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A Novel Synthesis of Substituted 4-Hydroxybenzo[*c*]pyran Quinones

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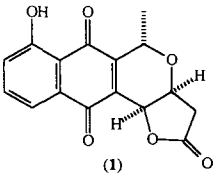
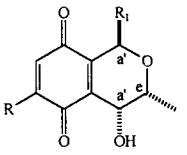
Abstract: The synthesis of three benzopyran quinones containing hydroxy substituents at the 4-position has been achieved. The key step in each of these syntheses involved an oxidative mercury-mediated ring closure. © 1997 Elsevier Science Ltd.

A large number of biologically active quinones contain a benzylic oxygen substituent, for example, nanaomycin D (**1**). This oxygen substituent appears to be important for biological activity.[1] To date, a number of methods have been developed for the construction of benzo- and/or naphtho[*c*]pyran ring systems containing an oxygen substituent at the 4 position.[2] In this communication we report on a method for the construction of the oxygenated benzopyran quinones (**2**), (**3**) and (**4**) that uses an oxidative ring closure mediated by mercury(II).

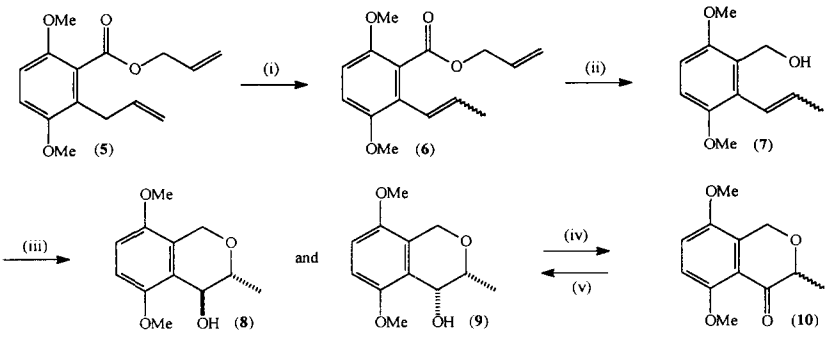


(1)



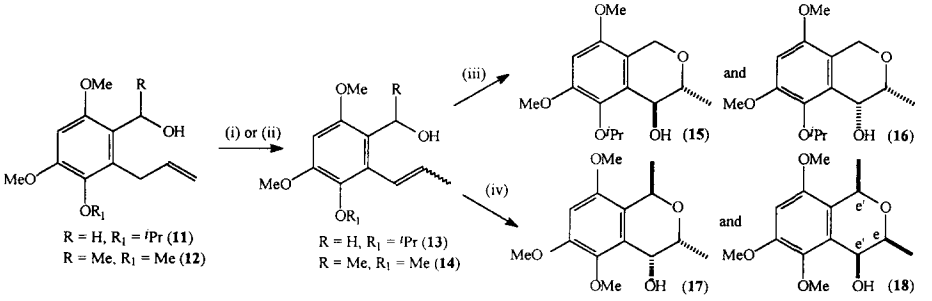
R = H, R_1 = H (**2**)
R = OMe, R_1 = H (**3**)
R = OMe, R_1 = Me (**4**)

Exposure of ester (**5**)[3] to potassium *t*-butoxide yielded styrene (**6**) which was then reduced to alcohol (**7**). Treatment of (**7**) with mercury(II) acetate and sodium borohydride in the presence of oxygen as described by Whitesides[4] yielded a diastereoisomeric mixture of products (**8**) and (**9**) in 86% yield. None of the corresponding isomeric benzofurans were isolated. This diastereoisomeric mixture could be separated on a silica gel column to afford the corresponding *trans*- and *cis*- hydroxypyrans (**8**) and (**9**) respectively. Alternatively, the *cis*- isomer could be obtained exclusively by initially oxidising the isomeric mixture to the racemic ketone (**10**) followed by reduction to afford diastereomerically pure dimethoxybenzo[*c*]pyran (**9**).[5] Finally, oxidation of (**9**) with silver(II) oxide[6] afforded the quinone (**2**) in 89% yield.



(i) $KOBu^t$, DMF, 72%; (ii) $LiAlH_4$, Et_2O, 99%; (iii) $Hg(OAc)_2$, O_2, $NaBH_4$, DMF, 86%; (iv) PCC, CH_2Cl_2, 74%; (v) $LiAlH_4$, Et_2O, 80%.

For the synthesis of quinones (**3**) and (**4**) it was necessary to isomerise the double bond in the side chains of alcohols (**11**) and (**12**)[7] into conjugation with the aromatic ring. The conversion of (**11**) into styrene (**13**) was achieved with potassium *t*-butoxide, while (**12**) was converted into styrene (**14**) upon treatment with palladium(II) chloride-bisacetonitrile complex.[8] Oxidative cyclisation of (**13**) with mercury(II) acetate as described previously then afforded a mixture of the racemic 4-hydroxybenzo[*c*]pyrans (**15**) and (**16**),[9] while (**17**) and (**18**) were similarly obtained from styrene (**14**). All isomers could be separated by silica gel chromatography. Finally, oxidation of (**16**) with silver(II) oxide afforded the desired quinone (**3**) in 89% yield, while oxidation of either (**17**) or (**18**)[10] somewhat surprisingly afforded only quinone (**4**)[11] in high yield (95%).



(i) 1 eq. KOBu^t, DMF, 79%; (ii) $PdCl_2(MeCN)_2$, CH_2Cl_2, 99%; (iii) $Hg(OAc)_2$, O_2, $NaBH_4$, DMF, 26% (**15**) and 22% (**16**); (iv) $Hg(OAc)_2$, NaBr, O_2, $NaBH_4$, DMF, 23% (**17**) and 22% (**18**).

Work is in progress towards optimising the yields of the oxidative ring closure, eliminating unwanted products, and using the reaction in the synthesis of naturally occurring quinones.

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7. The synthesis of alcohols (**11**) and (**12**) is similar to that described on the previous page and will be reported in the full paper.
8. Giles, R.G.F.; Lee Son, V.R.; Sargent, M.V. *Aust. J. Chem.* 1990, **43**, 777-781.
9. 6,8-Dimethoxy-5-isopropoxy-3-methyl-1*H*-benzo[*c*]pyran and 3,4-dihydro-6,8-dimethoxy-5-isopropoxy-3-methyl-1*H*-benzo[*c*]pyran were also isolated in a yield of 4% and 10% respectively. We assume the first product is formed by the elimination of water from products (**15**) and/or (**16**), and the second product by inefficient oxygenation.
10. A mixture of *trans*- and *cis*-3,4-dihydro-1,3-dimethyl-5,6,8-trimethoxy-1*H*-benzo[*c*]pyran was also isolated in 5% yield.
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