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Total Synthesis of Natural *p*-Quinol Cochinchinenone

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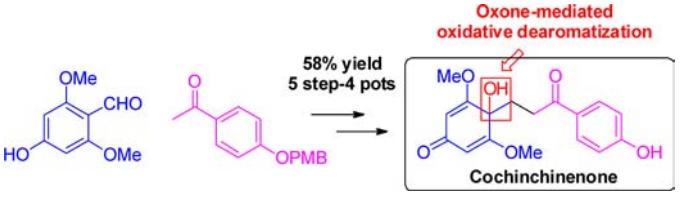
ABSTRACT



Cochinchinenone has been synthesized in only five steps and four pots and in 58% overall yield from commercially available 2,3-dimethoxy-4-hydroxy-benzaldehyde and OPMB-protected *p*-hydroxy acetophenone, the key step being the oxone-mediated oxidative dearomatization of the corresponding ketone-containing *p*-substituted phenol.

A group of important natural products with a central scaffold of aromatic ketone is known collectively as chalcones. These compounds possess different biological properties such as antifungal, antitumor, and anti-inflammatory.[1] Cardamonin (**1**, Figure 1), isolated from *Alpinia rafflesiana*, inhibits pro-inflammatory mediators in activated RAW 264.7 cells and whole blood.[2] Compound **2**, an analogue of chalcones from the trunk exudates of *Dalbergia sissoo*, is one of the most potent nitric oxide production inhibitors.[3] Tarennane (**3**) was first isolated in 2007[4a] from the whole plants of *Tarenna attenuate* and, in 2009, in minor quantities from the bark of *Magnolia officinalis*.[4b] Compound **3** was shown to have a potent antioxidant activity against H_2O_2-induced impairment in PC12 cells *in vitro*. Very recently, the first total synthesis of tarennane (**3**) has been reported.[5]

Cochinchinenone (**4**), a novel chalcone constituent having a *p*-quinol (2,5-cyclohexadien-1-one) moiety in ring A of its structure, was isolated in 2007 from the stems of *Dracaena cochinchinensis* and shows growth inhibitory effects against *Helicobacter pylori* (ATCC43504).[6] To the best of our knowledge, no total synthesis of this natural *p*-quinol derivative has been reported to date.

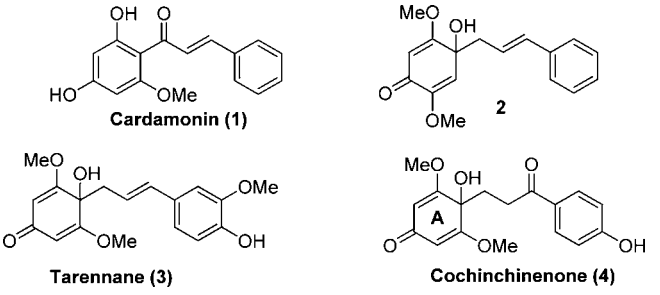


Figure 1. Natural *p*-quinol cochinchinenone (**4**) and its analogues.

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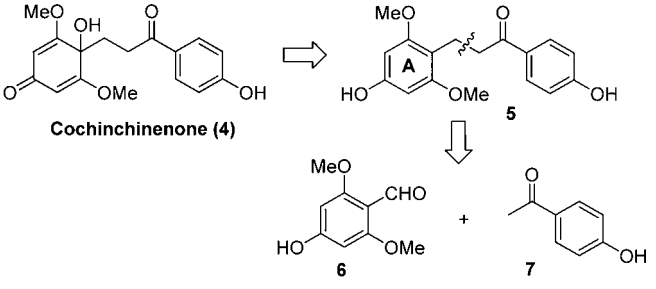
Among the numerous methods described in the literature for the preparation of *p*-quinols,[7] the oxidative dearomatization process[8] of the corresponding *p*-alkyl phenols using hypervalent iodine(III) oxidants[9] have been the most frequently used. This has been the method of choice to effect the transformation of adequately substituted phenols in the key step of a number of syntheses of complex natural products.[10]

We have recently reported a practical method for the simple and selective oxidative dearomatization of differently substituted *p*-alkyl phenols into *p*-peroxy quinols and *p*-quinols[11] using oxone in the presence of $NaHCO_3$, as a source of singlet oxygen.[12] We herein extend the oxone-mediated oxidative dearomatization of *p*-alkyl phenols to several ketone-containing derivatives, not previously studied, and apply this reaction to the first total synthesis of the natural *p*-quinol cochinchinenone (**4**), in a short synthetic sequence from suitable starting materials.

The retrosynthetic analysis of natural cochinchinenone (**4**) is depicted in Scheme 1. As can be seen, the *p*-quinol moiety present in **4** could be directly obtained from the ketone-containing *p*-alkyl *bis*-phenol **5**, by applying our oxone-mediated oxidative dearomatization process if the reaction took place exclusively on the more electron-rich phenol moiety A. This chemoselective transformation would be the expected one taking into account the mechanism of this reaction.[11a] Compound **5**, possessing all carbons present in the natural product, could be constructed from the disconnection shown in Scheme 1, through the aldol condensation between both commercially available aldehyde **6** and acetophenone **7**, followed by hydrogenation of the double bond of the corresponding chalcone initially formed.

Considering that the key step of this very short synthetic sequence would be the reaction of a ketone-containing *p*-alkyl phenol with oxone, not previously studied, we decided to perform the oxidative dearomatization process with differently substituted phenols with the aim of evaluating the influence of the ketone functionality on the reaction.

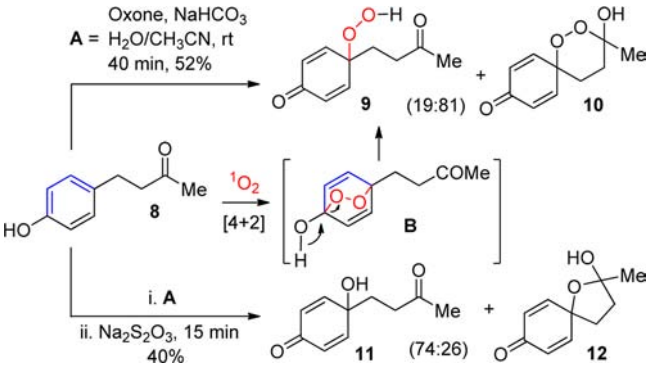
Scheme 1. Retrosynthesis towards Cochinchinenone (**4**)



Thus, the reaction of *p*-alkyl phenol **8**, containing a methyl ketone substituent, under the typical oxidative dearomatization conditions [oxone, $NaHCO_3$, H_2O/CH_3CN, rt, 40 min] afforded, in 52% yield, a 19:81 equilibrium mixture formed by the expected open chain *p*-peroxy quinol **9** and the corresponding spirocyclic peroxyhemiketal **10** (Scheme 2). Compound **9** was formed after [4 + 2] cycloaddition of **8** and $^1O_2$,[11a,13] followed by in situ opening of the initially formed endoperoxide intermediate **B**. Cyclic peroxides such as **10** are found in the structure of several antimalarial derivatives.[14]

When the same reaction was followed by the addition of a reducing agent such as $Na_2S_2O_3$ (Scheme 2), the *p*-quinol **11** was formed and characterized also as a 74:26 equilibrium mixture of **11** and the corresponding spirocyclic hemiketal **12** (40% yield). This type of cyclic spirocyclohexadienone structure is also found in several natural products with significant biological properties such as aculeatins and amomols.[15]

Scheme 2. Oxone-Mediated Oxidative Dearomatization of Methylketone-Containing *p*-Alkyl Phenol **8**



We were also interested in performing the oxidative dearomatization process with a phenylketone-containing phenol such as **14** (Scheme 3). This compound was prepared from commercially available chalcone **13** after double bond reduction [H_2, Pd(C), THF, rt, 17 h], in 79% yield. The reaction of **14** with oxone, in the presence of KOH as the base (H_2O/CH_3CN, rt, 2 h), gave rise to *p*-peroxy quinol **15**, as the unique product, in 62% yield.

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(12) Oxone is a 2:1:1 mixture of $KOSO_2OOH$, $KHSO_4$, and K_2SO_4 and decomposes in an aqueous basic medium to generate $^1O_2$. See: Ball, D. L.; Edwards, J. O. *J. Am. Chem. Soc.* **1956**, *78*, 1125.
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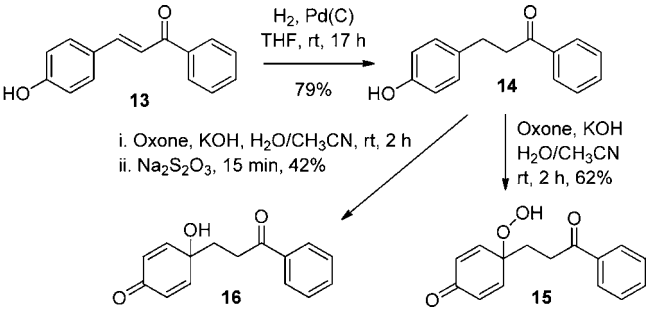
Scheme 3. Oxone-Mediated Oxidative Dearomatization of Phenylketone-Containing *p*-Alkyl Phenol **14**



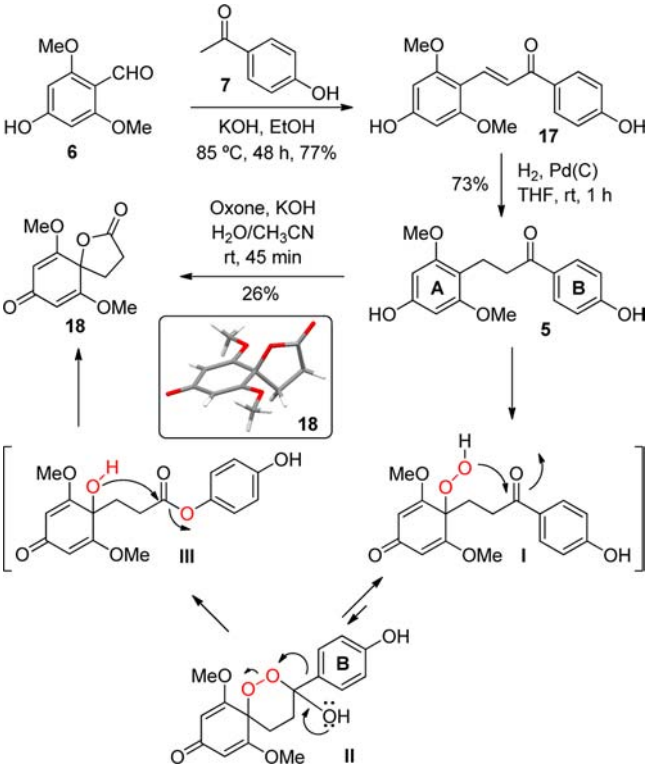
When we performed the same oxidative dearomatization process on **14** followed by the addition of $Na_2S_2O_3$ (Scheme 3), the corresponding *p*-quinol derivative **16** was obtained in 42% yield, again as the only reaction product.

With these preliminary results in hand, we turned our attention to the total synthesis of the natural *p*-quinol Cochinchinenone (**4**). As indicated in the retrosynthetic Scheme 1, the aldol reaction between commercially available aldehyde **6** and acetophenone **7** would allow us to construct the complete carbon skeleton of the natural product. Nevertheless, this was not an easy task. We tried several experimental conditions, under both acidic[16] or basic[17] conditions, to carry out this condensation. Finally, the best result was obtained working with an excess of the ketone **7** and KOH as the base, at 85 °C for 2 days (Scheme 4). Under these conditions, the reaction took place with 85% conversion and 77% yield, giving rise to the corresponding chalcone **17**.

The following step of the synthetic sequence, the reduction of the double bond of **17**, was performed with H_2 in the presence of catalytic amounts of Pd(C) in THF at rt for 1 h, to obtain the ketone-containing *p*-alkyl bis-phenol **5** in 73% yield, after chromatographic purification (Scheme 4).

With bis-phenol **5** in hand, we undertook the final key step of the synthetic sequence en route to natural *p*-quinol cochinchinenone, the oxone-mediated oxidative dearomatization of this unprotected phenol, with the aim of achieving the selective reaction of the more electron-rich phenol ring A in **5** (Scheme 3). Thus, the reaction of bis-phenol **5** with oxone in the presence of KOH as the base (H_2O/CH_3CN, rt, 45 min) gave rise to a sole product, as a white solid, albeit in a low 26% yield. Unfortunately, the NMR parameters of this new compound didn't match with those reported for the natural derivative and its structure was assigned as the spirolactone **18**[18] and unequivocally confirmed by X-ray diffraction (Scheme 3).[19] The formation of **18** should start with the desired oxone-mediated oxidative dearomatization of the A ring of **5**, through an intermediate similar to **B** shown in Scheme 2, to afford the expected *p*-peroxyquinol intermediate **I**. Traces of the peroxy hemiketal **II** could explain the Baeyer–Villiger migration of the B free phenol ring, favored by deprotonation, to the corresponding hydroxy ester **III**. This intermediate would suffer an intramolecular transesterification to afford the spirolactone **18**.

Scheme 4. Oxidative Dearomatization of 4-Hydroxyphenylketone-Containing *p*-Alkyl Phenol **5** en Route to Cochinchinenone



We thus decided to use an OH protected derivative of **5** to decrease the electron-donating character of the B phenol ring of intermedite **II**, thus avoiding the strongly favored rearrangement in the final oxidative dearomatization key step. To repeat the same synthetic sequence, we needed a protected 4-hydroxyacetophenone **7** as the starting material. The choice of the correct protective group was not an easy task since derivatives such as OMOM, OTBDMS, OTBDPS, OTHP, and OBn gave rise to negative results in the different steps of the planned synthesis. Finally, use of the OPMB protecting group was the only option which allowed us to complete the total synthesis of natural cochinchinenone (**4**) as explained in Scheme 5.

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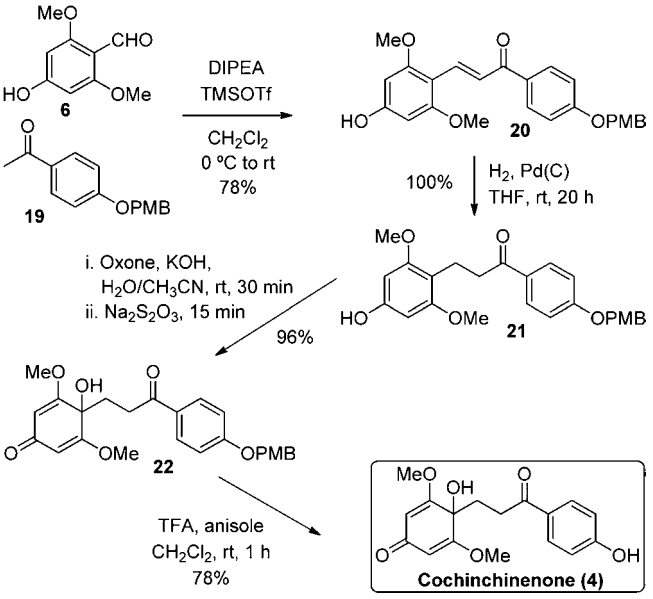
(19) CCDC-873559 for **18** contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Scheme 5. Total Synthesis of Natural *p*-Quinol Cochinchinenone (**4**)



The first step of the synthesis was the aldol reaction between aldehyde **6** and OPMB-protected acetophenone **19**, prepared from phenol **7** under typical conditions (PMBBr, K_2CO_3, acetone, 56 °C, 15 h, 77%). When we used the above-mentioned experimental conditions (excess of ketone **19** and KOH as the base, at 85 °C for 2 days) moderate yields were obtained due to several problems in the chromatographic purification. Finally, the use of a tandem silyl enol ether formation–Mukaiyama aldol reaction mediated by TMSOTf[20] between **6** and **19** allowed us to synthesize chalcone **20**, in 78% yield (DIPEA, TMSOTf, CH_2Cl_2, 0 °C to rt, overnight).

The reduction of the double bond of **20** was accomplished after hydrogenation in the presence of catalytic Pd(C) (THF, rt, 20 h) giving rise to the OPMB-protected *bis*-phenol **21** in quantitative yield, without the need for chromatographic purification. In this case, the oxidative dearomatization of **21** (Oxone, KOH, H_2O/CH_3CN, rt, 30 min), followed by in situ $Na_2S_2O_3$ reduction of the initially formed *p*-peroxy quinol, afforded the corresponding OPMB-protected *p*-quinol **22**, in an excellent 96% yield.

At this point, the last step of the synthesis of cochinchinenone (**4**), the OPMB deprotection of derivative **22**, was again troublesome. The use of typical oxidative [DDQ or DDQ (cat.)/$Mn(OAC)_3$] or reductive conditions [H_2, $Pd(OH)_2$] gave rise in all cases to complex mixtures of reaction. Finally, treatment of OPMB-protected compound **22** with trifluoroacetic acid (TFA) in the presence of anisole[21] (CH_2Cl_2, rt, 1 h) afforded, in 78% yield, cochinchinenone (**4**) whose physical and spectroscopic data were identical to those described for the natural product.[6]

In conclusion, we have described a very short and efficient synthesis of natural *p*-quinol cochinchinenone in only five steps and four pots and in 58% overall yield, using the Oxone-mediated oxidative dearomatization of the corresponding ketone-containing *p*-substituted phenol as the key step. We have also established that this reaction can be applied to methylketone-containing *p*-alkyl phenols to obtain peroxy derivatives that may be potentially useful as antimalarial agents. The oxone dearomatization reaction did not work when free-OH aromatic ketones are present since the Baeyer–Villiger evolution of the latter was preferred.

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Supporting Information Available. Experimental procedures, characterization data, NMR spectra, and X-ray data (CIF) for **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.