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ortho-Prenylphenol photooxygenation as a straightforward access to *ortho*-(2-hydroxy-3-methylbut-3-enyl)phenols

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Abstract

Photooxygenation ($^1O_2$) of *ortho*-prenylphenols followed by a reduction (PPh_3) at low temperature (–30°C) yields a mixture of *ortho*-(2-hydroxy-3-methylbut-3-enyl)phenols and *ortho*-(3-hydroxy-3-methylbut-1-enyl)phenols. However, by running the two-step sequence at a higher temperature (15°C), the secondary allylic alcohol could be selectively recovered.

As part of our continuous search for new biologically active natural products, we recently reported on a bioassay-directed fractionation of extracts from *Mesua racemosa*,[1] and *Calophyllum dispar*.[2] This work resulted in the selection of several *ortho*-prenylphenols as the most active compounds against various neoplasic cell lines. Among them, allylic alcohols such as *ortho*-(2-hydroxy-3-methylbut-3-enyl)phenol derivatives retained our attention. Due to their pharmacological interest and their low concentration in plant extracts, we needed a straightforward synthetic access to this type of derivative.

If the supposed biogenetic pathway leading to these compounds consists of an oxidation from the corresponding *ortho*-prenylphenol,[3] such a direct synthesis has never been reported. The transformation of a prenyl chain into a 2-hydroxy-3-methylbut-3-enyl appendage is only described for protected *ortho*-prenylphenols and relies either on a epoxide rearrangement[2] or on a photooxygenation.[4] In the latter method, singlet oxygen $^1O_2$ reacts with an olefin bearing allylic hydrogens in the so-called Schenck-ene reaction and leads via a double bond shift to an allylic hydroperoxide.[5] Then, the corresponding allylic alcohol is obtained by a quantitative reduction of this hydroperoxide.

Due to the mild oxidation conditions used during this photooxygenation process, we thus imagined that, applied to unprotected *ortho*-prenylphenols, the method could represent a new and straightforward access to 2-(2-hydroxy-3-methylpent-3-enyl)phenols. Before embarking on a totally natural product synthesis, we therefore decided to study this oxidation on a simpler model in the dihydroxyacetophone series.

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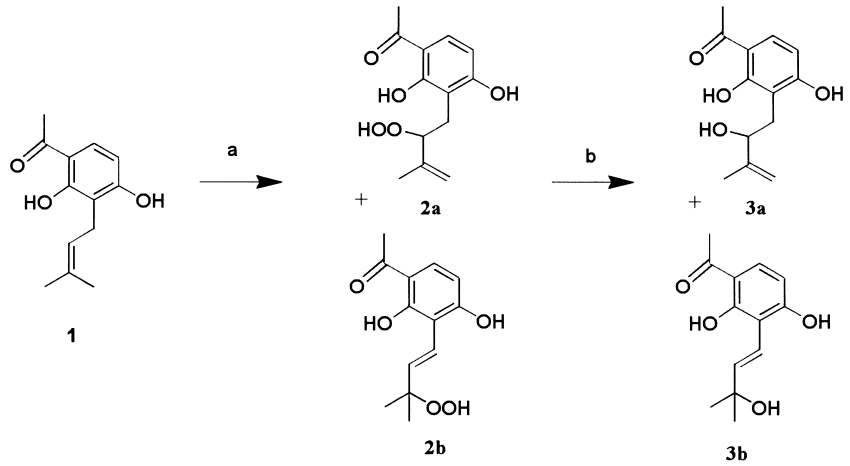
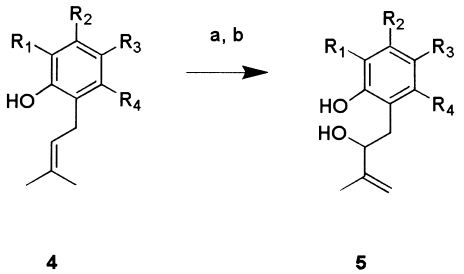
Photooxygenation of phenol **1** (Scheme 1), using tetraphenylporphin (TPP) as the photosensitizer, was first conducted at low temperature (–30°C). After PPh_3 reduction at the same temperature, two allylic alcohols **3a** and **3b** were obtained in 65 and 28% yield, respectively. The prenyl side chain was thus oxidized in 93% yield and no other product could be isolated.



Scheme 1. (a) O_2, TPP, hν, CH_2Cl_2; (b) PPh_3, CH_2Cl_2

Surprisingly, when the photooxygenation followed by the reduction was run at a higher temperature (15°C), **3b** was not recovered and alcohol **3a** was the sole isolated product in 66% yield. As the yield in **3a** was unchanged in both experiments, we suspected that the intermediate leading to **3b** could be unstable. To confirm this hypothesis, we analyzed the photooxidation (–30°C) products by low-temperature NMR spectroscopy. As expected, the ^1H NMR spectrum revealed in the mixture the presence of 67% of **2a** and 29% of **2b**. The mixture was then stirred for 3 h at 20°C before PPh_3 reduction and the secondary allylic alcohol **3a** was consequently isolated as the sole product in 65% yield. This experiment thus proved the thermal instability of the highly conjugated tertiary hydroperoxide **2b**.

As a consequence, the degradation of the tertiary hydroperoxide could be turned to our advantage: by running the two-step sequence at a sufficiently high temperature (15°C), secondary alcohols **5** could be selectively synthesized (Scheme 2).



Scheme 2. (a) O_2, TPP, hν, CH_2Cl_2, 15°C; (b) PPh_3, CH_2Cl_2, 20°C

The scope of this reaction was further studied on different related derivatives (Table 1). This oxidation could therefore be generalized, not only to diphenolic *ortho*-prenylphenols (Table 1, entries 1–4) but also to monophenols (Table 1, entries 5–9) with yield ranging from 43 to 84%. The lowest yield observed (Table 1, entry 5) may be explained by the *para*-alkylphenol sensibility to $^1O_2$ leading to 4-hydroperoxycyclohexa-2,5-dien-1-one derivatives.[6] However, it should be noted that alcohol **5** was always the only product that could be isolated except when using a biphenyl compound as the starting material (Table 1, entry 6). In this case, a higher temperature would be necessary to degrade the tertiary hydroperoxide.

Table 1
ortho-Prenylphenol photooxygenation at 15°C via Scheme 2

Entry	R_1	R_2	R_3	R_4	Yield **5** %
1	$COCH_3$	H	H	OH	66
2	H	OH	$COCH_3$	H	84
3	$COCH_3$	OH	H	H	65
4	$COCH_3$	H	CH_2-CH=C(CH_3)$_2$	OH	56[a]
5	H	H	CH_3	H	43
6	H	H	Ph	H	56[b]
7	H	H	$COCH_3$	H	58
8	H	H	Cl	H	51
9	H	H	Br	H	44

[a]As a bis(2-hydroxy-3-methylbut-3-enyl) derivative.
[b]Accompanied by 2-(3-hydroxy-3-methylbut-1-enyl)-4-phenylphenol in 32% yield

In summary, we have shown that by a careful choice of the temperature, *ortho*-(2-hydroxy-3-methylbut-3-enyl)phenols could be selectively isolated by photooxygenation of a wide variety of *ortho*-prenylphenols, and this without the need of any phenolic protecting group. We have also noted the thermal instability of the tertiary hydroperoxide that probably explains the absence of *ortho*-(3-hydroxy-3-methylbut-1-enyl)phenol derivatives in plant extracts. Thus, this method could be applied to synthesize natural *ortho*-(2-hydroxy-3-methylbut-3-enyl)phenol[3,7] and is currently being extended by us in the coumarin field.

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