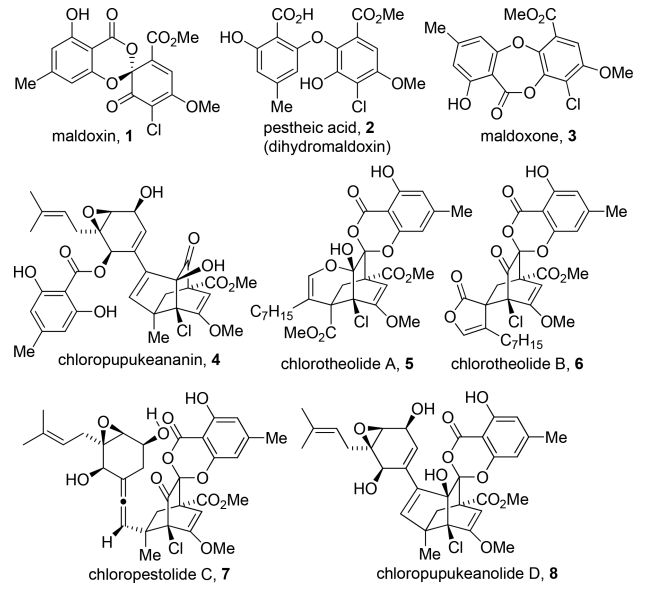


Figure 1. Maldoxin and related compounds.

Recently, Che and colleagues reported the isolation of (−)-**1** from the extract of the fermentation broth of *Pestalotiopsis theae* cultured on a potato dextrose agar medium.[5] Interestingly, maldoxin was not detected in the fermented rice culture of *P. theae*, although chlorotheolides A (**5**) and B (**6**) were isolated, along with its putative biosynthetic precursor, 1-undecene-2,3-dicarboxylic acid. These results indicate that **1** is very reactive as a diene and, hence, is difficult to isolate in the presence of other secondary metabolites that act as dienophiles.

Because several maldoxin-containing natural products[6] show inhibitory activity against HIV-1 replication and/or cytotoxic activity against human tumor cell lines, **1** is a potent intermediate for not only biosynthetic but also bioactivity studies. Although Yu and Snider have reported the total synthesis of *rac*-**1** and **2**,[7] the development of an effective and robust synthesis of (−)-**1** is an urgent task in order to achieve the total synthesis of members of the chloropupukeananin family and the SAR study of maldoxin-containing derivatives. In this context, we have reported synthetic studies[8] of **4** based on a biomimetic strategy via chloropestolide C (**7**) and chloropu-

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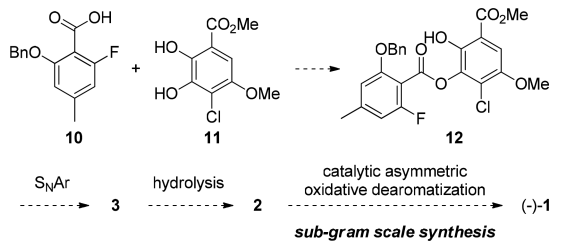
pukeanolide D (**8**) using model compounds of **1**. We herein report the subgram scale synthesis of (−)-**1** based on an intramolecular S_NAr reaction without a nitro group and a catalytic enantioselective oxidative dearomatization of pestheic acid using chiral hypervalent iodine compounds.

The synthetic strategies for pestheic acid and (−)-maldoxin are illustrated in Scheme 1. Normally, a nitro group is present

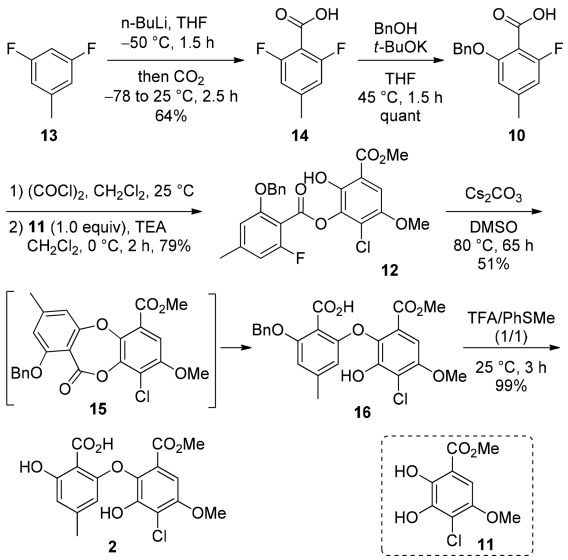
Scheme 1. Synthetic Strategy toward (−)-Maldoxin



in the electrophilic substrates of an S_NAr reaction, i.e., Sanger's reagent (1-fluoro-2,4-dinitrobenzene), to accelerate the reaction effectively. However, removal of the nitro group requires a stepwise reduction and decreases the convergency of the synthesis. Thus, we planned an intramolecular S_NAr reaction without nitro groups for the diaryl ether formation, as reported in the recent work of Ohmori and Suzuki.[9] We envisioned that the intramolecular S_NAr reaction of ester **12** would give **2** directly via the hydrolysis of **3**. Once a large amount of **2** was in hand, catalytic asymmetric oxidative dearomatization[10] would be attempted. Ester **12** can be easily prepared from benzoic acid **10** and catechol **11** by a site-selective esterification. In addition, preparation of catechol **11** has been reported in our previous studies.[8]

We commenced the total synthesis of pestheic acid **2** with the preparation of fragment **10** (Scheme 2) according to a procedure similar to the preparation of benzoic acid **14**,[11] in which lithiation of 3,5-difluorotoluene (**13**) and subsequent carboxylation provided benzoic acid **14**. The intermolecular S_NAr reaction with KOBn in THF gave Bn-protected 6-fluoro-4-methylsalicylic acid **10** in quantitative yield. Regioselective esterification via benzoyl chloride with the less hindered

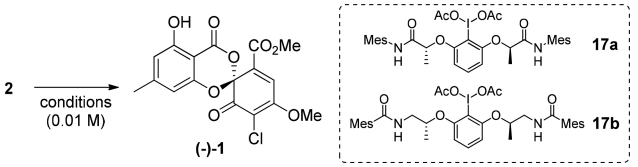
Scheme 2. Total Synthesis of Pestheic Acid (2)



hydroxyl group of fragment **11** was then achieved, providing benzoate **12** in 79% yield. After several experiments,[12] we found that treatment of benzoate **12** with Cs_2CO_3 in DMSO (0.05 M, 80 °C, 65 h) provided diaryl ether **16** in 51% yield, along with hydrolysates **10** (20%) and **11** (15%). Ether **16** was formed by the intramolecular S_NAr and successive hydrolysis of 7-membered lactone **15**. Removal of the Bn group was accomplished by treatment with a mixture of TFA and thioanisole[13] to give pestheic acid **2** in quantitative yield. All the spectral data of our synthetic **2** were identical to those of natural **2**.[2]

We next focused on the asymmetric oxidative dearomatization of pestheic acid (**2**) to (−)-maldoxin (**1**). At first, oxidation of **2** with stoichiometric amounts of chiral hypervalent organoiodine(III) reagents **17a** and **17b**[14] was attempted (Table 1). Oxidation of **2** with lactate-derived iodine(III) **17a**

Table 1. Stoichiometric Oxidative Dearomatization Using Chiral Organoiodine(III) Reagents



entry[a]	reagent (equiv)	solvent	temp (°C)	time (h)	yield (%)	ee (%)
1	**17a** (2.0)	CH_2Cl_2/HFIP[b]	0	5	47	59
2	**17a** (2.0)	toluene	25	15	50	67
3	**17a** (2.0)	CCl_4	25	15	51	76
4	**17a** (2.0)	$CHCl_3$	0	8	59	85
5	**17a** (2.0)	CH_2Cl_2	0	8	57	77
6	**17a** (2.0)	$CHCl_3$	−10	50	59[c]	90
7	**17b** (1.5)	$CHCl_3$	−20	15	61	99

[a]All reactions were carried out at 0.01 mmol scale. [b]CH_2Cl_2/HFIP = 2/1. [c]Starting material **2** (5%) was recovered.

gave (−)-**1** in moderate yield (entries 1−5), and the best enantioselectivity was observed when $CHCl_3$ was used as the solvent (entry 4). The enantioselectivity was improved further at lower temperature; however, the reaction did not complete, even after a long reaction time (entry 6). On the other hand, and to our delight, both the reaction rate and enantioselectivity could be improved by the use of the much more conformationally flexible organoiodine(III) **17b**,[14c] and enantiomerically pure (−)-**1** was obtained (entry 7). The X-ray crystallographic analysis of (−)-**1** confirmed the absolute stereochemistry of (−)-maldoxin as an (*R*)-configuration (Figure 2). The spectroscopic data of our synthetic (−)-maldoxin were in good agreement with those of natural (−)-maldoxin.[1,4,15]

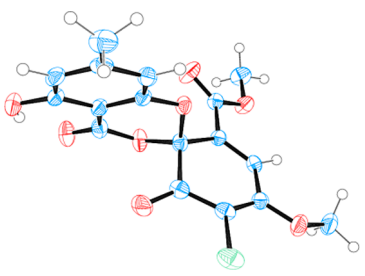


Figure 2. ORTEP drawing of (−)-maldoxin.

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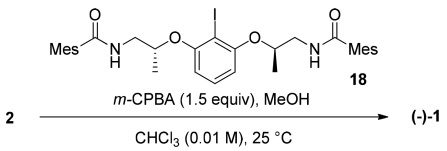
Next, we investigated the oxidative dearomatization of pestheic acid under catalytic conditions using organoiodine **18** and *m*-CPBA as a co-oxidant (Table 2). Treatment of **2** with

Table 2. Catalytic Oxidative Dearomatization Using Chiral Organoiodine 18



entry	scale (mmol)	**18** (mol %)	MeOH (equiv)	time (h)	yield (%)	ee (%)
1	0.01	20	-	8	65	96
2	0.01	20	10	14	71	98
3	0.01	20	25	6	75	98
4	0.01	20	37.5	6	76	99
5	0.01	20	50	6	75	99
6	0.01	20	75	7	61	98
7	0.01	20	100	13	36	87
8[a]	1.0	20	37.5	5	86	99
9[a]	0.10	10	20	18	93	99

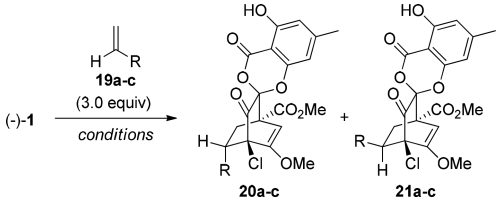
[a]The reactions were carried out at 0 °C.

20 mol % of **18** and 1.5 equiv of *m*-CPBA at room temperature resulted in a slight decrease in the enantiomeric excess compared to stoichiometric oxidation at low temperature (Table 2, entry 1 versus Table 1, entry 7). The additional effect of an alcohol[14c−e] was then examined under catalytic oxidation conditions (entries 2−7). The yield and enantioselectivity of the reaction improved with the use of an excess of methanol (10 to 50 equiv, entries 2−5). Moreover, the use of a large excess of methanol resulted in lower yield and enantioselectivity (entries 6 and 7). These results are very consistent with the previous findings.[14c−e] The best results with respect to chemical yield and enantioselectivity were obtained with the use of 37.5 equiv of methanol (entry 4). Importantly, the reaction proceeded much more efficiently at 0 °C on a 1.0 mmol scale, and optically pure (−)-**1** was obtained in 86% yield (entry 8). Furthermore, the yield and enantioselectivity were maintained (93% yield, 99% ee) when the loading amount of the catalyst was lowered to 10 mol % (entry 9).

Finally, we were interested in the reactivity of (−)-maldoxin as a diene in the Diels−Alder reaction with the typical dienophiles ethyl vinyl ether **19a**, styrene **19b**, and methyl acrylate **19c** (Table 3). A reaction with **19a** and **19b** (entries 1 and 2) proceeded smoothly at room temperature to give the corresponding cycloadducts **20** and **21** in excellent yields with good diastereoselectivity;[16] however, the reaction with **19c** required relatively harsh conditions (entry 3, 80 °C, 25 h). These results reveal that (−)-maldoxin is a good substrate for reverse-electron-demand Diels−Alder reactions.[17]

In conclusion, we have achieved the total synthesis of pestheic acid based on an intramolecular S_NAr reaction without a nitro group (9-step longest linear sequence (LLS) from commercial 5-methoxysalicylic acid) and the subgram scale synthesis of (−)-maldoxin by catalytic enantioselective oxidative dearomatization (overall 10% yield, 10-step LLS, 99% ee). This synthesis demonstrates usefulness of the catalytic enantioselective oxidative dearomatization using chiral organoiodine compound **18**. Moreover, we revealed the reactivity of (−)-maldoxin as a diene with simple alkenes. Studies toward

Table 3. Diels−Alder Reaction of (−)-Maldoxin with Typical Dienophiles 19a−c



entry	R	solvent	temp (°C)	time (h)	yield (%)	ratio 20:21
1	OEt (**19a**)	CH_2Cl_2	25	8	99	7.5:1
2	Ph (**19b**)	CH_2Cl_2	25	20	95	7.8:1
3	CO_2Me (**19c**)	toluene	80	25	quant	4.8:1

[a]The ratio was determined by ^1H NMR analysis.

the biomimetic synthesis of chloropupukeananin using (−)-maldoxin and (+)-iso-A82775C[18] will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01502.

Detailed experimental procedures, spectroscopic data, ^1H and ^{13}C NMR spectra, and X-ray crystallographic data of new compounds (PDF)

Accession Codes

CCDC 1829379 and 1833157 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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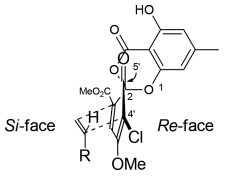
(15) The value of optical rotation of our synthetic **1** ($[\alpha]_D^{25}$ = −314.6 (c 0.1, MeOH)) is inconsistent with that of natural **1** ($[\alpha]_D^{25}$ = − 31.7 (c 0.12, MeOH)) reported by Che et al. (ref 5). We assumed that a partial racemization of natural **1** during the isolation process might occur. In fact, we found that our synthetic **1** (99% ee) underwent a partial racemization in some conditions: i.e., in a polar aprotic solvent (DMSO, rt, 48 h, 95% ee) and in the presence of silica gel (SiO_2, EtOAc, rt, 48 h, 97% ee).

(16) The stereochemistry of major product **20b** was determined by X-ray crystallographic analysis. Those of **20a** and **20c** were estimated by the similarity of NMR spectra. The observed diastereoselectivity can be explained as follows: (i) dienophiles tend to approach from the *Si*-face of C4′ because the dihedral angle of C4′−C5′−C2−O1 is −90° (calculated from the X-ray crystallographic analysis), and (ii) the secondary orbital interaction between C3′ and R favors cycloadducts **20a−c**. Alternatively, the diastereoselectivity can be explained by the hyperconjugative effects illustrated by Quideau et al. in the studies of cyclodimerization of similar *ortho*-benzoquinone monoketals, see: Gagnepain, J.; Méreau, R.; Dejugnac, D.; Léger, J.-M.; Castet, F.; Deffieux, D.; Pouységu, L.; Quideau, S. *Tetrahedron* **2007**, *63*, 6493−6505.



(17) For a recent example of the stereoselective Diels−Alder reaction of the chiral *ortho*-benzoquinone monohemiaminals with various alkenes, see: Saito, E.; Matsumoto, Y.; Nakamura, A.; Namera, Y.; Nakada, M. *Org. Lett.* **2018**, *20*, 692−695. Interestingly, the *ortho*-benzoquinone monohemiaminals derived from the 4-*tert*-butylcatechol derivative showed an opposite reactivity from our results.

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