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TOTAL SYNTHESIS OF ISOROBUSTIN

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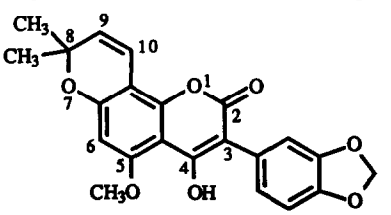
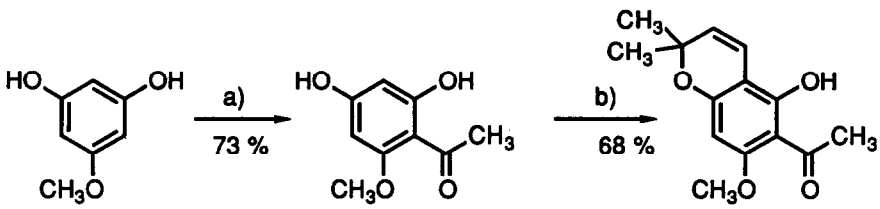
Abstract : *The synthesis of isorobustin* **1** *in four steps from 5-methoxyresorcinol proceeds in an overall yield of 34% . The key step involves the arylation of a 4-hydroxy-2H-1-benzopyran-2-one* **6** *by 3,4-methylenedioxyphenyllead triacetate* **2** *in a chemoselective and regioselective manner.*

A number of 3-aryl-4-hydroxy-*2H*-1-benzopyran-2-ones (common name 3-aryl-4-hydroxycoumarins), a class of isoflavonoid natural products, have been isolated from the genus *Derris* of the Leguminosae, subfamily Papillionoideae [1]. A common structural feature of such compounds is a cyclised prenyl group on ring A of the skeleton. For example, the 3-aryl-8,8-dimethyl-*2H*,*8H*-benzo [1,2-b:3,4-b']dipyran skeleton is observed in isorobustin, isorobustin methyl ether and scandenin, which were recently isolated[2] from *Derris spruceana*, a medium sized tree of the lower Amazon. To date, only one synthesis of this type of compound has been reported in a poor overall yield (4%).[3] It involved a low yielding desoxybenzoin synthesis, followed by a moderately good yielding ring closure of the desoxybenzoin. In this communication, we would like to report that our recently published[4] synthesis of 3-aryl-4-hydroxy-*2H*-1-benzopyran-2-ones involving regioselective arylation at C-3 of a preformed 4-hydroxy-*2H*-1-benzopyran-2-ones by aryllead triacetate can be successfully applied to the preparation of unsaturated compounds such as isorobustin **1** in high overall yields.



Isorobustin **1**



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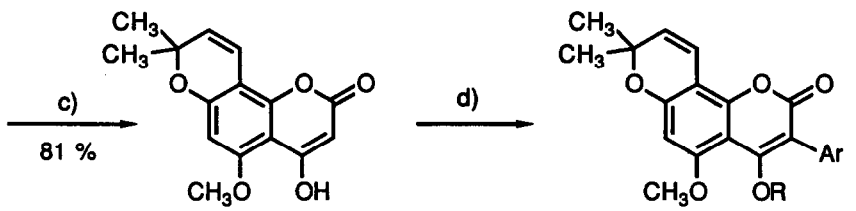

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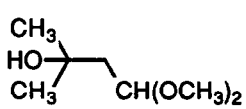
R = H Ar = 4-Anisyl **8**

Ar = 3,4-Methylene dioxyphenyl **1**

R = CH_3 Ar = 3,4-Methylene dioxyphenyl **10**



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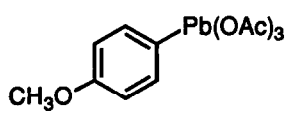

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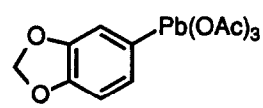


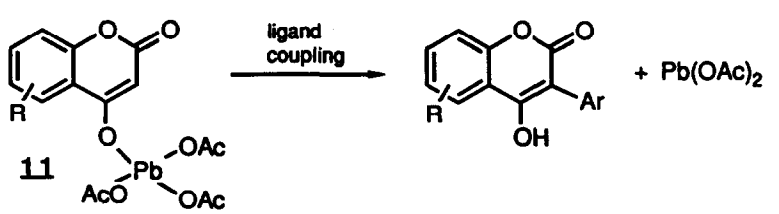
9

a) CH_3CN, HCl (g), zinc chloride, anhydrous diethyl ether, 0°C, 16h .
b) **4** , pyridine, 170 °C, 10h .
c) NaH, $(EtO)_2CO$, reflux, 20min .
d) $ArPb(OAc)_3$, anhydrous pyridine, anhydrous chloroform, 60°C,12h : **7** gives **8** (78%), **9** gives **1** (84%) .

Although the 2,2-dimethylchromen system is found in many widely varied natural products[5], comparatively few methods are available for its construction. The older methods, *e.g.* reaction of methylmagnesium halides with 2*H*-1-benzopyran-2-ones[6], reaction of phenols with 3-hydroxy-3-methylbut-1-yne[7] and reduction of 4*H*-1-benzopyran-4-ones[8] generally give poor yields and are limited in scope. The more recent methods, thermal rearrangement of arylpropargyl ethers, formed from the reaction of phenols with 3-chloro-3-methylbut-1-yne, in boiling N,N-diethylaniline[9] and pyridine catalysed condensation of 3-methylbut-2-enal with *meta*-dihydric phenols[10] are more efficient. The usefulness of the last reaction is diminished by the relative instability of 3-methylbut-2-enal, which resinifies readily even at room temperature. However, 1,1-dimethoxy-3-methylbutan-3-ol was developed[11] as a more stable yet equally efficient reagent for the elaboration of the 2,2-dimethylchromen ring.

In the present investigation, the reaction of methylmagnesium bromide with acetoacetaldehyde dimethyl acetal afforded the dimethylchromenylating agent, 1,1-dimethoxy-3-methylbutan-3-ol **4**, in 67% yield. This was heated (pyridine, 170° C, 10 hours) with the required *ortho*-hydroxyacetophenone[12] **3** (formed in 73% yield from the Hoesch condensation of 5-methoxyresorcinol **2** and acetonitrile), to afford the chromene **5** (68%, m.p. 127-128.5°C , lit.[13] 128.5-129° C) with no trace of the linear isomer. Condensation of the chromene **5** with diethyl carbonate in the presence of sodium sand led to complex mixture whereas condensation in the presence of sodium hydride afforded the 4-hydroxy-2*H*-1-benzopyran-2-one **6** (81%, m.p. 189.5-191° C). Arylation of **6** with *p*-methoxyphenyllead triacetate **7** in chloroform in the presence of pyridine afforded the known 4-hydroxy-5-methoxy-3-(4-methoxyphenyl)-8,8-dimethyl-2*H*,8*H*-1-benzo-[1,2-b : 3,4-b']-dipyran-2-one **8** in good yield (78%, m.p. 220-221.5° C, lit.[14] 220-221° C). Similarly the reaction of **6** with 3,4-methylenedioxyphenyllead triacetate **9** [15] afforded the naturally occuring isorobustin **1** (84%, 199-200° C, lit.[2] 202-204° C). This represents an overall yield for isorobustin of 34% which is far superior to that obtained using the desoxybenzoin ring closure method (4%). Isorobustin is also the synthetic precursor of the naturally occuring isorobustin methyl ether **10**. Thus this represents a total synthesis of isorobustin **1** and a formal total synthesis of its methyl ether.

The inertness of the 9,10 double bond is further evidence to support an intermediate such as **11**, involving a lead to oxygen covalent bond, that we have previously proposed[16] for these lead mediated arylations.



This intermediate ligand couples to afford the arylated product. This coupling involves the overlap of the π-system of the aryl and enolate ligands with concomitant cleavage of the lead to oxygen and lead to aryl bonds. The reaction may be viewed as a formal nucleophilic displacement of lead by the enolate anion with the driving force provided by the change in oxidation state of lead.

In conclusion this letter illustrates the chemoselective as well as regioselective properties of the aryllead triacetates and their exploitation in the high yielding total synthesis of the naturally occurring 3-aryl-4-hydroxy-2*H*-1-benzopyran-2-one isorobustin **1**.

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