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# An Organoiron Approach to the Benzophenone Appendage of the Protein Kinase C Inhibitor Balanol

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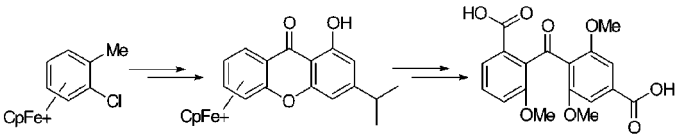
## ABSTRACT




**A new synthetic route to the benzophenone appendage of balanol, based on sequential iron-assisted nucleophilic aromatic substitution and ring-opening as well as regioselective oxidative cyanation, is described.**

The exceptionally potent protein kinase C inhibitor balanol **(1)** was isolated from the fungus *Verticillium balanoides* in 1993,[1] and later from species of *Fusarium merismoides*.[2] Balanol consists of two principal structural domains, a chiral hexahydroazepine-containing core and a benzophenone fragment, and it is an isomer to the previously known antifungal ophiocordin **(2)**[3] (Figure 1). The prominent biological activity

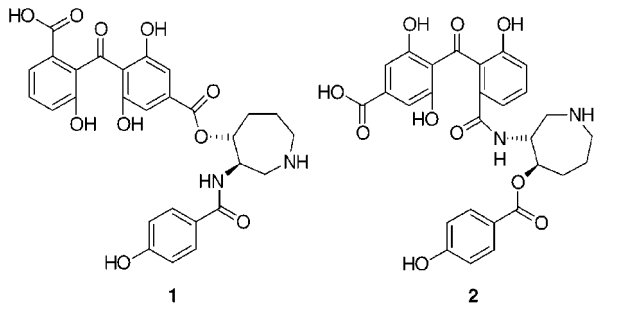



**Figure 1.** Balanol **(1)** and ophiocordin **(2)**.

of balanol has prompted several total syntheses[4] as well as structure−activity studies addressing inhibitory potency and kinase selectivity.[5] However, structural variations have mainly focused on the hexahydroazepine core, and only a few examples of modifications in the benzophenone moiety **3** (Figure 2) have appeared.[5a,6] Interestingly, such modifications have been reported to result in changes in kinase selectivity.[7]

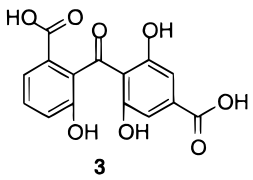



**Figure 2.** The benzophenone appendage of balanol and ophiocordin.

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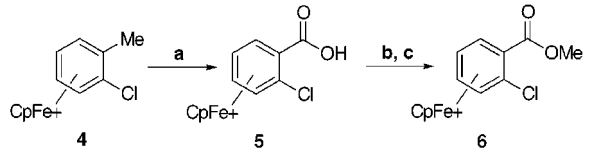
We have developed a divergent route to *ortho*-substituted benzophenones based on cationic arene iron complexes,[8] and in this Letter we describe its application to the synthesis of balanol appendage **3**.

The known $\eta^6$-*o*-chlorotoluene-$\eta^5$-cyclopentadienyliron hexafluorophosphate **(4)**[9] was oxidized, using aqueous potassium permanganate,[10] to the benzoic acid complex **5**, which could be converted into the methyl ester **6**, in high overall yield,[11] via reflux in thionyl chloride followed by reaction with excess methanol (Scheme 1).

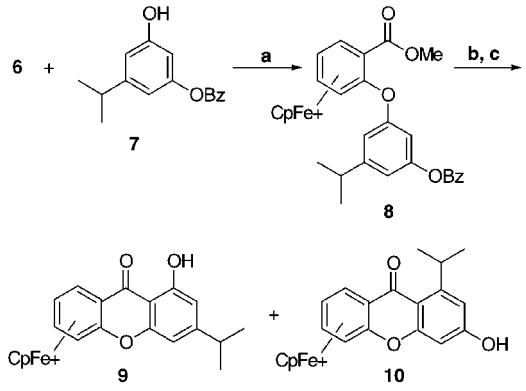
**Scheme 1**[a]




[a] (a) (i) $KMnO_4$, $MgSO_4$, $H_2O$, reflux; (ii) $HPF_6$ (60% in water), 83%; (b) $SOCl_2$, reflux; (c) MeOH, rt, 91% for two steps.

Treatment of **6** with the phenol **7**[12] and potassium carbonate in dimethylformamide at room temperature smoothly and regioselectively produced the diaryl ether **8** (Scheme 2).

**Scheme 2**[a]

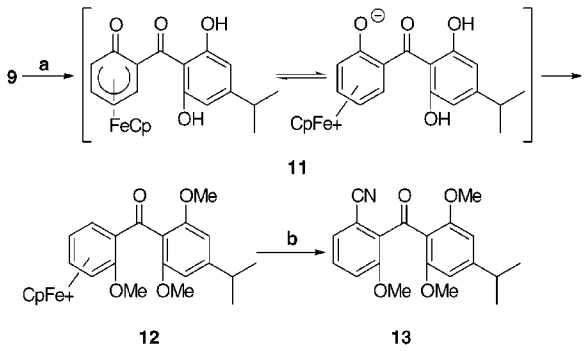



[a] (a) $K_2CO_3$, DMF, rt, 79%; (b) LiOH, $MeOH/H_2O$, rt, 95%; (c) $MeSO_3H$ (concentrated), rt, 72%.

Since the methyl *o*-chlorobenzoate complex **6** is highly activated toward nucleophilic aromatic substitution of chloride, the introduction of a wide range of suitable substituted nucleophiles under similarly mild conditions should allow this synthetic approach to accommodate significant diversity. After hydrolysis of the methyl and aryl esters with lithium hydroxide in a mixture of water and methanol, the xanthone complex **9** was obtained through an intramolecular Friedel–Crafts reaction in concentrated methanesulfonic acid at room temperature. The use of methanesulfonic acid for this transformation[13] turned out to be superior to our previously described method utilizing hot polyphosphoric acid,[8] due to the easier handling of the former reagent, a simpler workup procedure, fewer degradation products, and a significantly higher yield. Noteworthy is the excellent regioselectivity for **9** over **10** (30:1 according to NMR) (Scheme 2).

Treatment of $\eta^6$-xanthone-$\eta^5$-cyclopentadienyl iron hexafluorophosphate with oxygen,[8] nitrogen,[14] or stabilized carbon[14b] nucleophiles has been shown to result in neutral pentahapto oxo-, imino-, or methylenecyclohexadienyl complexes (tautomeric to the corresponding zwitterionic compounds), from the regioselective ring opening at the iron-bearing arene. The latter are easily transformed into the corresponding cationic complexes by protonation or alkylation. Importantly, in the present context, this key ring-opening reaction provides an opportunity to gain access to benzophenones carrying different heteroatom substituents in the 2- and 2′-positions. Our initial experiments on carrying out the transformation from **9** to **12** (Scheme 3) involved the isolation, in quantitative yield, of the neutral oxocyclohexadienyl complex **11**, a task accomplished by treating **9** with sodium hydroxide in a mixture of water and methanol. However, a wide range of methods investigated for exhaustive alkylation of **11** resulted in either incomplete reaction

**Scheme 3**[a]




[a] (a) KOH, MeI, DMSO, rt, 59%; (b) n-$Bu_4NCN$, DDQ, $CH_2Cl_2$, rt, 72%.

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(11) All yields refer to material purified by chromatography and/or recrystallization.

(12) All new compounds were characterized by NMR, IR, and HRMS spectroscopy.

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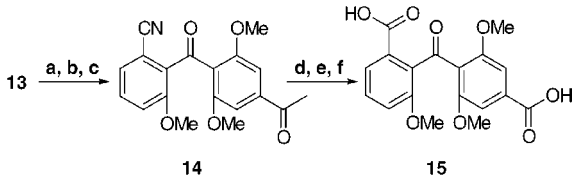
or degradation of the starting material. Interestingly, by varying the conditions used, we were able to distinguish between the hydroxy groups on the different arene rings,[15] providing access to orthogonally protected hydroxy groups.

The most efficient way to achieve exhaustive alkylation turned out to be to expose intermediate **11** to an alkylating agent in situ. This was accomplished by reacting **9** with a mixture of potassium hydroxide and methyl iodide in dimethyl sulfoxide at ambient temperature, providing access to the fully alkylated benzophenone complex **12** in good yield (Scheme 3).

Certain electron-withdrawing substituents have been found to facilitate regioselective addition of cyanide ion to arene iron complexes, furnishing isolable, neutral pentahapto complexes which could be oxidatively demetalated.[16] We found that by slightly altering the conditions from Sutherland's published procedure, this addition/decomplexation sequence could be accomplished in a one-pot procedure, employing a mixture of tetrabutylammonium cyanide and 2,3-dichloro-5,6-dicyanoquinone in dichloromethane, providing the advanced intermediate **13** in good yield (Scheme 3).

By subjecting **13** to *N*-bromosuccinimide and catalytic amounts of azobis(isobutyronitrile) in carbon tetrachloride, two benzophenones could be isolated: one containing a brominated isopropyl group and one in which elimination had occurred to give the corresponding isopropenyl-substituted compound. This mixture was homogenized by base-induced elimination of HBr, employing sodium acetate in dimethylformamide. The isolated isopropenyl-substituted benzophenone showed a marked tendency to polymerize when subjected to silica gel flash chromatography, and therefore the crude mixture was immediately oxidized. A Lemieux−Johnson procedure, employing osmium tetroxide and sodium periodate in tetrahydrofuran, provided methyl ketone **14** in good yield after purification (Scheme 4). This ketone was transformed into the desired carboxylic acid by means of a classical haloform reaction. Sodium hypobromite, formed in situ by mixing bromine and aqueous sodium hydroxide at 0 °C, was added to compound **14** dissolved in a mixture of water and dioxane. Acidic workup provided the carboxylic acid in fair yield.

**Scheme 4**[a]




[a] (a) NBS, AIBN, $CCl_4$, reflux; (b) NaOAc, DMF, 60 °C; (c) $OsO_4$, $NaIO_4$, THF, rt, 70% for three steps; (d) NaOH, $Br_2$, $H_2O$, dioxane, 5−10 °C, 56%; (e) HCl(concentrated)/MeOH, 80 °C; (f) LiOH, MeOH/$H_2O$, 50% for two steps.

Hydrolysis of the nitrile functionality turned out to be somewhat troublesome. Standard methods (sulfuric acid at various concentrations or highly alkaline conditions) gave only complex mixtures and/or degradation products. However, after warming the nitrile in a mixture of concentrated hydrochloric acid and methanol and subsequent careful lithium hydroxide treatment, the diacid **15** could be isolated in acceptable yield (Scheme 4).

Compound **15** is a known intermediate in the synthesis of **1**.[17]

Given the degrees of freedom in our synthetic approach, we conclude that organoiron methodology shows promising features with respect to preparation of substituted benzophenones relevant as building blocks for balanol and ophiocordin analogues.

Complete details of further iron-mediated synthetic studies toward substituted benzophenones will be reported in due course.

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