Published in final edited form as:

Org Lett. 2011 August 19; 13(16): 4224–4227. doi:10.1021/ol201561w.

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 sulfonyl 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*.¹ These compounds were suggested to arise by an inverse electron demand Diels-Alder reaction between maldoxin (**1b**)² as the diene and isopropenylallene **2**, which was also isolated from *Pestalotiopsis fici*, as the dienophile (see Scheme 1).¹ We decided to synthesize maldoxin (**1b**) and then explore the regio- and stereoselectivity of the Diels-Alder reaction of maldoxin with a simpler isopropenylallene.³

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).⁴ Oxidative cyclization could give spirofuran-3-one **6b**, which could be hydrolyzed to give dihydromaldoxin (RES-1214-2, pestheic acid, **7b**).^{2,4,5} A second oxidative cyclization could then lead to maldoxin (**1b**).² A similar oxidative cleavage of physcion (**4a**) would give isosulochrin (**5a**),^{4,6} which could be oxidatively cyclized to give

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Supporting Information Available: Complete experimental procedures, copies of ¹H and ¹³C 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>.

dechlorodihydromaldoxin (RES-1214-1, **7a**).^{2,5} Although only dihydromaldoxin was isolated by Liu and Che from *Pestalotiopsis fici*,¹ isosulochrin (**5a**), chloroisosulochrin (**5b**), and dihydromaldoxin (pestheic acid, **7b**) were all isolated from *Pestalotiopsis theae*,⁴ both dechloro-dihydromaldoxin (RES-1214-1, **7a**) and dihydromaldoxin (RES-1214-2, **7b**) were isolated from *Pestalotiopsis* sp. RES-1214,⁵ and dechlorodihydromaldoxin (**7a**), dihydromaldoxin (**7b**), and maldoxin (**1b**) were all isolated from an unidentified *Xylaria* species.² 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_A receptor) with IC₅₀ values of 1.5 μ M and 20 μ M, respectively.⁵ They also inhibit the increase in intracellular Ca²⁺ concentration elicited by 1 nM ET-1 in A10 cells.⁵

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** is well precedented.⁷ 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,⁸ but the 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.⁹

We started with resorcinol **8**,¹⁰ 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.¹¹ Our initial attempt with NCS and benzoyl peroxide in CCl₄ 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 SO₂Cl₂ and primary or secondary amines in toluene.¹² 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 SO₂Cl₂ and *t*-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.^{12b} Presumably, 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**¹³ and **13**¹⁴ with sulfuryl chloride and *t*-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). Deprotonation¹⁵ 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 dihydroisobenzofuran **20a/b**, which still has two benzylic oxygen substituents that are susceptible to hydrogenolysis. Hydrogenolysis of **17a** was best accomplished over 20% Pd(OH)₂/C with 1 atm of H₂ 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)₂/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.¹⁶ Chloride **17b** was best hydrogenolyzed over 5% Pd/BaSO₄¹⁷ with 1 atm of H₂ 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.¹⁸ 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 CO₂Me instead of a CH₂OBn group. Deprotection of all three MOM ethers of **21a/b** with TsOH in MeOH at reflux cleanly afforded isosulochrin (**5a**)⁶ and chloroisosulochrin (**5b**).⁴

Oxidation⁷ of **5a** with potassium ferricyanide in aqueous *t*-butanol afforded spirofuranone **6a**, which was hydrolyzed⁷ with 65% sulfuric acid to give diaryl ether dechlorodihydromaldoxin^{2,4} (**7a**) in quantitative yield. A similar oxidation of **5b** afforded spirofuranone **6b**, but hydrolysis of **6b** with 65% sulfuric acid initially gave a mixture of maldoxone² (**22b**) and dihydromaldoxin (**7b**) that was converted to maldoxone in 70% yield at longer reaction times. Hydrolysis of maldoxone with K₂CO₃ in aqueous *t*-butanol afforded dihydromaldoxin^{2,4,5} (**7b**) in 91% yield. Oxidative cyclization of **7a** with PhI(OAc)₂ in CF₃CH₂OH 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 five-step sequence from **21b**. The Diels–Alder reactions of both dihydromaldoxin (**1a**) and maldoxin (**1b**) with an isopropenylallene will be described elsewhere.³

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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We are grateful to the National Institutes of Health (GM-50151) for support of this work. We thank the National Science Foundation for grant CHE-0521047 for a new X-ray diffractometer.

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Scheme 1.

Scheme 2.
Biosynthesis of Maldoxin

Scheme 3.
Selective Ortho Chlorination

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

Scheme 5.
Completion of the Chloroisosulochrin Synthesis

Scheme 6.
Biomimetic Conversion of Chloroisosulochrin to Maldoxin