

**OXIDATION OF MARCHANTIN A TRIMETHYL ETHER
AND RELATED AROMATIC COMPOUNDS WITH
m-CHLOROPERBENZOIC ACID**

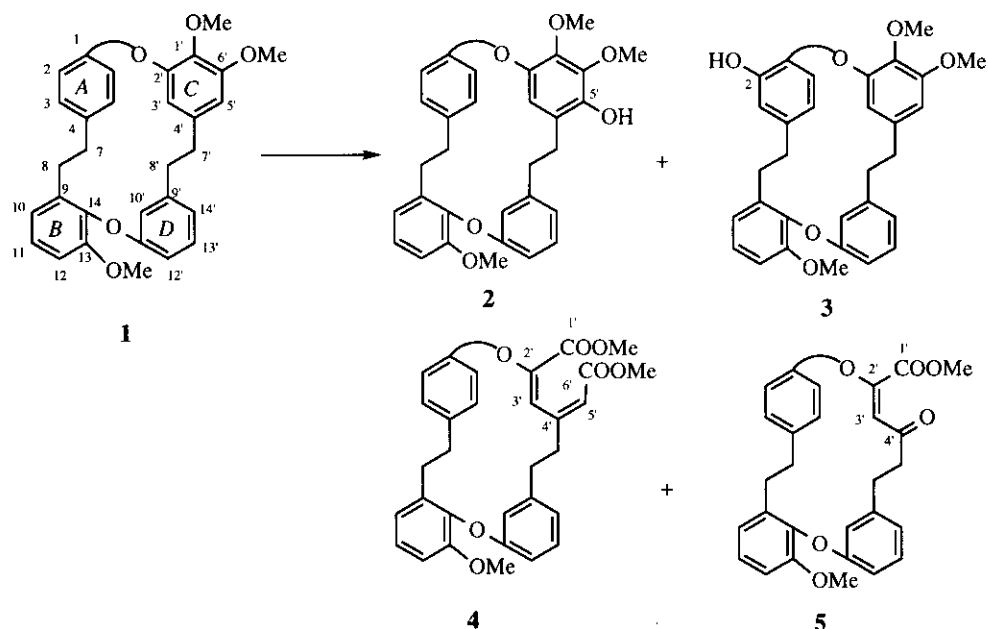
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Abstract — Marchantin A trimethyl ether was subjected to react with *m*-chloroperbenzoic acid to yield hydroxylated derivatives as well as ring C degraded esters. This reaction was confirmed by application to catechol dimethyl ether and dihydroeugenol dimethyl ether.

Oxidation reactions are very common in the living cells and usually have very important roles. We have been interested in oxidation reactions using *m*-chloroperbenzoic acid (*m*CPBA) or ozone at an unactivated sites of various kinds of natural and unnatural substances.¹ Oxidation occurred at the tertiary positions, which are sp³ carbons of terpenoids and in the case of phenols or related aromatic compounds, quinones are the common products.¹ We have further investigated oxidation reactions of related aromatic compounds including marchantin A, a macrocyclic bis(bibenzyl) isolated from the liverwort *Marchantia polymorpha* and related species,² and have found that muconate and *m*-chlorobenzoate derivatives can be isolated as well as quinones. Because marchantin A itself exhibits a variety of biological activities, it is expected to test more compounds with further hydroxyl groups on any aromatic ring.²

Marchantin A trimethyl ether (**1**) was subjected to react with *m*CPBA (1.5 equiv.) in CHCl₃ to afford four products, two (**2** and **3**) were phenolic and the other two (**4** and **5**) were esters. Compound (**2**) (14.7% yield) showed a molecular ion at *m/z* 498 and its formula was determined as C₃₁H₃₀O₆ by HRMS. The IR spectrum showed the presence of the hydroxyl group. Therefore one hydroxyl group was introduced into either aromatic ring. The 400 MHz NMR analyses suggested that rings A, B, and D were untouched, while one of the ring C protons disappeared. The proton at C-3' for compound (**1**) (δ 5.30) is very strongly shielded by the neighboring aromatic rings.³ Because the proton at δ 5.55 (H-3') for compound (**2**) was detected as singlet, the position of the hydroxyl group must be at C-5'. Therefore the structure of **2** was established as depicted in the formula. The HRMS of compound (**3**) (2.0% yield) showed that one



hydroxyl group was introduced as in the case of **2**, which was supported by the IR spectrum. The 400 MHz NMR spectrum indicated that rings B, C, and D were untouched, because the coupling patterns for protons in these rings are almost the same as those of the starting material (**1**). The protons in ring A usually appear as two sets of doublets, because this ring is thought to rotate and the protons at C-2 and 6, and those at C-3 and 5 have the same chemical shifts.³ The ¹H NMR spectrum of compound (**3**) does not show an A₂B₂ pattern and thus the hydroxyl group must be introduced into ring A. Since NOE's into H-3 and 5 were observed on irradiation of benzylic protons, the position of the hydroxyl group was established at C-2.

The molecular formula of **4** (1.9% yield) was determined as C₃₁H₃₀O₇ by the HRMS and the IR spectrum indicated the presence of the ester carbonyl group. The detailed analyses of the 400 MHz NMR including 2D spectra suggested that proton systems for rings A, B, and D were untouched. While the protons of ring C were somewhat different from those of the starting material (**1**). However, there were two protons assignable to H-3' at δ 5.11 as doublet with *J* = 2.2 Hz and that to H-5' at δ 5.74 as doublet with *J* = 2.2 Hz, and three methoxyl groups were also observed. These observation indicated that degradation reaction occurred to ring C. The ¹³C NMR spectrum showed that there were two carbonyl groups at δ 162.8 and 166.6 as well as 22 aromatic or olefinic carbons, suggesting that two aromatic carbons were converted into two carbonyl groups. When the benzylic protons were irradiated, NOE's into H-3' and 5' as well as H-10', 14', 3, 5, and 10 were observed. Therefore the structure of **4** was established as depicted in the formula. In the case of **5** (0.5% yield), the molecular formula was C₂₈H₂₆O₆, two carbons less than that of **4**. There were only two methoxyl groups and a ketone was observed at δ 199.2 in the ¹³C NMR spectrum. The

proton assignable to H-3' was observed at δ 4.57 as singlet, which was considerably high field as an aromatic proton and should be an olefinic proton. Therefore, it was concluded that both 5' and 6' carbons were removed from compound (4) and the structure of 5 was established as depicted in the formula.

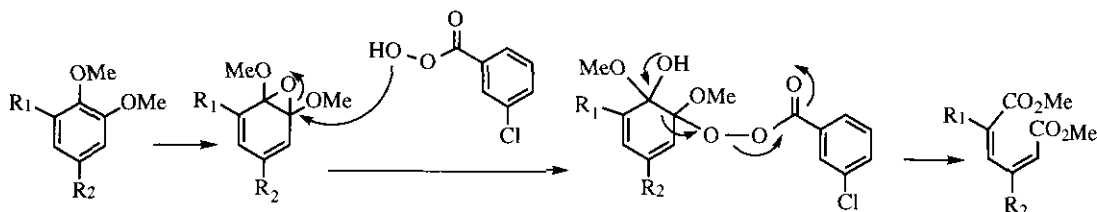
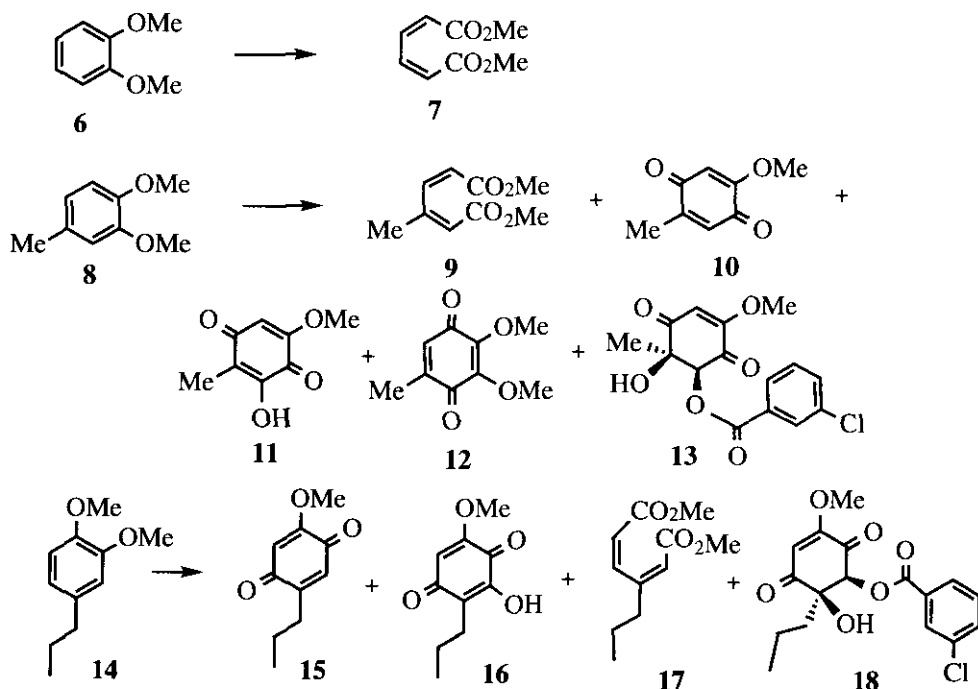


Figure 1. The probable mechanism for producing muconic acid ester.

These reactions from 1,2-dimethoxybenzene derivatives may be explained by the mechanism shown in Figure 1. The muconate derivative was further degraded into compound (5).

We next tried to oxidize catecholic substances with methoxyl groups. When catechol dimethyl ether (6) was treated with *m*CPBA, dimethyl *cis,cis*-muconate (7) was produced in 5.2% yield. Thus 4-methyl-1,2-dimethoxybenzene (8) was next subjected to react with *m*CPBA to afford a muconate (9) (0.7% yield), a quinone (10) (7.5% yield), a hydroxyquinone (11) (0.8% yield), dimethoxyquinone (12) (0.5% yield), and a *m*-chlorobenzoate (13) (4.4% yield). The stereochemistry of 13 was deduced from the results of 18 (*vide infra*).



Dihydroeugenol dimethyl ether (**14**) was similarly treated with *m*CPBA to isolate a quinone (**15**) (8.7% yield), a hydroxy quinone (**16**) (0.2% yield), a muconate (**17**) (6.8% yield), and an ester (**18**) (6.5% yield). The IR spectrum of the ester (**18**) showed the presence of an ester and a hydroxyl groups at 1730 and 3450 cm^{-1} , respectively, and the MS spectrum exhibited its molecular ion at m/z 342 and 340 (1:3). The ^1H and ^{13}C NMR spectra clearly showed the presence of a methoxyl, a propyl, and a *m*-chlorobenzoyl groups. Because this compound afforded good crystals, the X-Ray analysis⁴ was carried out and two oxygen functions were revealed to be *cis* each other. Therefore the structure of **18** was established as depicted in the formula.

In summary, activated aromatic rings, such as methoxylated benzenes, are easy to be oxidized with *m*CPBA to afford phenols as well as quinones. Marchantin A trimethyl ether produced two phenols and two kinds of degraded compounds with *m*CPBA. Muconates were derived from a partial structure of catechol dimethyl ether.

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4. Data for compound (**18**): Crystals from EtOAc solution; $\text{C}_{17}\text{H}_{19}\text{O}_6\text{Cl}$, triclinic, P1, $a=6.647$, $b=11.272$, $c=11.559$, $\alpha=78.39^\circ$, $\beta=83.80^\circ$, $\gamma=79.57^\circ$, $V=832.0\text{\AA}^3$, $Z=2$, $R=0.053$; Mac Science MXC18; details will be published elsewhere.