Photosensitized Oxidation of Isoeugenol in Protic and Aprotic Solvents

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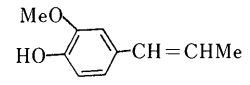
Sensitized photooxygenation of isoeugenol gave seven products in methanol, seven products in ethanol, six products in acetone, and five products in acetonitrile. One of the products is a 7,7′-linked lignan of a type which has not yet been observed in nature. The structures of these products were elucidated and the mechanisms of their formation are discussed.

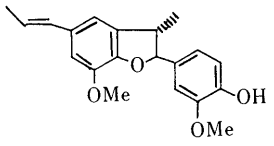
Keywords photooxidation; isoeugenol; lignan with 5–8′-, 8–O–4′-or 7–7′-linkage; biomimetic study; mechanism

The oxidation of isoeugenol (**1**) has been studied previously as a model of the formation of lignan-related dimers during ferric chloride oxidation[1] and enzymatic oxidation.[2] Photolysis[3] and free radical oxidation[4] of isoeugenol also give similar products. Further studies showed that free radical oxidation of isoeugenol[5] produced four trilignols. The anodic oxidation of isoeugenol gave dimerization products of a different type.[6] Few studies have been reported on the observation of the formation of lignan-related dimers in sensitized photooxidation. In connection with our interest in lignan and biomimetic studies, we recently studied sensitized photooxidation of methyl (*E*)-ferulate.[7] Sensitized photooxidation of isoeugenol (**1**) in methanol[8] (MeOH) had been reported to give dehydrodiisoeugenol (**2**) and **3a** (*erythro*+*threo*) (purified by acetylation and hydrogenation). The paper did not discuss the formation mechanism. In a previous communication, we described the result of photooxidation of isoeugenol in acetone solution.[9] In this paper, we present in detail the results of photooxidation of isoeugenol in alcohols, acetone, and acetonitrile. A solution of isoeugenol (**1**) and methylene blue in a solvent was irradiated using a fluorescent lamp. Seven products (**4a**, **3a**, **5a**, **2**, **6**, **7a**, and **8a**) in MeOH, seven products (**4b**, **3b**, **5b**, **2**, **6**, **7b**, and **8a**) in ethanol (EtOH), six products (**2**, **6**, **9**, **10a**, **11a**, and **8a**) in acetone, and five products (**2**, **6**, **10a**, **12a**, and **8a**) in acetonitrile, listed in the order of elution upon chromatography, were isolated from the reaction mixture after purification of silica gel. Compound **2** is the major product, and **6** is the next most major product. Products **2**, **3** and **8** represent three different linkages of lignans (5–8′, 4–O–7′; 8–O–4′; 7–7′, 8–O–O–8′). The presence of three differently linked lignans in one species of plant is very rare. Products **8a** and **9** are stable endoperoxides. The structures of all the products were elucidated as follows.

Compounds **3a** and **3b** were purified by acetylation and hydrogenation, so their original structures would have been **12b** and **12c**, respectively. Meanwhile compounds **5a**, **7a**,



1 (*trans*+*cis*)



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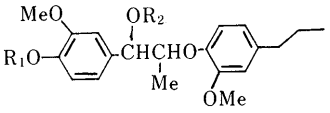
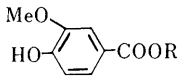
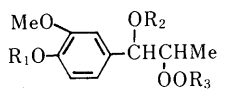




4a : R=Me
4b : R=Et

3a : R_1=Ac, R_2=Me (*erythro*+*threo*)
3b : R_1=Ac, R_2=Et (*erythro*+*threo*)
3c : R_1=H, R_2=Me (*erythro*+*threo*)



threo form
5a : R_1=Ac, R_2=Me, R_3=H
5b : R_1=R_3=H, R_2=Et
5c : R_1=R_3=H, R_2=Me
5d : R_1=R_3=Ac, R_2=Et

erythro form
7a : R_1=R_3=Ac, R_2=Me
7b : R_1=R_3=Ac, R_2=Et
7c : R_1=R_3=H, R_2=Me
7d : R_1=R_3=H, R_2=Et

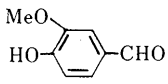


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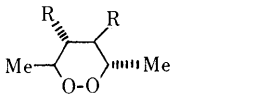
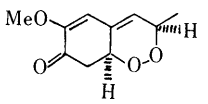
TABLE I. ^{1}H-NMR Data for **5a**, **5b**, **5d**, **7a**, **7b**, and **13**

H	5a	5b	5d	7a	7b	13
2, 5, 6	6.89—7.25 ABX system	6.69—6.88 ABX system	6.89—7.03 ABX system	6.82—7.05 ABX system	6.88—7.10 ABX system	6.31—6.94 ABX system
7	4.08 d (4.2)[a)]	3.98 d (5.0)	4.31 d (5.0)	4.30 d (4.4)	4.13 d (7.0)	3.04 d (7.0)
8	3.89 m	3.75 m	5.00 m	5.03 m	4.92 m	4.30 m
9	1.13 d (6.2)	1.10 d (6.9)	1.16 d (7.0)	1.20 d (7.0)	1.00 d (7.0)	1.04 d (6.2)
CH_3CH_2O–		1.18 t (7.0)	1.23 t (7.0)		1.17 t (7.0)	
CH_3CH_2O–		3.36 m	3.43 m		3.36 m	
CH_3O–Ar	3.83 s	3.89 s	3.83 s	3.84 s	3.82 s	3.62 s
CH_3O–R	3.30 s			3.32 s		
CH_3COOR			1.97 s	2.00 s	1.97 s	
CH_3COO–Ar	2.31 s		2.30 s	2.31 s	2.24 s	2.28 s

a) Figures in parenthesis are coupling constants in Hz.

7b, and **12a** were isolated after acetylation, so their original structures would have been **5c**, **7c**, **7d**, and **12d**, respectively. Products **2** (mp 132—134 °C) and **6** (mp 80—82 °C) were identical with dehydrodiisoeugenol,[1,8] and vanillin, respectively. By comparison of the spectral data with reported values,[8] the structures of **3a** and **3b** were elucidated to be as shown. Chemical correlation between **3a** and **3b** was made as follows. When **3b** was treated with *p*-toluenesulfonic acid in MeOH solution, it gave **3c** which was identical with the product obtained from **3a** by basic hydrolysis. Compounds **4a** and **4b** were identical with methyl vanillate and ethyl vanillate, respectively. Compounds **5a**, **5b**, **7a**, **7b**, **8a**, and **9** give a positive KI test in acidic acetone solution. The results show that these compounds are peroxides. Compounds **5a** and **7a** showed similar proton nuclear magnetic resonance (^{1}H-NMR) spectra (Table I), except for an additional acetyl group in **7a**. Further, the H-8 proton exhibits different chemical shifts: δ 5.03 (1H, m) in **7a** and δ 3.89 (1H, m) in **5a**. Chemical correlation between **5a** and **7a** was achieved on catalytic hydrogenolysis with Pd–C as the catalyst in MeOH, compounds **5a** and **7a** gave the same product (**13**), which shows infrared (IR) absorption bands at 3600 (–OH), 1750 (Ar-OAc) cm^{-1}. Dehydration of **13** in acetone with *p*-toluenesulfonic acid under reflux afforded *trans*-isoeugenol (**1**). From the foregoing results, **5c** and **7c** are diastereomers. The *threo* form (**5**) favors hydrogen bonding (as in formula **14**), rather than the *erythro* form. Compounds **5b** and **5c** were eluted with less polar eluent (5% ethyl acetate in hexane) and **7c** and **7d** with more polar eluent (20% ethyl acetate in hexane). Therefore, we can assign **5** as *threo* form and **7** as *erythro* form, because **5** with greater hydrogen bonding ability to hydroxyl groups is less well adsorbed by silica gel and is eluted more easily by a less polar solvent. Compound **5a** resisted acetylation with Ac_2O/pyridine at room temperature overnight. The result also indicates that **5a** is a *threo* form. Acetylation of **5b** with Ac_2O/pyridine at 60 °C afforded **5d** which showed similar ^{1}H-NMR signals to **7b**. The assignment of the structures of **5b** and **7b** was based on their physical data. Meanwhile **5a**, **5d**, **7a**, and **7b** gave the same product **13** on catalytic hydrogenolysis with Pd–C as the catalyst. Compound **9**, mp 74—76 °C (from MeOH), is an endoperoxide, giving a positive KI test in acidic acetone solution and no hydroxyl absorption band in its IR spectrum. The ultraviolet (UV) spectrum (λ_{max} 209, 250, 275 nm) and IR spectrum (ν_{max} 1690, 1650, 1610 cm^{-1}) suggested the presence of a dienone moiety with a methoxyl group at the α-position. The ^{1}H-NMR data confirm the structure to be as shown. Compound **10a**, mp 73—75 °C (from $CHCl_3$), an aldehyde, exhibits IR absorption bands at 3470, 3050, 1660, 1110 cm^{-1} and ^{1}H-NMR signals at δ 1.41 (3H, d, J=7.0 Hz), 3.51 (1H, m), 3.88 and 3.92 (each 3H, s, –OMe), 5.23 (1H, d, J=10 Hz), 6.24 (1H, br s, –OH), 6.82—7.38 (5H, m), 9.82 (1H, s). Compound **10a**, on reaction with Ac_2O in pyridine, gave an amorphous monoacetate (**10b**) [ν_{max} 3050, 1770, 1680 cm^{-1}; δ 2.28 (3H, s)]. Upon reduction with $NaBH_4$, **10a** afforded an alcohol (**15**) [mp 84—85 °C (from $CHCl_3$); ν_{max} 3390 cm^{-1}; δ 4.68 (2H, s)]. From the above data, the structure of **10a** is similar to that of dehydrodiisoeugenol (**2**) except for a formyl group instead of a propenyl group. It is proposed that **10a** was derived from **2** by photooxidation. Indeed **2** yielded **10a** upon sensitized photooxidation. Compound **11a**, mp 134—136 °C (from MeOH), contains a hydroxyl group (ν_{max} 3350 cm^{-1}), two methoxyl groups [δ 3.89 and 3.98 (each 3H, s)], one aldehyde [ν_{max} 1680 cm^{-1}; δ 9.96 (1H, s)], an ester group (ν_{max} 1720 cm^{-1}), and six phenyl protons [δ 6.96—7.88 (6H, m)]. The acetylation of **11a** with Ac_2O–pyridine at room temperature yielded a monoacetate (**11b**) [mp 158—160 °C; ν_{max} 1750 cm^{-1}; δ 2.34 (3H, s)], Methyl vanillate (**4a**) and vanillin (**6**) were obtained from **11a** by heating in acidic MeOH solution. Compound **8a** (mp 192—194 °C), a six membered ring endoperoxide, is stable to $NaBH_4$ reduction and gave a positive KI test under acidic conditions. The formula $C_{20}H_{24}O_6$ was derived from a mass measurement (mass spectra (MS) m/z=360) and elemental analysis. Compound **8a** shows ^{1}H-NMR signals at δ 1.01 (6H, d, J=6.0 Hz), 2.66 (2H, m, AA′, –CHAr), 3.74 (6H, s, 2×–OMe), 4.51 (2H, m, XX′, –CHMe), 5.41 (2H, s, 2×–OH), 6.34 (2H, d, J=1.8 Hz), 6.59 (2H, dd, J=8.1, 1.8 Hz), and 6.86 (2H, d, J=8.1 Hz). Irradiation of the methyl signal (δ 1.01) simplified the multiplet at δ 4.51





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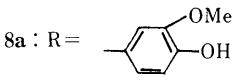
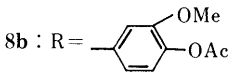
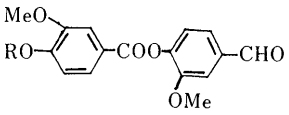


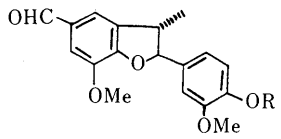
8a : R=



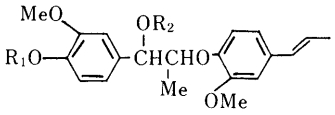
8b : R=



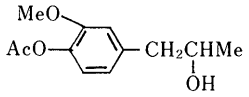
11a : R=H
11b : R=Ac



10a : R=H
10b : R=Ac



12a : R_1=R_2=Ac (*erythro*+*threo*)
12b : R_1=H, R_2=Me (*erythro*+*threo*)
12c : R_1=H, R_2=Et (*erythro*+*threo*)
12d : R_1=R_2=H (*erythro*+*threo*)



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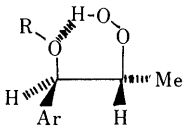
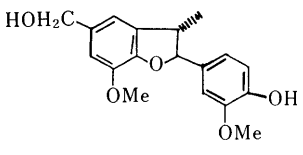


14(*threo*)



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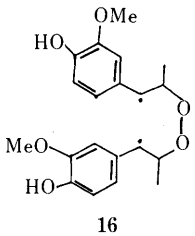

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to a doublet (J=8.0 Hz). Irradiation of the multiplet at δ 4.51 caused the multiplet at δ 2.66 and the doublet at δ 1.01 to collapse to a singlet each. The signal at δ 4.51 became a quartet (J=6.0 Hz) upon irradiation of the multiplet at δ 2.66. According to the above evidence, **8a** is a symmetric compound, and the four substituents are all in equatorial orientation as shown in the formula. Its diacetate (**8b**) (ν_{max} 1770 cm^{-1}; no hydroxyl absorption band) gave a similar ^{1}H-NMR spectrum to **8a**, except for a signal at δ 2.25 (6H, s) instead of the signal at δ 5.41. Compound **12a**, a mixture of *erythro* and *threo* forms with 1 : 1 ratio, was structurally elucidated as shown from the spectra. Hydrogenation of **12a** (PtO_2 catalyst in ethyl acetate) and treatment with *p*-toluenesulfonic acid gave **3c** (*erythro* + *threo*), which was also obtained from **3a** by saponification.

The formation of the products by photosensitized oxidation of isoeugenol (**1**) may be rationalized in terms of the mechanisms depicted in Charts 1—3. As shown in Chart 1, the phenolic hydrogen of **1** is abstracted by $^1O_2$ or ^{3}sen*[10] to afford the RO· radical, which exhibits two other resonance hybrids, Rβ· and R5· radicals. Coupling of Rβ· and RO· radicals yields the 8–O–4′ type quinone intermediate (**17**), which subsequently adds ROH (R=H, Me or Et) to afford **12b**, **12c**, or **12d**. Combination of Rβ· and R5· radical mesomers produced the intermediate (**18**) that generates **2** *via* spontaneous cyclization. The reaction of singlet oxygen with a strained[11] or electron-rich[12] double bond gives the perepoxide. Dehydrodiisoeugenol (**2**) yields the perepoxide (**19**) by the addition of $^1O_2$ and is then transformed to the dioxetane (**20**),[13] which is cleaved (*via* the diradical or through concerted cleavage based on solvent)[14] to afford **10a**. The formation of **4a**, **4b**, **5b**, **5c**, **7c** or **7d** from isoeugenol (**1**) is *via* the perepoxide (**21**) (see Chart 2) obtained by the addition of $^1O_2$ to **1**. The perepoxide **21** rearranges into two species, the zwitterion (**22**) and the dioxetane (**23**). The addition of MeOH of EtOH to the zwitterion (**22**) would yield **5b**, **5c**, **7c** or **7d**. The product vanillin (**6**) would be obtained from the cleavage of the dioxetane (**23**). The formation of **4a** or **4b** presumably involves cleavage of the hydroperoxide (**25**) derived from the MeOH acetal (**24**) by oxidation with triplet oxygen. The acetal (**24**) would be derived from **6** during the sensitized photooxidation. With methylene blue as the sensitizer the acidity of the solution is increased, and it has been reported that aldehyde is converted to acetal in MeOH solution under such photooxidation conditions.[15] We[16] have reported that the sensitized photooxidation conditions catalyze the coupling of formaldehyde and benzamide (or acetamide) and convert maleic aldehydeacid and fumaric aldehydeacid to their corresponding pseudoesters. In order to prove the proposed mechanism, the following reaction was performed. When **6** was exposed to $^3O_2$ in alcohol solution (MeOH or EtOH) in the dark, no product was observed. But **6** can be oxidized with $^1O_2$ in alcohols (MeOH or EtOH) to produce **4a** or **4b**. Meanwhile, **4a** or **4b** can be prepared by oxidation with $^3O_2$ in alcohols with *p*-toluenesulfonic acid as a catalyst in the dark. Compounds **11a**, **9**, and **8a** derived from **6**, **1**, **21**, respectively, are shown in Chart 3. Abstraction of the phenolic hydrogen from vanillin (**6**) by $^1O_2$ or ^{3}sens* yields the radical (**26**), which adds to the aldehyde of **6** to produce

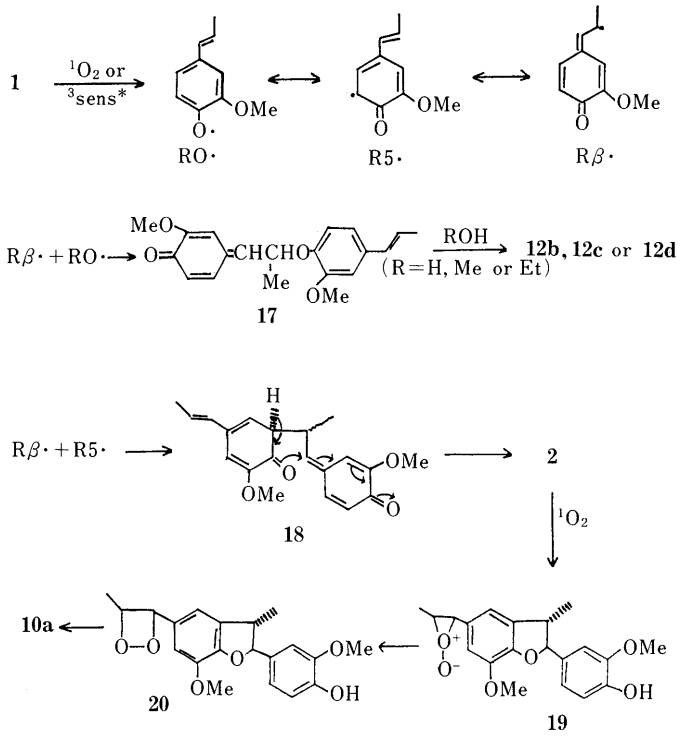

Chart 1

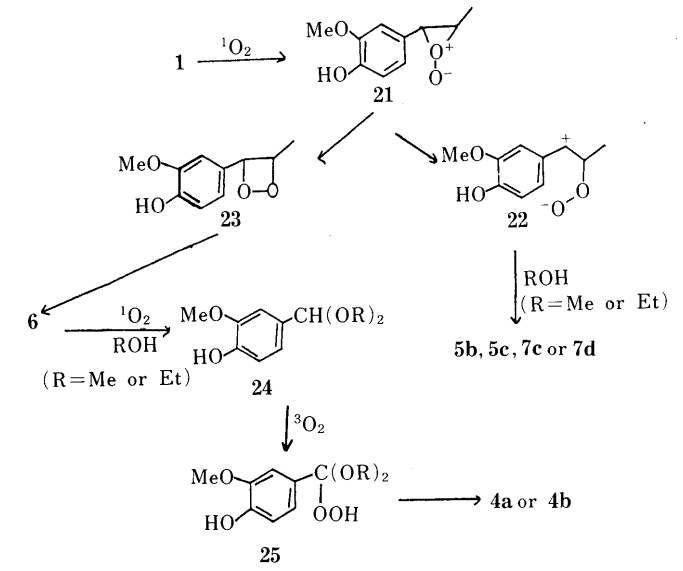

Chart 2

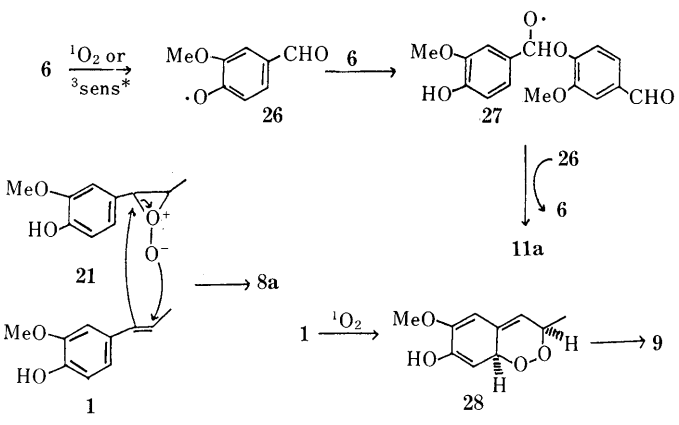

Chart 3

another radical (**27**). The generation of **11a** was achieved by transfer of hydrogen from **27** to **26**. The oxidation of vanillin (**6**) with $^1O_2$ in acetone solution was performed but it gave the ester **11a** in low yield. The [2+4] reaction is usually found in photooxidation of a styrene-type olefin and the thermally stable endoperoxide is formed stereospecifically.[17] The reaction of $^1O_2$ with isoeugenol (**1**) produced the enol (**28**) by [2+4] reaction, and then **28** tautomerized to the stable ketone (**9**). The formation of the endoperoxide (**8a**) is unique, resulting from cyclization between **21** and **1**. The other route for the formation of (**8a**) may be *via* the biradical (**16**), which may be formed by the addition of $^3O_2$ to two molecules of **1**, but this pathway can be excluded because oxidation of **1** with $^3O_2$ in the dark did not give **8a**, which is an unnatural lignan. No 7,7′-linked lignan has been found in nature.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer model 137 spectrometer. ^{1}H-NMR spectra were run on a JEOL TNM-FX-100 at 100 MHz with tetramethylsilane as an internal standard. Chemical shifts are given in δ values and coupling constants (J) are given in hertz (Hz). Electron impact mass spectra (EIMS) were taken on a Hitachi RMS-4.

Photooxidation of 1 in Alcohols, Acetone and Acetonitrile A solution of **1** (6 g) and methylene blue (100 mg) in MeOH, EtOH, acetone or acetonitrile (100 ml) was irradiated with 3 × 20 W fluorescent lamp. During the irradiation, oxygen was bubbled through the solution, which was cooled to 10—15 °C. The reaction was completed within 5 d. After removal of the solvent *in vacuo*, the residue was subjected to chromatography on silica gel. Seven products, **4a** (10 mg), **3a** (45 mg), **5a** (20 mg), **2** (0.94 g), **6** (0.65 g), **7a** (25 mg), and **8a** (5 mg), listed in their order of elution, were isolated from the MeOH solution. Seven products [**4b** (80 mg), **3b** (40 mg), **5b** (30 mg), **2** (1.0 g), **6** (0.6 g), **7b** (30 mg), and **8a** (4 mg)], six products [**2** (2.5 g), **6** (0.8 g), **9** (17 mg), **10a** (15 mg), **11a** (80 mg), and **8a** (10 mg)], and five products [**2** (1.63 g), **6** (1.32 g), **10a** (60 mg), **12a** (15 mg), and **8a** (7 mg)] were purified from the EtOH, acetone, and acetonitrile solutions, respectively, under the same conditions. Compounds **3a** and **3b** were purified by acetylation (Ac_2O/pyridine, room temperature, overnight) and hydrogenation (in ethyl acetate using Adams catalyst). Compounds **5a**, **7a**, **7b**, and **12a** were isolated after acetylation (same conditions as above). Products **2** (mp 132—134 °C), **6a** (mp 80—82 °C), **4a** (mp 68—70 °C), and **4b** were identical with dehydrodiisoeugenol,[1,8] vanillin,[7] methyl vanillate,[18] and ethyl vanillate,[19] based on comparison of their physical data with reference values or data for authentic samples. The physical data of new products were as follows.

3b: Oil. IR ν_{max}^{neat} cm^{-1}: 3040, 1758, 1600, 1500, 1420, 1265, 1200, 1140, 1040, 920, 845. ^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, t, J=7.0 Hz), 1.34 (3H, d, J=6.5 Hz), 1.60 (2H, m, Ar-CH_2C<u>H</u>$_2$$CH_3$), 2.28 (3H, s), 2.49 (2H, t, J=7.0 Hz, Ar-C<u>H</u>$_2$$CH_2CH_3$), 3.48 (2H, q, J=6.5 Hz, -OC<u>H</u>$_2$$CH_3$), 3.75 and 3.79 (each 3H, s), 4.25—4.55 (2H, m, -C<u>H</u>ORC<u>H</u>O-), 6.63—7.02 (6H, m, phenyl protons). NMR data of the two epimers were almost identical, except for a methyl signal of one isomer at δ 1.23 (3H, t, J=7.0 Hz, C<u>H</u>$_3$$CH_3$O-). *Anal.* Calcd for $C_{24}H_{34}O_6$: C, 69.21; H, 7.74. Found: C, 69.41; H, 7.79.

5a: Oil. IR ν_{max}^{neat} cm^{-1}: 3400, 3040, 1760, 1580, 1510, 1180, 1105, 1040, 955, 870, 825, 755. *Anal.* Calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71. Found: C, 57.90; H, 6.63.

5b: Oil. IR ν_{max}^{neat} cm^{-1}: 3450, 1600, 1500, 1280, 1220, 1088, 1040, 925, 822, 775. *Anal.* Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.30; H, 7.55.

7a: Oil. IR ν_{max}^{neat} cm^{-1}: 3045, 1750, 1720, 1600, 1500, 1250, 1200, 1150, 1025, 915, 820, 790, 750. *Anal.* Calcd for $C_{15}H_{20}O_7$: C, 57.68; H, 6.46. Found: C, 57.81; H, 6.53.

7b: Oil. IR ν_{max}^{neat} cm^{-1}: 3045, 1762, 1735, 1605, 1510, 1255, 1210, 1130, 1050, 925, 860, 800, 785. *Anal.* Calcd for $C_{16}H_{22}O_7$: C, 58.88; H, 6.80. Found: C, 58.70; H, 6.88.

8a: mp 192—194 °C. IR ν_{max}^{KBr} cm^{-1}: 3450, 1600, 1500, 1275, 1250, 1200, 1120, 1040, 870, 830, 780, 767. MS m/z (%); 360 (M^+, 25), 345 (17), 300 (21), 285 (25), 274 (32), 273 (100), 211 (26), 207 (19), 164 (92), 151 (52), 148 (38), 137 (78), 136 (64), 107 (46). *Anal.* Calcd for $C_{20}H_{24}O_6$: C, 66.65; H, 6.71. Found: C, 66.82; H, 6.69.

9: mp 74—76 °C. UV λ_{max}^{MeOH} nm (log ε): 209 (3.97), 250 (3.73), 305 (4.10). IR ν_{max}^{KBr} cm^{-1}: 3050, 1690, 1650, 1610, 1265, 1150. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, d, J=6 Hz), 2.40 (1H, dd, J=15.0, 13.5 Hz), 2.91 (1H, dd, J=15.0, 6.0 Hz), 3.71 (3H, s), 5.06 (2H, m), 5.93 (1H, br s), 6.19 (1H, s). *Anal.* Calcd for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17. Found: C, 61.47; H, 6.25.

10a: mp 73—75 °C. IR ν_{max}^{KBr} cm^{-1}: 3470, 3050, 1660, 1570, 1500, 1355, 1300, 1250, 1225, 1100, 1000, 840, 790. *Anal.* Calcd for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found: C, 68.89; H, 5.82.

11a: mp 134—136 °C. IR ν_{max}^{KBr} cm^{-1}: 3350, 1720, 1680, 1600, 1500, 1250, 1120, 1055, 1020, 920, 875, 860, 813, 782, 754, 725. *Anal.* Calcd for $C_{16}H_{14}O_6$: C, 63.57; H, 4.67. Found: C, 63.78; H, 4.58.

12a: Oil. IR ν_{max}^{neat} cm^{-1}: 3040, 1750, 1630, 1250, 1190, 1140, 1110, 1020, 890, 850, 820, 775. ^{1}H-NMR ($CDCl_3$) δ: 1.14 (3H, d, J=6.0 Hz), 1.85 (3H, dd, J=6.0, 1.0 Hz), 1.97 and 2.25 (each 3H, s), 3.85 (6H, s), 4.55 (1H, m, ArOC<u>H</u>CH_3), 5.65 (1H, m, CH_3C<u>H</u>=CH-), 5.91 (1H, d, J=6.5 Hz, ArC<u>H</u>OAc), 6.35 (1H, br d, J=15.5 Hz, ArC<u>H</u>=$CHCH_3$), 6.70—7.05 (6H, m). One of the epimers: ^{1}H-NMR ($CDCl_3$) δ: 1.29 (3H, d, J=6.1 Hz), 1.80 (3H, d, J=6.0 Hz), 1.97 and 2.25 (each 3H, s), 3.85 (6H, s), 4.55 (1H, m), 5.65 (1H, m), 5.91 (1H, d, J=4.7 Hz), 6.35 (1H, br d, J=15.5 Hz), 6.70—7.05 (6H, m). *Anal.* Calcd for $C_{24}H_{28}O_7$: C, 67.27; H, 6.59. Found: C, 67.73; H, 6.50.

Conversion of 3b to 3c by Acid **3b** (10 mg) was dissolved in 1 N HCl MeOH solution (1 ml) and kept at room temperature overnight. The reaction mixture was treated by a usual method to give **3c** (6 mg). Oil. IR ν_{max}^{neat} cm^{-1}: 3450, 1600, 1500, 1240, 1120, 1030, 820. ^{1}H-NMR ($CDCl_3$) δ: 0.96 (3H, t, J=7.1 Hz), 1.36 (3H, d, J=6.0 Hz), 1.57 (2H, m), 2.44 (2H, t, J=7.1 Hz), 3.32, 3.78 and 3.87 (each 3H, s), 4.30 (2H, m, ArC<u>H</u>-C<u>H</u>Ar), 5.60 (1H, br s, -OH), 6.64—6.91 (6H, m). One of the epimers: ^{1}H-NMR ($CDCl_3$) δ: 0.96 (3H, t, J=7.1 Hz), 1.06 (3H, d, J=6.0 Hz), 1.60 (2H, m), 2.50 (2H, t, J=7.1 Hz), 3.28, 3.82, 3.89 (each 3H, s), 4.34 (2H, m), 6.50 (1H, br s, -OH), 6.64—6.91 (6H, m).

Saponification of 3a by Base **3a** (10 mg) was dissolved in 1 N NaOH MeOH solution (1 ml) and kept at room temperature for 5 h under a nitrogen atmosphere. The reaction mixture was treated by a usual method to give **3c** (6 mg).

Catalytic Hydrogenolysis of 5a, 5d, 7a or 7b Compound **5a** (15 mg), **5d** (18 mg), **7a** (16 mg) or **7b** (18 mg) was dissolved in 5 ml of MeOH, then 10 mg of 5% Pd–C suspended in 5 ml of MeOH was added and the mixture was saturated with H_2. After 1 d, the catalyst was removed by filtration and washed several times with MeOH. After purification, the combined filtrate yielded **13** (11 mg). mp 68—70 °C. IR ν_{max}^{KBr} cm^{-1}: 3630, 1750, 1600, 1520, 1270, 1230, 1115, 1035, 1025, 920, 835, 745. ^{1}H-NMR ($CDCl_3$) δ: 1.04 (3H, d, J=6.1 Hz), 2.28 (3H, s), 3.04 (2H, d, J=6.3 Hz), 3.62 (3H, s), 4.30 (1H, m), 5.16 (1H, br s, -OH), 6.31—6.94 (3H, ABX system).

Dehydration of 13 with Acid **13** (10 mg) and *p*-toluenesulfonic acid (10 mg) were heated at 50 °C for 6 h in 5 ml of MeOH. Purification yielded a product (5 mg) identical with isoeugenol (**1**).

Acetylation of 5b with Ac_2O and Pyridine at 60 °C **5b** (10 mg) was dissolved in a mixture of 1 ml of Ac_2O and 1 ml of pyridine, and the reaction mixture was heated at 60 °C for 6 h. The usual work-up afforded **5d** (11 mg). Oil. IR ν_{max}^{neat} cm^{-1}: 1760, 1730, 1600, 1510, 1250, 1210, 1120, 1090, 1050, 925. ^{1}H-NMR ($CDCl_3$) δ: 1.16 (3H, d, J=7.0 Hz), 1.23 (3H, t, J=7.0 Hz), 1.97, 2.30, and 3.83 (each 3H, s), 3.43 (2H, m, AB system, -OC<u>H</u>$_2$$CH_3$), 4.31 (1H, d, J=5.1 Hz), 5.00 (1H, m), 6.89—7.03 (3H, m, phenyl protons).

Acetylation of 10a with Ac_2O and Pyridine A solution of **10a** (46 mg) in Ac_2O (1 ml) and pyridine (1 ml) was left overnight at room temperature. The reaction mixture was treated by the usual method to give an oil (**10b**) (40 mg). IR ν_{max}^{neat} cm^{-1}: 3050, 1755, 1680, 1580, 1500, 1250, 1150, 1020, 915, 850, 715. ^{1}H-NMR ($CDCl_3$) δ: 1.48 (3H, d, J=7.0 Hz), 2.28, 3.82 and 3.92 (each 3H, s), 3.52 (1H, m), 5.28 (1H, d, J=10.1 Hz), 6.89—7.38 (5H, m, phenyl protons), 9.83 (1H, s).

Sodium Borohydride Reduction of 10a An excess of sodium borohydride (50 mg) was added in small portions to a solution of **10a** (60 mg) in 1 ml of MeOH, and after 4 h the solution was poured into water (30 ml). The product (**15**) had mp 84—85 °C (42 mg). IR ν_{max}^{KBr} cm^{-1}: 3390, 1598, 1500, 1260, 1200, 1120, 1010, 930, 810, 730. ^{1}H-NMR ($CDCl_3$) δ: 1.41 (3H, d, J=7.0 Hz), 3.51 (1H, m), 3.92 and 3.98 (each 3H, s), 4.68 (2H, s), 5.18 (1H, d, J=10.0 Hz), 5.95 (1H, br s, phenolic -OH), 6.78—6.92 (3H, m, phenyl protons), 7.01 (2H, br s, phenyl protons).

Photooxidation of 2 in Acetonitrile A solution of **2** (500 mg) and methylene blue (10 mg) in acetonitrile (20 ml) was irradiated with a fluorescent lamp. The reaction was continued for 3 d at 10—15 °C and

gave **10a** (30 mg).

Conversion of 11a to 6 and 4a **11a** (45 mg) and *p*-toluenesulfonic acid (5 mg) were dissolved in 20 ml of MeOH and heated under reflux for 8 h. The product was purified by silica gel chromatography to give two products **4a** (20 mg) and **6** (18 mg).

Acetylation of 8a and 11a Acetylation of **8a** and **11a** by using the above-mentioned method afforded **8b**: mp 180—182 °C. IR ν_{max}^{KBr} cm^{-1}: 1770, 1600, 1500, 1270, 1180, 1150, 1125, 1060, 1035, 935, 915, 835, 768. ^{1}H-NMR ($CDCl_3$) δ: 1.04 (6H, d, J=6.1 Hz), 2.25 and 3.64 (each 6H, s), 2.68 and 4.59 (each 2H, m), 6.34 (2H, d, J=1.7 Hz), 6.60 (2H, dd, J=8.1, 1.7 Hz), 6.84 (2H, d, J=8.1) and **11b**: mp 158—160 °C. IR ν_{max}^{KBr} cm^{-1}: 1750, 1735, 1670, 1600, 1500, 1235, 1160, 1065, 1025, 900, 845, 770, 755. ^{1}H-NMR ($CDCl_3$) δ: 2.34, 3.89 and 3.92 (each 3H, s), 7.11—7.89 (6H, m), 9.90 (1H, s), respectively.

Conversion of 12a to 3c **12a** (10 mg) and PtO_2 (5 mg) were added to 3 ml of MeOH, then hydrogen was bubbled through the solution under stirring. After 4 h, the reaction mixture was filtered and 5 mg of *p*-toluenesulfonic acid was added to the filtrate. The mixture was kept at room temperature overnight. After purification by silica gel chromatography, it afforded **3c** (5 mg).

Photooxidation of 6 in MeOH and EtOH Vanillin (**6**) (8 g) was oxidized with singlet oxygen under the conditions mentioned above. After 6 d, it gave **4a** (30 mg), **4b** (35 mg), and **11a** (40 mg) from MeOH, EtOH, and acetone solutions, respectively.

Autooxidation of 6 in MeOH and EtOH A solution of vanillin (5 g) and *p*-toluenesulfonic acid (0.1 g) in 50 ml of MeOH or EtOH was oxidized with air in the dark. After 7 d, it gave **4a** (5 mg) and **4b** (7 mg) from the MeOH and EtOH solutions, respectively.

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