

# Syntheses of Chloroisosulochrin and Isosulochrin and Biomimetic Elaboration to Maldoxin, Maldoxone, Dihydromaldoxin, and Dechlorodihydromaldoxin

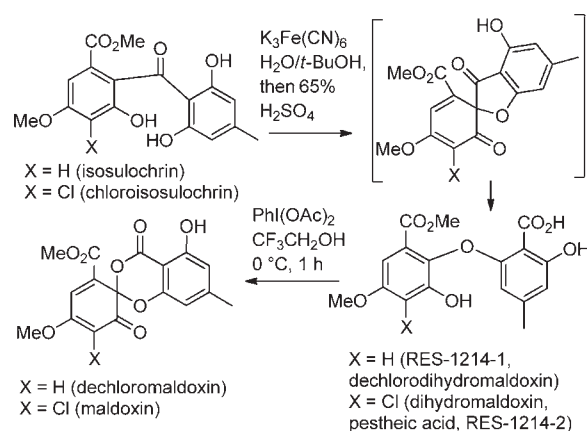
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## ABSTRACT



An efficient synthesis of chloroisosulochrin was accomplished using a novel ortho-selective chlorination of a phenol with sulfuryl chloride and 2,2,6,6-tetramethylpiperidine as the key step. Further elaboration by a biomimetic route converted chloroisosulochrin to dihydromaldoxin, maldoxone (lactone formed by dehydration of dihydromaldoxin), and maldoxin and isosulochrin to dechlorodihydromaldoxin and dechloromaldoxin.

Liu, Che, and co-workers recently reported the isolation of the cytotoxic natural product chloropestolide A (**3**) and several congeners from the fermentation of the plant endophytic fungus *Pestalotiopsis fici*.<sup>1</sup> These compounds were suggested to arise by an inverse electron demand Diels–Alder reaction between maldoxin (**1b**)<sup>2</sup> as the diene

and isopropenylallene **2**, which was also isolated from *Pestalotiopsis fici*, as the dienophile (see Scheme 1).<sup>1</sup> We decided to synthesize maldoxin (**1b**) and then explore the regio- and stereoselectivity of the Diels–Alder reaction of maldoxin with a simpler isopropenylallene.<sup>3</sup>

The biosynthesis of maldoxin (**1b**) may proceed by oxidative cleavage of the anthraquinone fragilin (**4b**) and methylation of the carboxylic acid to give chloroisosulochrin (**5b**) (see Scheme 2).<sup>4</sup> Oxidative cyclization could give spirofuran-3-one **6b**, which could be hydrolyzed to give

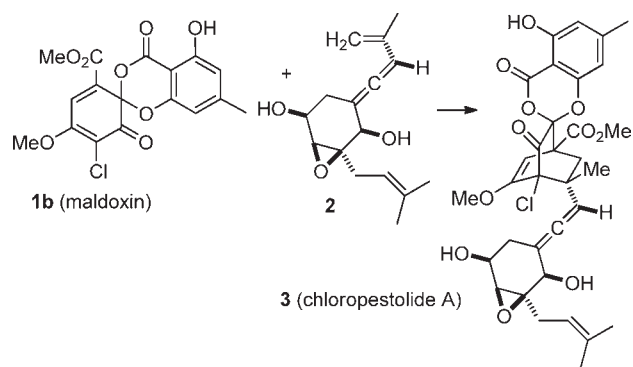
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### Scheme 1



dihydromaldoxin (RES-1214-2, pestheic acid, **7b**).<sup>2,4,5</sup> A second oxidative cyclization could then lead to maldoxin (**1b**).<sup>2</sup> A similar oxidative cleavage of physcion (**4a**) would give isosulochrin (**5a**),<sup>4,6</sup> which could be oxidatively cyclized to give dechlorodihydromaldoxin (RES-1214-1, **7a**).<sup>2,5</sup> Although only dihydromaldoxin was isolated by Liu and Che from *Pestalotiopsis fici*,<sup>1</sup> isosulochrin (**5a**), chloroisosulochrin (**5b**), and dihydromaldoxin (pestheic acid, **7b**) were all isolated from *Pestalotiopsis theae*,<sup>4</sup> both dechlorodihydromaldoxin (RES-1214-1, **7a**) and dihydromaldoxin (RES-1214-2, **7b**) were isolated from *Pestalotiopsis* sp. RES-1214,<sup>5</sup> and dechlorodihydromaldoxin (**7a**), dihydromaldoxin (**7b**), and maldoxin (**1b**) were all isolated from an unidentified *Xylaria* species.<sup>2</sup> The isolation of both chlorinated and unchlorinated **5** and **7** from the same source suggests that chlorination might occur after oxidative cleavage of anthraquinone **4**. RES-1214-1 (**7a**) and -2 (**7b**) selectively inhibit ET-1 binding to endothelin type A receptor (ET<sub>A</sub> receptor) with IC<sub>50</sub> values of 1.5 and 20 μM, respectively.<sup>5</sup> They also inhibit the increase in intracellular Ca<sup>2+</sup> concentration elicited by 1 nM ET-1 in A10 cells.<sup>5</sup>

We planned to synthesize chloroisosulochrin (**5b**) and convert it to maldoxin (**1b**) by the biomimetic sequence shown in Scheme 2. The oxidative cyclization of 2, 2'-dihydroxybenzophenones analogous to **5** to give spirofuranones analogous to **6** and acid-catalyzed hydrolysis of the spirofuranones to provide 2-(2-hydroxyphenoxy)benzoic acids analogous to **7** are well precedented.<sup>7</sup> The oxidative cyclization of 2-(4-hydroxyphenoxy)benzoic acids to give benzo[*d*][1.3]dioxin-4-ones spiro fused at the 4-position to 2,5-cyclohexadienones is known,<sup>8</sup> but the

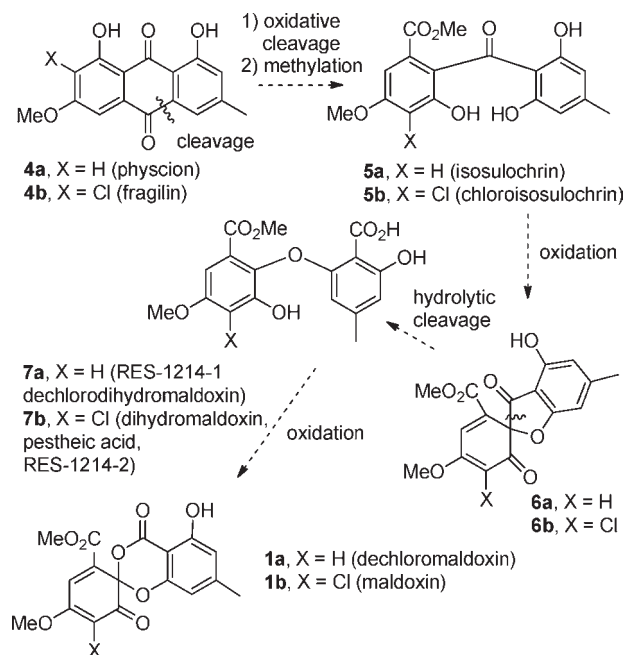
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### Scheme 2. Biosynthesis of Maldoxin



analogous preparation of benzo[*d*][1.3]dioxin-4-ones such as maldoxin that are spiro fused at the 6-position to 2,4-cyclohexadienones is unknown, possibly because of the susceptibility of such dienones to dimerization.<sup>9</sup>

We started with resorcinol **8**,<sup>10</sup> an intermediate in Katoh's synthesis of geodin. Selective methylation of the less hindered hydroxy group of **8** provided phenol **9a** in 92% yield (see Scheme 3). We needed to selectively chlorinate **9a** ortho to the phenol. Unfortunately, ortho chlorination of complex phenols has proved to be very challenging.<sup>11</sup> Our initial attempt with NCS and benzoyl peroxide in CCl<sub>4</sub> provided a disappointing 1:8 mixture of the desired ortho chlorophenol **9b** and the para chlorophenol **10**. Gnaim and Sheldon reported that phenol can be selectively ortho chlorinated with SO<sub>2</sub>Cl<sub>2</sub> and primary or secondary amines in toluene.<sup>12</sup> They suggested that the high regioselectivity with phenol results from the *in situ* formation of an *N*-chloroamine, which hydrogen bonds to the phenol forming a complex that delivers chlorine intramolecularly to the ortho position. We were disappointed to find that chlorination of **9a** with SO<sub>2</sub>Cl<sub>2</sub> and *tert*-butylamine in toluene provided only a 1:2.6 mixture of **9b** and **10**, although these conditions provide an 11.4:1 ortho/para mixture from phenol itself.<sup>12b</sup> Presumably,

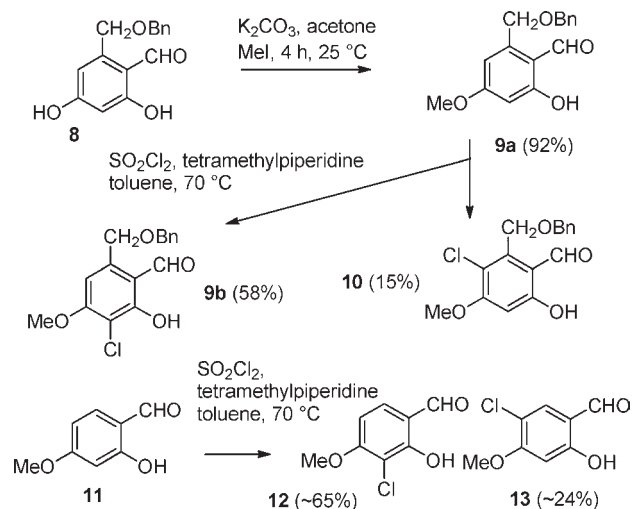
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**Scheme 3.** Selective Ortho Chlorination

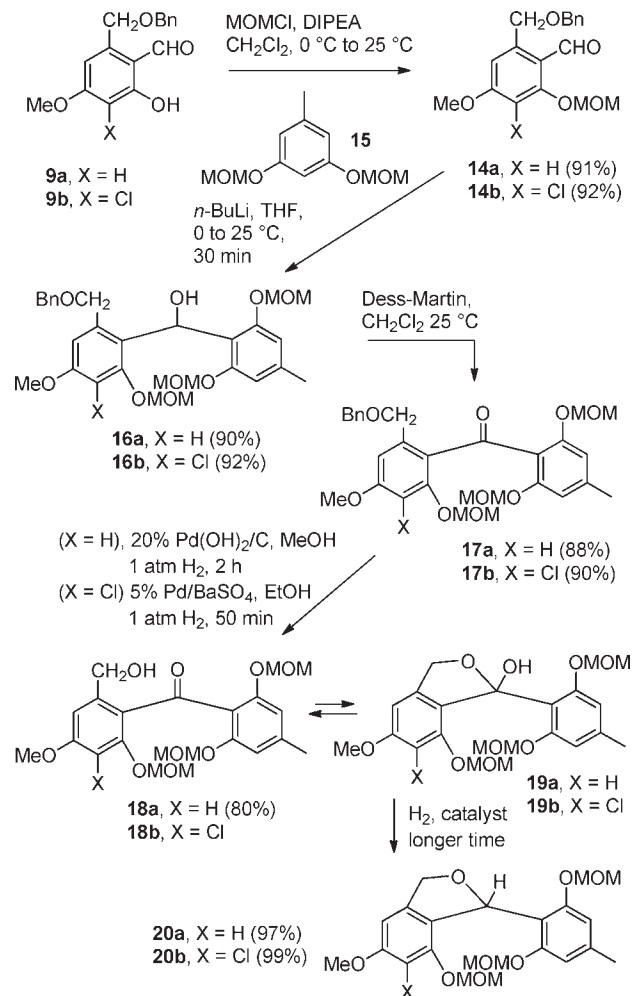


intermolecular chlorination to give **10** occurs more rapidly with the more nucleophilic aromatic ring of **9a**. We reasoned that hindered secondary amines would form a more hindered and therefore less reactive *N*-chloroamine that would favor chlorination via the hydrogen bonded complex that leads to **9b**. We were pleased to find that the selectivity increased as we changed to more hindered secondary amines, increasing to 1.8:1 with dipropylamine, to 3.3:1 with diisopropylamine, and to 3.9:1 with 2,2,6,6-tetramethylpiperidine. Fortunately the products are easily separated so that using the latter amine we were able to obtain **9b** (58%) and **10** (15%) on a gram scale. We observed a similar effect of amine bulk on the chlorination selectivity with phenol **11**, which gave a 0.8:1, 1.8:1, 2.4:1, or 2.6:1 mixture of **12**<sup>13</sup> and **13**<sup>14</sup> with sulfuryl chloride and *tert*-butylamine, dipropylamine, diisopropylamine, or 2,2,6,6-tetramethylpiperidine, respectively.

We proceeded in parallel with both maldoxin precursor **9b** and the unchlorinated phenol **9a**, which should give rise to dechloromaldoxin and allow us to explore the effect of the chlorine atom on the Diels–Alder reaction. Protection of phenols **9a/b** with MOMCl and DIPEA afforded MOM ethers **14a** (91%) and **14b** (92%) (see Scheme 4). Deprotonation<sup>15</sup> of bis MOM ether **15** with *n*-BuLi and addition of the aryllithium to **14a/b** afforded alcohols **16a** (90%) and **16b** (92%), which were oxidized by Dess–Martin periodinane to give benzophenones **17a** (88%) and **17b** (90%).

Not surprisingly, the hydrogenolysis of the benzyl ether of **17a/b** proved to be challenging. Product **18a/b** is a hydroxy ketone that can cyclize to form hemiketal **19a/b**, which is readily hydrogenolyzed to form dihydroiso-

**Scheme 4.** Preparation of Hydroxymethyl Ketone **18**



benzofuran **20a/b**, which still has two benzylic oxygen substituents that are susceptible to hydrogenolysis. Hydrogenolysis of **17a** was best accomplished over 20% Pd(OH)<sub>2</sub>/C with 1 atm of H<sub>2</sub> in MeOH for 2 h to give **18a** (80%). However, **20a** was isolated in 97% yield when the reaction was run for 5 h. Hydrogenation of chloride **17b** over 20% Pd(OH)<sub>2</sub>/C afforded a mixture of hydroxy ketone **18b** and hemiketal **19b**, which was rapidly reduced to **20b**. The effect of substituents on the equilibration of related hydroxy ketones and hemiketals has been previously noted.<sup>16</sup> Chloride **17b** was best hydrogenolyzed over 5% Pd/BaSO<sub>4</sub><sup>17</sup> with 1 atm of H<sub>2</sub> in EtOH for 50 min to give **18b**. However, **20b** was isolated when the reaction was run for 2 h. Replacing the benzyl protecting group with a 2-naphthylmethyl group should solve the overreduction problem because hydrogenolysis of the 2-naphthylmethyl group is much faster than that of a benzyl group.<sup>18</sup>

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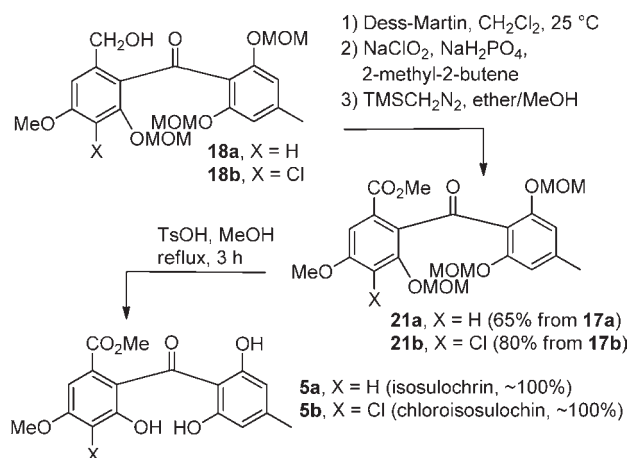
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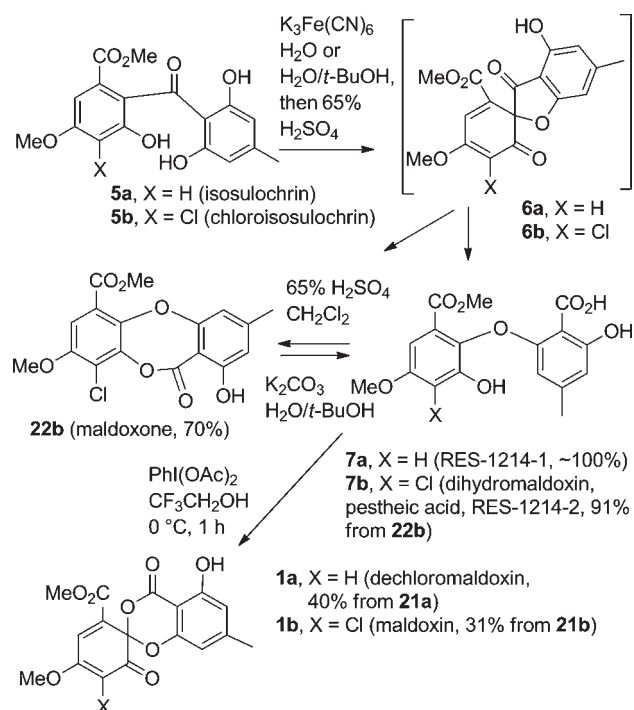
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**Scheme 5.** Completion of the Chloroisosulochrin Synthesis

Unfortunately, chlorination of the 2-naphthylmethyl analog of **9a** proceeded in only 40% yield with only 1.6:1 ortho/para selectivity and addition of the lithium reagent prepared from **15** to the 2-naphthylmethyl analog of **14b** proceeded in only 68% yield.

The standard three-step sequence shown in Scheme 5 converted hydroxy ketones **18a** and **18b** to keto esters **21a** (65% from **17a**) and **21b** (80% from **17b**). The four-step conversion of the benzyl ethers of **17a/b** to the methyl esters of **21a/b** is cumbersome but was used because we were unable to add the aryllithium reagent prepared from **15** to the aldehyde analogous to **14a** with a CO<sub>2</sub>Me instead of a CH<sub>2</sub>OBn group. Deprotection of all three MOM ethers of **21a/b** with TsOH in MeOH at reflux cleanly afforded isosulochrin (**5a**)<sup>6</sup> and chloroisosulochrin (**5b**).<sup>4</sup>

Oxidation<sup>7</sup> of **5a** with potassium ferricyanide in water afforded spirofuranone **6a**, which was hydrolyzed<sup>7</sup> with 65% sulfuric acid to give diaryl ether dechlorodihydromaldoxin<sup>2,4</sup> (**7a**) in quantitative yield (see Scheme 6). A similar oxidation of **5b** in aqueous *tert*-butanol afforded spirofuranone **6b**, but hydrolysis of **6b** with 65% sulfuric acid initially gave a mixture of maldoxone<sup>2</sup> (**22b**) and dihydromaldoxin (**7b**) that was converted to maldoxone in 70% yield at longer reaction times. Hydrolysis of maldoxone with K<sub>2</sub>CO<sub>3</sub> in aqueous *tert*-butanol afforded dihydromaldoxin<sup>2,4,5</sup> (**7b**) in 91% yield. Oxidative cyclization of **7a** with PhI(OAc)<sub>2</sub> in CF<sub>3</sub>CH<sub>2</sub>OH at 0 °C afforded dechloromaldoxin (**1a**) in 40% overall yield for the four-step sequence from **21a**. The structure of **1a** was confirmed by X-ray crystallography. A similar oxidative cyclization of **7b** afforded maldoxin (**1b**) in 31% overall yield for the

**Scheme 6.** Biomimetic Conversion of Chloroisosulochrin to Maldoxin

five-step sequence from **21b**. The Diels–Alder reactions of both dihydromaldoxin (**1a**) and maldoxin (**1b**) with an isopropenylallene will be described elsewhere.<sup>3</sup>

In conclusion, an efficient synthesis of chloroisosulochrin (**5b**) was accomplished using a novel ortho-selective chlorination of a phenol with sulfonyl chloride and 2,2,6,6-tetramethylpiperidine as the key step. Further elaboration by a biomimetic route converted chloroisosulochrin to dihydromaldoxin, maldoxone, and maldoxin and isosulochrin to dechlorodihydromaldoxin and dechloromaldoxin.

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**Supporting Information Available.** Complete experimental procedures, copies of <sup>1</sup>H and <sup>13</sup>C NMR spectral data, and CIF file and drawing of X-ray crystal structure of **1a**. This material is available free of charge via the Internet at <http://pubs.acs.org>.