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# A synthetic route to 1,3-dihydroisobenzofuran natural products: the synthesis of methyl ethers of pestacin

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ABSTRACT

A synthetic route to 1-(2,6-dihydroxyphenyl)phthalan natural products is described. It is typified by the synthesis of permethyl and monomethyl ethers (**21** and **22**) of pestacin (**1**), a 1,3-dihydroisobenzofuran natural product. The key step is hydrodeoxygenation of the corresponding isobenzofuranone **19** in 2 steps: reduction and intramolecular etherification. A route involving hydrodesulfurization of a thionophthalide to a phthalan (e.g., **8**) is also reported.



## 1. Introduction

Phthalans (1,3-dihydroisobenzofurans) are a well-known class of compounds. They exhibit fascinating pharmacological activities[1] and chemistry.[2] In 2003, pestacin (**1**),[3] the first member of the phthalan natural products[4] was isolated as a racemic mixture from the microorganism *Pestalotiopsis microspora* and assigned structure **1** on the basis of analysis of NMR and X-ray data (Fig. 1). It displays potent antioxidant activity and moderate antifungal properties. More recently, 7-bromo-1-(2,3-dibromo-4,5-dihydroxyphenyl)-5,6-dihydroxy-1,3-dihydroisobenzofuran has been found applicable for the treatment of malignant tumors.[5] Thus, they represent an important class of targets for chemical synthesis.

Our recent studies on the total synthesis[6] of isopestacin (**2**) and cryphonectric acid (**3**) have shown that the regioselective synthesis of 3-(2,6-dihydroxyaryl)phthalides can be achieved by the combination of two key reactions: (i) condensation of phthalaldehydic acids with appropriate cyclohexane-1,3-diones and (ii) aromatization of the resulting cyclohexenylphthalide moieties. An obvious extension of the strategy is the synthesis of structurally analogous pestacin (**1**) in a similar manner from the respective phthalide **4**. However, we were concerned about the formation of the phthalan motif, since there is a lack of methods for hydrodeoxygenation of readily accessible phthalides. The existing routes[7] to 3-arylphthalans encompass (i) cycloetherification of the *ortho* substituted aromatics, (ii) deoxygenation of lactols, (iii) oxa-Pictet-Spengler reaction, (iv) intramolecular Diels–Alder reaction, (v) cyclotrimerization of alkynes, and (vi) hydrogenation of benzoisofurans. None of the approaches appeared to be well suited for the present target. Consequently, we considered a cognate preparation of phthalide **4** and its conversion to **5**, which on hydrodesulfurization was expected to furnish the target, that is, **1** (Scheme 1).

## 2. Results and discussion

The study for the hydrodesulfurization is depicted in Scheme 2. Phthalide **6**,[6] obtained in 2 steps from the commercially available starting materials, was converted to thionolactone **7** in 72% yield by interaction with Lawesson reagent.[8] The structure of phthalide **7** was unequivocally established by analysis of spectroscopic data. When it was subjected to treatment with Raney nickel, the desired phthalan **8** was obtained. But the yield was far from satisfactory (<5%). Attempted reduction of **7** with tributyltin hydride also resulted in an intractable mixture of products.

Alternatively, formyl hydroxy ester **9a** and formyl hydroxy acid **10a** were planned to be utilized. However, their condensation with cyclohexane-1,3-dione (**11**) could not be effected by the use of DBU or *p*-TSA,[6] probably due to the presence of free phenolic OH groups. When the benzyl-protected acid **10b**, prepared from **9b**, was reacted with 1,3-dione **11** in the presence of DBU, 3-cyclohexenylphthalide **12** was obtained in good yield.[9] To our surprise, the desired aromatization of **12** did not take place with either $Hg(OAc)_2$[10] or $CuCl_2$[11] to give **13**, prohibiting further progress on the synthesis of phthalan **14** (Scheme 3).

In a revised plan (Scheme 4), permethylated phthalide **15** was targeted, hoping that its demethylation, followed by reduction and cyclization would permit the synthesis of pestacin (**1**). The

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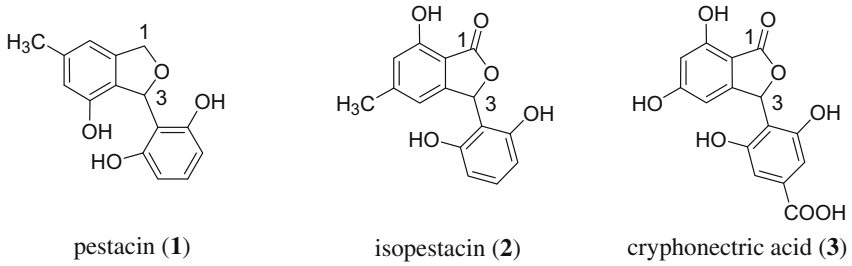
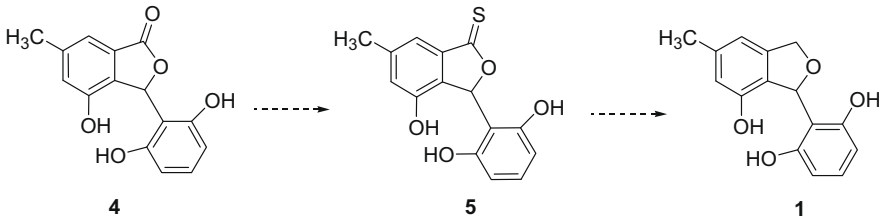
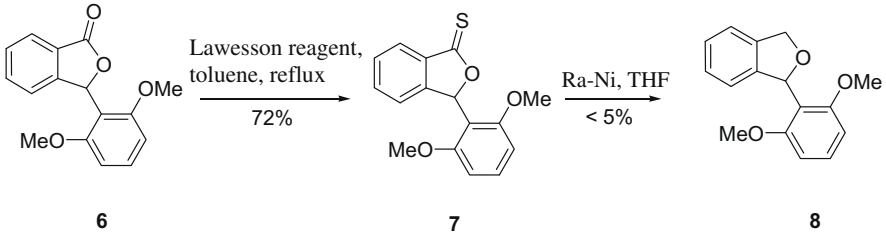


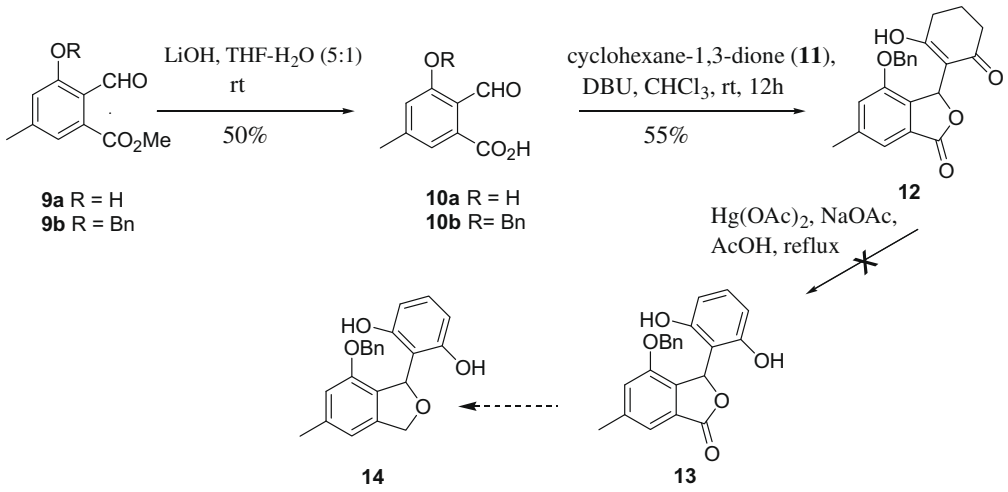

**Figure 1.** Structure of pestacin and allied natural products.




**Scheme 1.** Hydrodesulfurization route to pestacin (**1**).

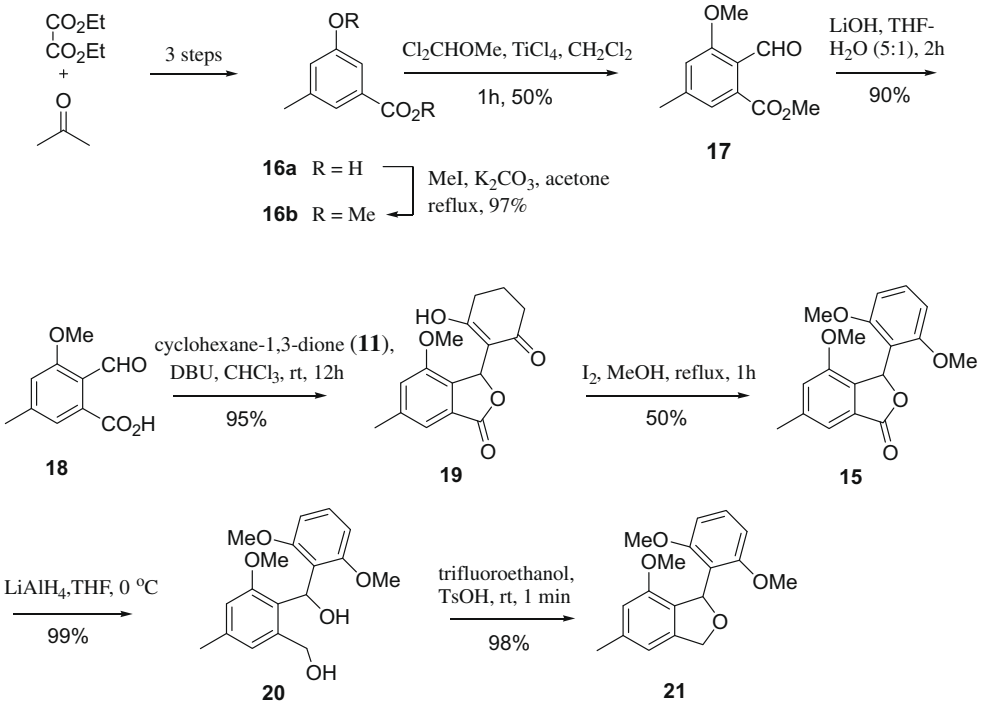



**Scheme 2.** Model study on hydrodesulfurization of **7**.




**Scheme 3.** Approach to *O*-benzyl ether of pestacin (**14**).

starting unsymmetrically substituted hydroxybenzoic acid **16a** was prepared from acetone and diethyl oxalate by the reported 3-step procedure[12] and derivatized to **16b** by the reaction with MeI–$K_2CO_3$ in acetone.[13] It was then formylated with $Cl_2CHOMe$–$TiCl_4$[14a] to furnish a 1:1 mixture of formyl esters[14b] from which the desired one **17** was isolated. The formyl ester **17** was hydrolyzed by LiOH[15] to give phthalaldehydic acid **18** in 90% yield. The crucial condensation of **18** with cyclohexane-1,3-dione (**11**) was performed to yield 3-cyclohexenylphthalide **19** in excellent yield under the previously established conditions involving DBU. Treatment of **19** with iodine and methanol[16] at reflux afforded trimethoxyarylphthalide **15** in moderate yield. It was then expectedly reduced with $LiAlH_4$ to diol **20** in almost quantitative yield. The initial attempts to effect the ring closure of **20** to **21** with TsCl or

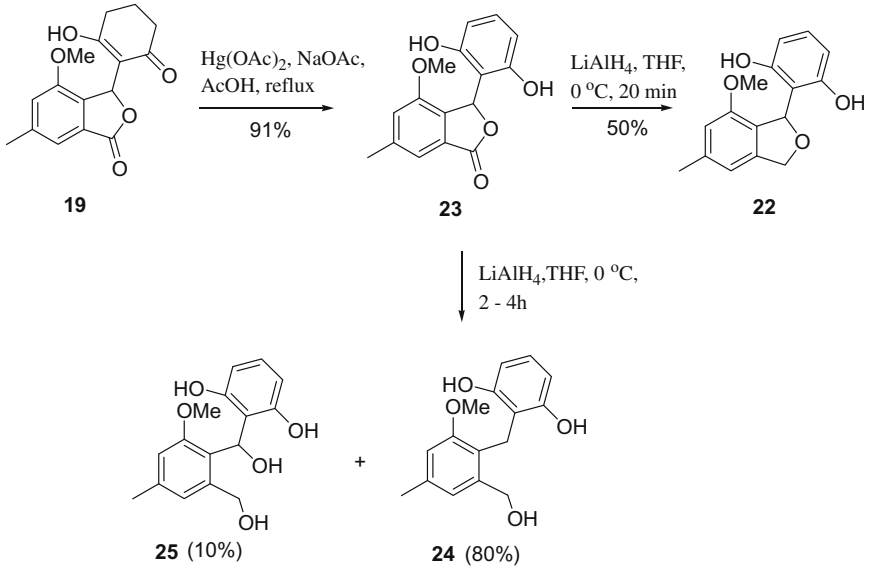



**Scheme 4.** Synthesis of permethylated pestacin (**21**).

MsCl–$NEt_3$[17] produced permethylated pestacin **21** in low yields. However, Kirmse and Kund system: trifluoroethanol–tosic acid[18] proved to be the best, giving **21** in 98% yield. To our dismay, the desired demethylation of **21** to the target **1** remained to be the daunting task. Several reagents, known for demethylation of methyl aryl ethers, were examined. They were $BBr_3{\cdot}SMe_2$–1,2-dichloroethane[19], $BBr_3$, HBr–AcOH, LiI–collidine,[20] EtSH–NaH, $Et_2N(CH_2)_2SH{\cdot}HCl$–*t*-BuONa,[21] iodocyclohexane–DMF,[22] and $AlCl_3$. None were found to be suitable for the purpose, probably due to the sensitivity of the furan ring to acids.[23]

In order to define the problem of demethylation of **21**, we decided to prepare monomethyl ether of pestacin, that is, **22** (Scheme 5). Application of mercuric acetate promoted aromatization to phthalide **19** furnishing resorcinolylphthalide **23** in 91% yield. Exposure of **23** to LAH in THF gave deoxygenated alcohol **24** along with the diol **25** as a minor product. Optimization of the same reaction with respect to time served to give phthalan **22** directly. The intermediate diol **25** was not isolated. The attempts to demethylate compound **22** by various methods were unsuccessful.

In summary, the first synthetic route to 1-(2,6-dihydroxyphenyl)phthalan natural products is illustrated by the synthesis of permethyl ether **21** and monomethyl ether **22** of pestacin (**1**). The synthesis has been achieved via (i) cyclocondensation of cyclohexane–1,3-dione (**11**) with a phthalaldehydic acid and (ii) formation of the phthalan moiety by reduction of a phthalide followed by




**Scheme 5.** Synthesis of monomethyl ether of pestacin (**22**).

cycloetherification. The potential application of dehydrosulfurization of phthalides for the formation of phthalans has been demonstrated. Work is underway for the completion of the synthesis of pestacin (**1**).

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## Supplementary data

Supplementary data (physical data of selected new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.04.079.

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