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# Total Synthesis of Khellinone and Khellin
## The Pyrogallol Route
## Regiospecific Methoxylation of a Benzofuran

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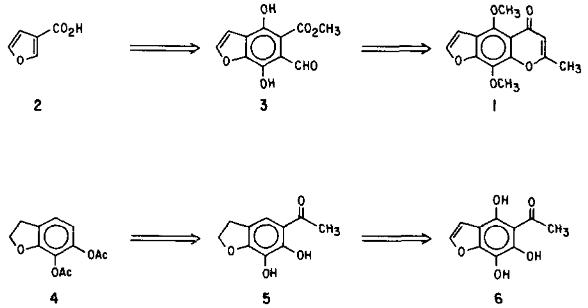
Summary: Khellinone is prepared in 5 steps from the readily available triacetoxybenzofuran **7**. The key step in the synthesis is a regiospecific oxidative methoxylation of benzofuran **9**.

We have recently reported a new synthetic approach to the antiatherosclerotic furochromone khellin (**1**) which began with 3-furoic acid (**2**) and involved appending a fully substituted aromatic ring onto **2** to give benzofuran **3**.[1] This strategy successfully addressed several of the major difficulties encountered in the total synthesis of highly oxygenated furochromones; namely, the efficient construction of the fully substituted B ring, differentiation of the four oxygen atoms on that ring which must eventually find their place in either a furan or pyrone ring or, as a methoxyl group, and flexibility in A ring modifications.

Numerous furochromone syntheses have as their origin pyrogallol. For example, dihydrobenzofuran **4**[2], readily available from pyrogallol, has been recognized as an attractive intermediate for furochromone synthesis.[3a] Thus far, however, utilization of **4** in the construction of furochromones has been thwarted by the inefficient introduction of the C-4 oxygen on a properly functionalized benzofuran. For example, while Fries rearrangement of **4** proceeds regiospecifically to give **5**, the subsequent potassium persulfate oxidation afforded the desired intermediate **6** in only 30% yield.[3a]

SCHEME I

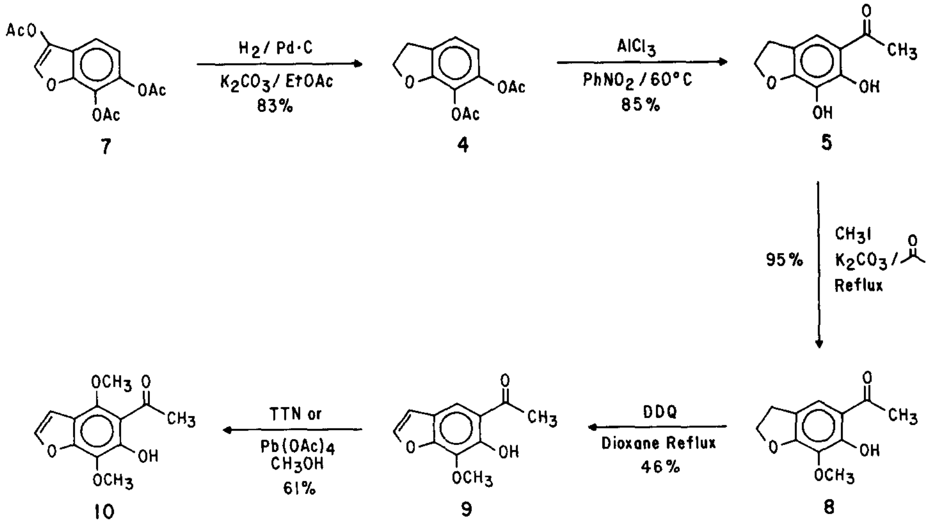


Khellin syntheses which originate from pyrogallol require, at some stage, an oxidation to introduce the C-4 oxygen. Historically, introduction of that C-4 oxygen has either required the use of protecting groups and thus additional steps and/or low yields in the actual oxidation step.[3b]

In this letter we describe the conversion of the known and readily available triacetoxybenzofuran **7** to khellinone **10**. This synthesis utilizes a novel oxidation which introduces the C-4 oxygen as a methoxyl group on an advanced intermediate.

Triacetoxybenzofuran **7** is prepared from pyrogallol in three steps. We have found that conversion of pyrogallol to **7** was best achieved using $ZnCl_2$ and chloroacetonitrile (Hoesch conditions) rather than $POCl_3$/α-chloroacetic acid as previously reported.[4,5] Hydrogenation of **7** (Pd-C/EtOAc/$K_2CO_3$) afforded the diacetate **4** (83%; white solid, MP 114-5°C;lit[2] 116°C).[6] Fries rearrangement of **4** ($AlCl_3$/$PhNO_2$/60°C) afforded the dihydroxyketone **5** (85%, MP 190.0-190.5°C,lit.[3a] 190°C). Methylation of **5** ($K_2CO_3$/$CH_3I$/acetone/reflux 18 h) afforded 5-acetyl-6-hydroxy-7-methoxydihydrobenzofuran **8** (pale yellow solid, mp 95-7°C) in 95% yield.[7,8] Dehydrogenation of **8** (1.35 equiv DDQ/dioxane/reflux)[8] then provided the oxidation substrate **9** as a yellow crystalline solid (46%; MP 62.1-63.5°C) after chromatography (silica gel, $CH_2Cl_2$). Addition of a methanolic solution of thallium (III) nitrate trihydrate (TTN)[9] (1.1 equiv/-25°C/over 30 min.) to **9** followed by a brief reflux (2-3 min) afforded khellinone (**10**) in 61% recrystallized yield.[10] In a slightly modified manner lead tetraacetate ($Pb(OAc)_4$)[13] was also used to oxidize **9**.

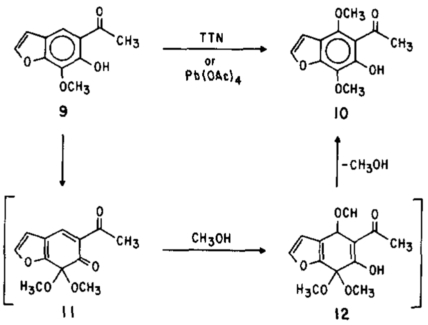
SCHEME II



Addition of **9** to a methanolic solution of $Pb(OAc)_4$ (1.25 equiv/0°C/1.3 h) followed by quenching with a saturated $NaHCO_3$ solution afforded a mixture of compounds which by $^1H$-NMR consisted of khellinone **10**, quinone monoketal **11**, and Michael adduct **12** (see Scheme III). Upon heating, this mixture was quickly converted to khellinone **10** also in 61% yield.

As illustrated in Scheme III, it appears that quinone monoketal **11** is formed initially. However, under the strongly acidic conditions of the TTN oxidation methanol adds rapidly to **11** to give **12**, which subsequently loses methanol at C-7 upon brief heating.[14] With $Pb(OAc)_4$, a less acidic medium exists and **11** does not add methanol as readily and thus requires heat to drive the reaction to completion.

SCHEME III



The success of the above strategy has enabled us to accomplish several objectives with respect to furochromone synthesis. First, it provides methodology for the regiospecific introduction of the C-4 oxygen as a methoxyl group and thereby precludes the problem of differentiating the four oxygen atoms on the B ring. Secondly, as noted above, addition of the final functional group onto a heavily substituted system such as **5** is often a low yield process. In the case described in this letter, the yield is quite acceptable with either TTN or $Pb(OAc)_4$. Most importantly, this strategy will allow the consideration of new targets originating from pyrogallol.

## References and Notes

1. Gammill, R. B.; Hyde, B. R., J. Org. Chem. (1983), **48**, 3863.
2. Davies, J. S. H.; Deegan, T., J. Chem. Soc. (1950), 3202.

## References and Notes
Continued

3. a) Row, L. R.; Rukmini, C.; Rao, G. S. R. S., Indian J. of Chem. (1967), **5**, 105.

   b) For a dated review of synthetic approaches to furochromones, particularity khellin and visnagin see: Mustafa, A., "Furopyrans and Furopyrones", in "The Chemistry of Heterocyclic Compounds", Vol. 23, Weissberger, A., Ed., John Wiley and Sons, New York, (1967), p. 103.

4. Geissman, T. A.; Moje, W., J. Am. Chem. Soc. (1951), **73**, 5765.

5. The reaction using $ZnCl_2/ClCH_2CN$ does not produce the black tar generated in the $POCl_3/\alpha\text{-}ClCH_2CO_2H$ reaction. This makes isolation less time consuming and easier.

6. In the absence of potassium carbonate 2,3-dihydro-3,6,7-triacetoxybenzofuran (MP 97.0-8.8°C) was isolated in 17% yield along with **4**(50%).

7. All new compounds had spectral and analytical data (combustion analysis) consistent with their assigned structures.

8. Lin, Y. Y.; Thom, E.; Libman, A. A., J. Heterocyclic Chem. (1979), 799.

9. McKillop, A.; Perry, D. H.; Edwards, M.; Antus, S.; Farkas, L.; Nogradi, M.; Taylor, E. C., J. Org. Chem. (1976), **41**, 282. For an example of an anodic oxidation to yield an ortho quinone monoketal see: Dolson, M. G.; Swenton, J. S., J. Am. Chem. Soc. (1981), **103**, 2361.

10. It is worth pointing out that in the case of the TTN oxidation, there were at least two other processes that could have occurred. Taylor has shown that treatment of benzofuran with TTN in methanol results in the formation of 2,3-dimethoxy-2,3-dihydrobenzofuran[11] and that treatment of aryl methyl ketones with TTN can lead to methyl arylacetates.[12] On several occasions trace amounts of the methanol adducts where observed in our TTN oxidations, however, in no case did we see evidence of methyl arylacetates.

11. McKillop, A.; Hunt, J. D.; Kiengle, F.; Bigham, E.; Taylor, E. C., J. Am. Chem. Soc. (1973), **95**, 3635.

12. McKillop, A.; Swann, B. P.; Taylor, E. C., J. Am. Chem. Soc. (1971), **93**, 4919.

13. To our knowledge this is the first report of the use of $Pb(OAc)_4$ to generate quinone ketals. For several reports on the preparation of quinol diacetates using $Pb(OAc)_4$ see: Brother, A. E.; Meijer, T. M.; Schmid, H. Helv. Chim. Acta. (1952), **35**, 910; Wessely, F.; Kotlan, J., Monatsh. Chem. (1953), **84**, 124; Wessely, F.; Holzer, L. ibid., (1952), **83**, 1253.

14. For examples of methanol adding to quinone monoketals see: Foster, C. H.; Payne, D. A., J. Am. Chem. Soc. (1978), **100**, 2834; Henton, D. R.; Anderson, K.; Manning, M. J.; Swenton, J. S., J. Org. Chem. (1980), **45**, 3422.

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