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Oxidation reaction of 4-allyl-4-hydroperoxy-2-methoxycyclohexa-2,5-dienone in the presence of potassium permanganate without a co-oxidant

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Abstract: 4-Allyl-4-hydroperoxy-2-methoxycyclohexa-2,5-dienone **(5)** was synthesized by photooxygenation of commercially available *Eugenol* in the presence of tetraphenylporphyrin (TPP) as a singlet oxygen sensitizer. The brief and one-pot syntheses of some natural product skeletons were conducted using the corresponding allylic hydroperoxide at different temperatures (0^{o}C and room temperature) with potassium permanganate ($KMnO_4$) in mild condition at N_2(g) atm.

Keywords: Allylic hydroperoxide; singlet oxygen; photooxygenation; eugenol, natural product.

1. Introduction

Eugenol is an allyl chain-substituted guaiacol and a member of the phenylpropanoids class in natural product chemistry. In addition, it is a colorless to pale yellow oily liquid extracted from certain essential oils and a variety of natural plants. Eugenol is used as a local antiseptic and anesthetic also flavorings in perfumes. It can be reacted with zinc oxide to form ZnO-eugenol which has restorative and prosthodontic applications in dentistry.[1,2]

Attempts have been made to develop eugenol derivatives as intravenous anesthetics, as an alternative to propanidid which produces unacceptable side effects around the site of injection in many patients. Eugenol derivatives and degradation products from eugenol are same as flavonoids in their structure. Flavonoids are identified as components of numerous plants or their essential oils. They can exhibit various pharmacological and biological activities such as antimicrobial, antioxidant, antifungal, antitumor and anti-inflammatory. In addition, flavonoids and their derivatives were recognized as enzyme inhibitors. Therefore, isolation from some plants or synthesis of flavonoids is quite important for both synthetic organic and drug chemists. [3,4,5] For instance, 3,4,5-trihydroxy-6-(((S)-1-hydroxy-3-(4-hydroxy-3-methoxyphenyl)propan-2-yl)oxy)tetrahydro-2*H*-pyran-2-yl)methyl 3,4,5-trihydroxybenzoate (**1**) and 6-(3,4-dimethoxyphenoxy)-3,4,5-trihydroxytetrahydro-2*H*-pyran-2-yl)methyl 3,4,5-trihydroxybenzoate (**2**), which are macropteranthol derivatives are well known as potent tyrosyl-DNA phosphodiesterase I inhibitory.[6] 3-(4-hydroxy-3-methoxyphenyl)propane-1,2-diol (**3**) exhibits antimicrobial activity against some pathogenic microorganisms.[7]

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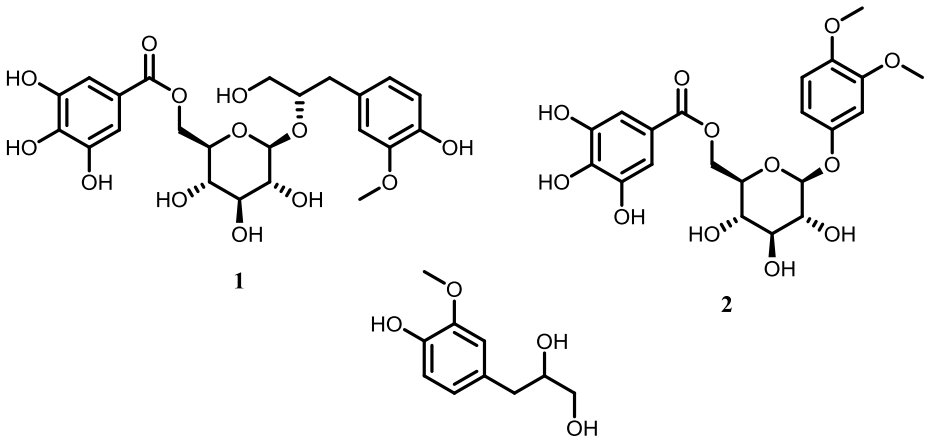


1 2 3

Several oxidants such as hypervalent iodine compounds, manganoxides, osmiumtetraoxides[8] ruthenium oxides[9] and chromium oxides[10] reagents were reported for the oxidation of many compounds containing olefin groups. An eco-friendly reagent, $KMnO_4$, is used as a strong oxidant in organic syntheses which is non-toxic, stable and cost-effective. Additionally, it is applied as an antiseptic in medicine and as a water cleaner in industry.[11,12,13,14]

Our group previousely developed an oxidation technique to synthesize 1/2,3 triols from the corresponding allylic hydroperoxides, which involved intramolecular oxygen atom transfers from hydroperoxide group to the double bond, using catalytic amount of OsO_4 (Figure 1).[15] The reaction did not require any co-oxidant as the hydroperoxide group served as a co-oxidant.

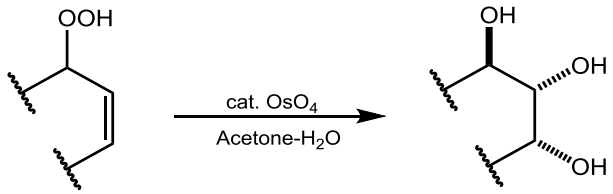


Figure 1. General reaction of the 1/2,3-triols formation from allylic hydroperoxides

2. Experimental

The IR spectra were obtained by using Satellite 3000 Mid infrared FTIR spectrometer in KBr pellets. The ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX 400 MHz spectrometer. The synthesis was carried out using standard procedures and commercially available reagents. The eugenol used in the oxidations were purchased from Sigma-Aldrich. The chemicals were used without further purification.

2.1 General procedure for photochemical oxygenation of eugenol:

Eugenol (50 mmol) and TPP (5-10 mg) was dissolved in CH_2Cl_2. The solution was placed in a jacketed glass balloon and irradiated using tungsten lamb (500 Watt) with air bubbling (oxygen gas) at 14 ^{0}C. The photooxygenation reaction was monitored by TLC. Most of the reactions were completed within 48 h. The solvent (CH_2Cl_2) was evaporated at 20 ^{o}C and 20 mm Hg at the end of the reaction. The residue was separated by (silica gel) thin layered chromatography (TLC) with dichloromethane:hexane (v/v=1:5). The allylic hydroperoxide were determined by ^1H and ^{13}C nuclear

magnetic resonance (NMR) spectroscopy using $CDCl_3$ as the solvent, depending on the separated product. All of the spectra data of compounds are given in supporting information.

2.2 General procedure for oxidation reaction of allylic hydroperoxide with $KMnO_4$ [16]:

To a well-stirred solution of $KMnO_4$ (0.5 eq.) in 3 mL of H_2O was added in three parts to 4-allyl-4-hydroperoxy-2-methoxycyclohexa-2,5-dienone (**5**) solution (0.5 g in 6 mL acetone) at 0 ^oC. Until completion of the reactions were kept at about ambient temperature. The reaction progress was monitored by TLC. The reactions were completed around 26 h. After completion of the reaction the insoluble solid particles were removed by filtration. Finally, the crude residue was directly purified by column chromatography on silica gel using ethyl acetate/hexane mixture (v/v=1:5).

The following compounds were synthesized using the same method (Figure 2). While the molecules **5, 7, 7a, 8a, 9, 9a** are known in the literature, the molecule **8** was synthesized in this protocol for the first time.

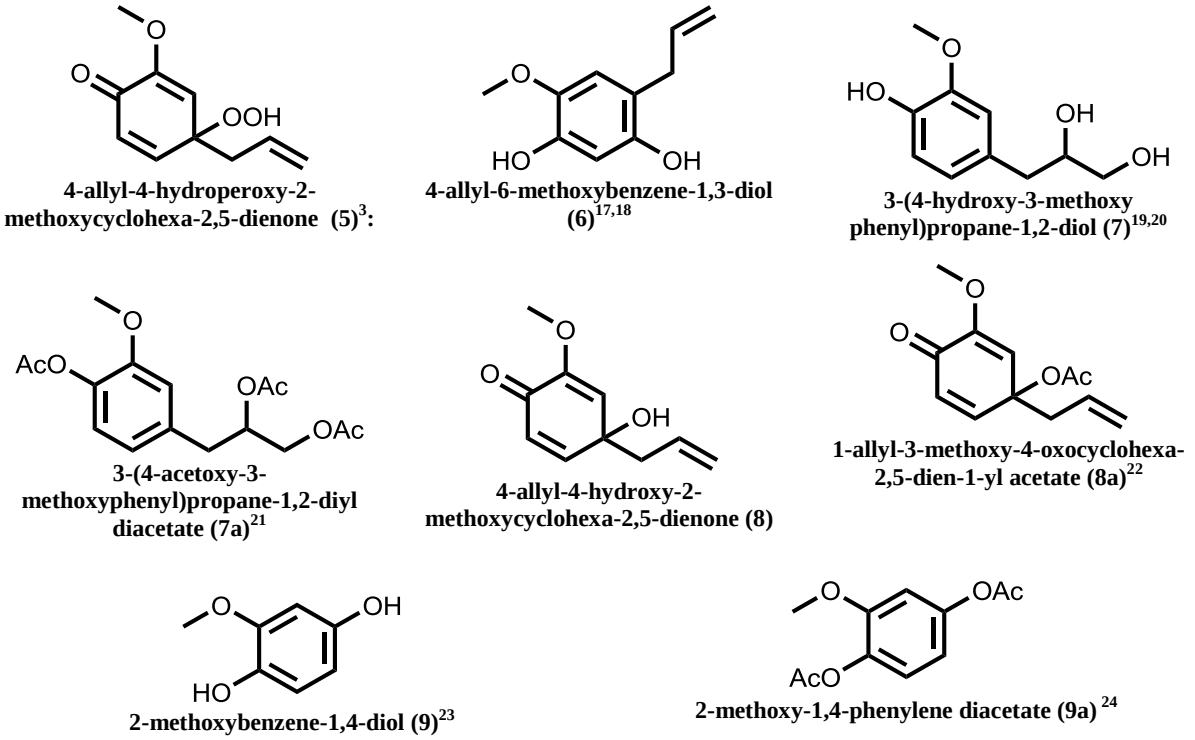


Figure 2. Synthesized compounds oxidation reaction of allylic hydroperoxide with $KMnO_4$

3. Results and Discussion

A strong oxidant $KMnO_4$ has been used as the *cis*-dihydroxylation reagent for the oxidation of olefins accompanied with co-oxidants such as NMO (N-methylmorpholine oxide)[16] $NaIO_4$[25] and H_2O_2[26]. While it gives *cis*-dihydroxylation reactions at low temperatures, it produces various degradation products at high temperatures. In this study, oxidation reactions were carried out at ~~in~~ low and high temperatures and eugenol **3** was used as a starting material. It was converted to 4-allyl-4-hydroperoxy-2-methoxycyclohexa-2,5-dienone (**5)** in dichloromethane in 60% yield within 48 h by singlet oxygen in the presence of TPP as a sensitizer. After compound **5** was isolated, it was reacted with $KMnO_4$ in 9 mL of water/acetone (v/v=1/2) at both 0 ^0C low and room temperature in the

absence of a co-oxidant under nitrogen atmosphere. Surprisingly, some degradation and rearrangement products were produced in addition to the desired products. 3-(4-Hydroxy-3-methoxyphenyl) propane-1,2-diol (**7**) was formed as dihydroxylation product at both temperatures. But, as expected, compound **7** was formed with higher yield (35%) at 0 ^{0}C. In addition, it was found that there were four flavonoid derivatives in the reaction mixture, which were purified by column chromatography on silica gel using ethyl acetate/hexane mixture (v/v=1:5) as an eluent. Four compounds, i.e 4-allyl-6-methoxybenzene-1,3-diol (**6**), 3-(4-hydroxy-3-methoxyphenyl) propane-1,2-diol **(7)**, 4-allyl-4-hydroxy-2-methoxycyclohexa-2,5-dienone (**8**) and 2-methoxybenzene-1,4-diol (**9**) were obtained. Both the reaction conditions led to the formation of the corresponding products (Figure 3).

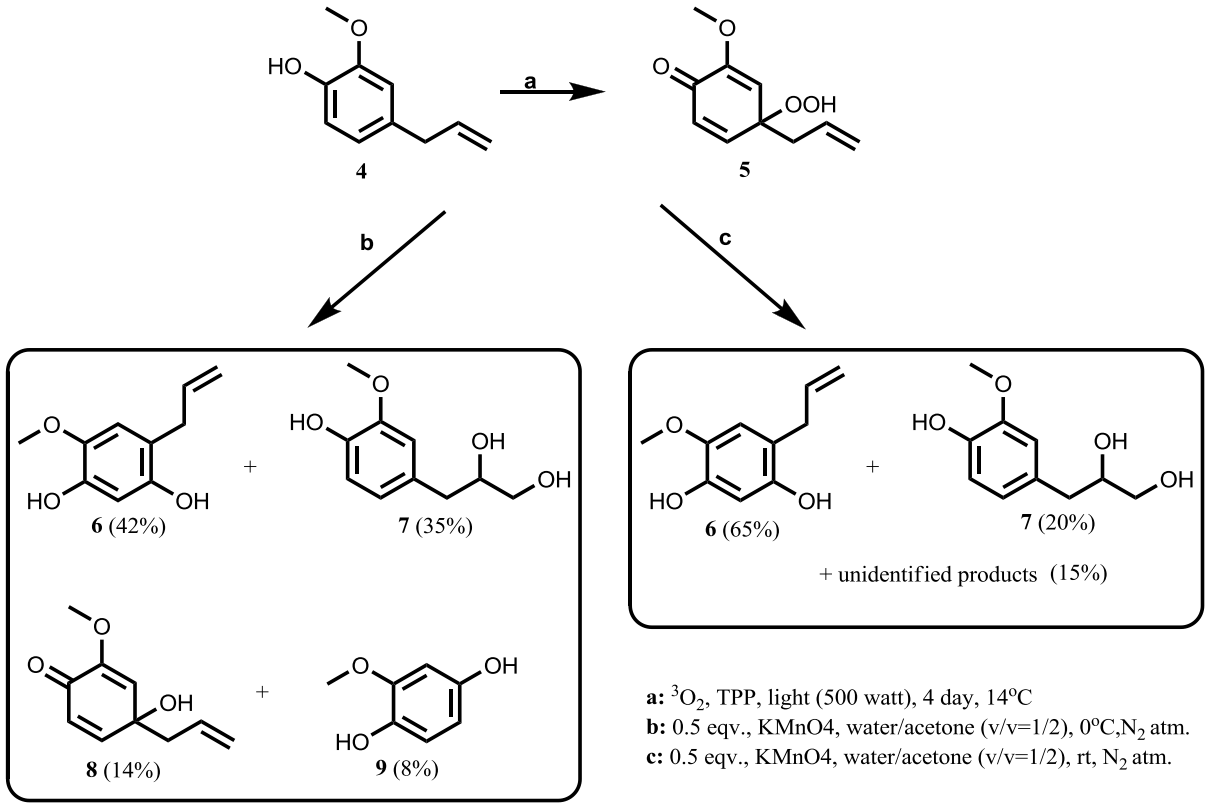


Figure 3. Synthetic pathway for oxidation of 4-allyl-4-hydroperoxy-2-methoxycyclohexa-2,5-dienone (**5**)

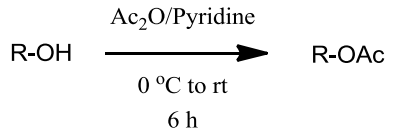
In this study, we report a method for an easy, practical synthesis of 4-allyl-4-hydroperoxy-2-methoxycyclohexa-2,5-dienone **(5)** *via* rearrangement reaction of hydroperoxide group. This reaction was performed in the presence of $KMnO_4$ (0.5 eq.) which is less than 1.0 eq. as an oxidant and 10.0 mmol of 4-allyl-4-hydroperoxy-2-methoxycyclohexa-2,5-dienone (**5)** (1.0 eq.) as a co-oxidant. Compared to the methods reported in the literature, our method provides shorter reaction times, higher yields and a practical approach. In this rearrangement, various manganese oxide intermediates were formed by hydroperoxide group in molecule **5** as an oxidant during the oxidation reaction. We think that Mn_3O_4 nanoaggregates were occurred as the main component among several manganese oxide derivatives as reported in the literature.[13]

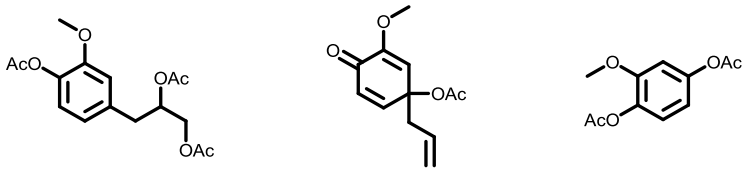
The results revealed that the use of hydroperoxide group in molecule **5** as a co-oxidant is the key feature for our method for the syntheses of rearrangement products (**6, 7, 8, 9**). Additionally, manganese oxides, which have active role in the oxidation reactions, possibly through the transformation of manganese oxide intermediates into manganese dioxide. This delays the disruption

of manganese oxide intermediates and the rearrangement reaction with the hydroperoxide group in molecule **5** takes places.

In summary, the Mn_xO_y oxide intermediates were generated in situ from 0.5 eq. $KMnO_4$/ 1.0 eq ROOH **5** during the synthesis of **6,7,8,9** from **5**. Molecule **5** was used as both substrate and oxygen source in place of H_2O_2. For further characterization, the compounds containing hydroxyl (-OH) group (**7-9**) were converted to the 3-(4-acetoxy-3-methoxyphenyl) propane-1,2-diyl diacetate (**7a**), 1-allyl-3-methoxy-4-oxocyclohexa-2,5-dien-1-yl acetate (**8a**) and 2-methoxy-1,4-phenylene diacetate (**9a**) in quantitative yields within 6 h (Table 1). They were prepared as described in the literature.[13]

Table 1. Acetylation reaction of oxidation products[a]





7a; >90% **8a**; >90% **9a**; >90%

[a]Unless otherwise stated, 10 mmol of oxidation product, 5 mL of pyridine and 30 mmol of acetic anhydride were used.

Supporting Information

Supporting information accompanies with this paper on http://www.acgpubs.org/OC

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