Studies on Chromium Trioxide-Based Oxidative Coupling Reagents and Synthesis of Lignan-Cagayanone

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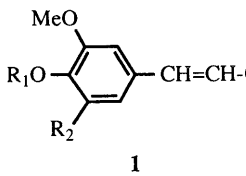
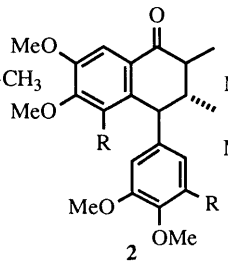
Oxidation of 1-arylprop-1-enes by using the reagent system CrO_3–$HClO_4$–CH_3CN at 0—5 °C gave seven products from methyl isoeugenol, five from ethyl isoeugenol, four from benzyl isoeugenol, and five from isosafrole. Cagayanone was obtained from isosafrole in one step. The structures of the products were elucidated and the mechanism of their formation is discussed.

Keywords oxidative coupling; chromium trioxide–perchloric acid–acetonitrile; lignan; cagayanone

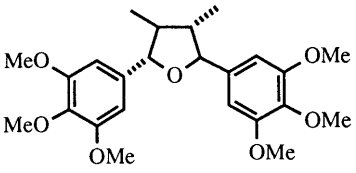
Oxidative coupling of monolignol has been studied as a model of the formation of lignan-related dimers during $FeCl_3$ oxidation,[1] enzyme oxidation[2] and free radical oxidation.[3] Anodic oxidation of monolignol gave a different type of lignan,[4] but photolysis[5] gave products of a similar type. In connection with our interest in lignan and biomimetic studies, we have examined the sensitized photooxidation of methyl (*E*)-ferulate,[6] ferric chloride oxidation of isoeugenol,[1] and photooxidation of isoeugenol in protic and aprotic solvents.[7] In 1983, Takeya[8] showed



1
a:R_1=Me, R_2=H
b:R_1=Me, R_2=OMe
c:R_1=Et, R_2=H
d:R_1=Bn, R_2=H



2
a:R=H
b:R=OMe



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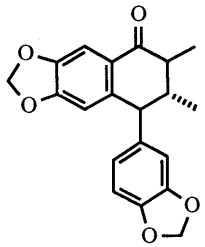

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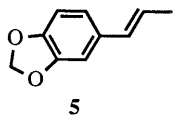

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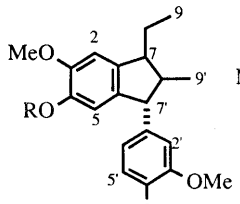

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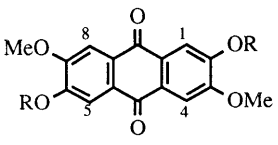
a:R=Me c:R=Bn
b:R=Et d:R=H



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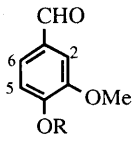
a:R=Me
b:R=Et
c:R=Bn



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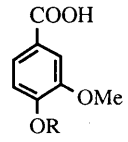
a:R=Me
b:R=Et
c:R=Bn



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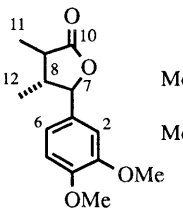
a:R=Me
b:R=Et
c:R=Bn



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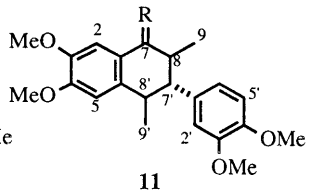
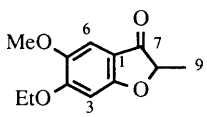


11
a:R=O
b:R=H, α-OH



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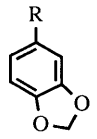

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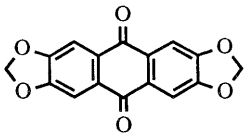
b:R=COOH



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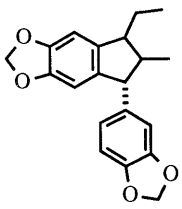

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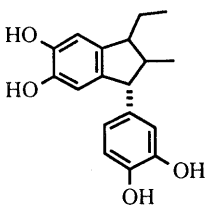

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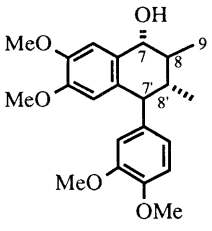

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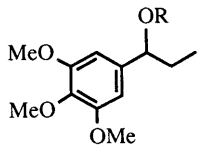
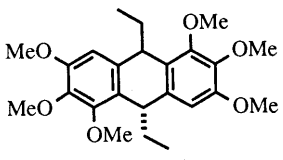


18
a:R=H
b:R=Ac



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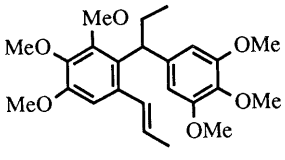

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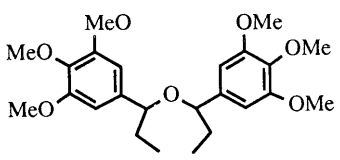

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that the oxidation of (*E*)-1-(3,4-dimethoxyphenyl)prop-1-ene (**1a**) (methyl isoeugenol) and 1-(3,4,5-trimethoxyphenyl)prop-1-ene (**1b**) by the reagent system CrO_3–HBF_4–MeCN or CrO_3–$HClO_4$–MeCN gave 4-oxogalbulin (**2a**, 16% yield), tetralone (**2b**, 14.3% yield) and grandisin (**3**, 17.7% yield), respectively. In that report, the description of the oxidative conditions is ambiguous and the reaction mechanism has not been described. We re-examined the oxidation conditions and reaction mechanism since we wished to synthesize cagayanone (**4**) (a new lignan isolated from *Myristica cagayanesis* by us)[9] from isosafrole (**5**) by using this oxidative reagent system.

Four 1-arylprop-1-enes (**1a**, **1c**, **1d**, and **5**) were used as starting materials. Compounds **1a**, **1c**, and **1d** were prepared from isoeugenol. Compound **1a** was dissolved in CH_3CN at 0—5 °C, and a solution of CrO_3–H_2O–$HClO_4$ was added dropwise during 30 min. The mixture was stirred for 3 h at 0—5 °C. Silica gel chromatography gave seven products **6a**, **7a**, **8a**, **9a**, **2a**, **10**, and **11a**. On similar reaction, **1c** gave **6b**, **8b**, **7b**, **12**, and **9b**, compound **1d** afforded **6c**, **8c**, **7c**, and **9c**, and compound **5** yielded **13a**, **14**, **15**, **13b**, and **4**. The structure elucidation of all the products was conducted, and mechanisms are proposed for their formation.

Compounds **6a**, **6b**, **6c**, and **15** are nonnatural lignans formed by acidic coupling. The infrared (IR) spectrum shows characteristic aromatic absorptions at 1620—1480 cm^{-1} in **6a**, **6b**, **6c**, and **15**, and the proton nuclear magnetic resonance (^{1}H-NMR) spectrum (Table I) indicated one ethyl group, one methyl group, two methoxy groups, three methine protons, two singlet aromatic protons, and three aromatic protons with ABX system coupling signals in **6a**, **6b**, and **6c**. In addition, two methoxy signals in **6a**, two ethoxy signals in **6b**, and two benzyloxy signals in **6c** are observed. Diisoeugenol (**6d**) (prepared from isoeugenol by acidic coupling)[5] reacted with CH_3I and K_2CO_3 in refluxing acetone to yield a product which was identical with compound **6a**. Similarly, when **6d** reacted with ethyl iodide or benzyl bromine and K_2CO_3 in refluxing acetone, **6b** or **6c** was obtained, respectively. Compound **15** is also a 1-arylindane derivative which is an acidic coupling product derived from **5**. The ^{1}H-NMR spectrum (Table I) of compound **15** indicated that it contains one methyl group, one ethyl group, three methine protons, five aromatic protons, and two methylenedioxy groups. The structure of **15** is similar to that of **6a** except that it has two methylenedioxy groups instead of four methoxy groups. Compound **15** can be prepared in two ways. One involves demethylation of **6a** with BBr_3 in CH_2Cl_2 at −5 °C to yield a tetraol **16** (mp 133—135 °C; ν_{max} 3283 cm^{-1}), which was subsequently reacted with CH_2I_2–K_2CO_3 in refluxing acetone to afford **15**. When isosafrole was heated in formic acid, the product was also identified as **15**.

Compounds **7a**, **7b**, **7c**, and **14** are all yellow crystals. From the UV, MS, and ^{1}H-NMR (Table II) spectra, the above four compounds were considered to be 2,3,6,7-tetraoxygenated anthraquinone derivatives. Compounds **8a**, **8b**, **8c**, and **13a** were assigned as benzaldehyde derivatives due to the signals at δ 9.82, 9.85, 9.81, and 9.72, respectively. The ABX system of aromatic protons indicated that the above four compounds are 3,4-dioxygenated. Compounds **9a**, **9b**, **9c**, and **13b** are all benzoic acid derivatives showing characteristic carboxylic acid and aromatic absorption bands in their IR spectra. Also 3,4-dioxygenated substitutions were apparent from the ABX system of aromatic protons in their ^{1}H-NMR spectra. Oxidation of compounds **8a**, **8b**, **8c**, and **13a** with CrO_3 in AcOH gave products identical with compounds **9a**, **9b**, **9c**, and **13b**, respectively. Compound **10** is a γ-lactone (ν_{max} 1767 cm^{-1}) with two methyl groups and a 3,4-dimethoxyphenyl moiety substituted at α, β and γ-positions, respectively. On the basis of its MS and ^{1}H-NMR spectra and nuclear Overhauser effects (NOE's), compound **10** can be assigned the shown structure. It might be formed from 4-oxogalbuline (**2a**). Compound **11a** was formulated as $C_{22}H_{26}O_5$ on the basis of the MS [M^+ peak at m/z 370 (100%)]. It is an isomer of compound **2a**. The IR spectrum shows characteristic absorption bands at 1664 cm^{-1} due to conjugated carbonyl and at 1597 and 1510 cm^{-1} due to an aromatic ring. The presence of two methyl and four methoxy groups was shown by the signals at δ 0.94 and 1.14 (each 3H, d, J=6.7 Hz, H-9, H-9′), and 3.86, 3.87, 3.91, and 3.92 (each 3H, s). The signals of three methine protons appear at δ 2.57 (1H, dd, J=10.8, 12.6 Hz, H-7′), 2.75 (1H, m, H-8), and 3.20 (1H, m, H-8′). Further, there were four aromatic protons centered at δ 6.75 (m, H-5, -2′, -5′, -6′) and one aromatic proton

TABLE I. ^{1}H-NMR Data for **6a**, **6b**, **6c**, and **15** ($CDCl_3$)

H	6a	6b	6c	15
2	6.71 s	6.78 s	6.74 s	6.68 s
5	6.36 s	6.41 s	6.45 s	6.36 s
7	2.92 m	2.89 m	2.89 m	2.88 m
8	1.37 m	1.36 m	1.37 m	1.35 m
	1.69 m	1.68 m	1.67 m	1.70 m
9	0.96 t (7.5)	0.95 t (7.3)	0.95 t (7.4)	0.95 t (7.4)
2′	6.59 d (1.3)	6.61 d (1.2)	6.64 d (1.9)	6.59 d (1.2)
5′	6.80 d (8.5)	6.79 d (7.9)	6.79 (8.0)	6.75 d (7.9)
6′	6.70 dd (8.5, 1.3)	6.66 dd (7.9, 1.2)	6.59 dd (8.0, 1.9)	6.62 dd (7.9, 1.2)
7′	3.75 d (9.0)	3.75 d (9.2)	3.72 d (9.1)	3.71 d (9.4)
8′	2.45 m	2.45 m	2.45 m	2.45 m
9′	1.03 d (7.0)	1.02 d (6.9)	1.01 d (7.0)	1.02 d (7.0)
OMe	3.70 s, 3.78 s 3.85 s, 3.86 s	3.76 s, 3.86 s	3.80 s, 3.88 s	
OCH_2O				5.78, 5.89 d (1.2), 5.91 s
$OCH_2\underline{C}H_3$		1.34 t (7.0) 1.44 t (6.9)		
$OC\underline{H}_2CH_3$		3.91 q (6.9) 4.08 q (7.0)		
$OC\underline{H}_2Ph$			5.11 s	
Ph-H			7.31 m	

Figures in parentheses are coupling constants in Hz.

TABLE II. ^{1}H-NMR Data for **7a**, **7b**, **7c**, and **14** ($CDCl_3$)

H	7a	7b	7c	14
1, 5	7.49 s	7.48 s	7.49 s	7.43 s
4, 8	7.49 s	7.46 s	7.53 s	7.43 s
OMe	3.99 s	3.99 s	3.98 s	
$OCH_2C\underline{H}_3$		1.49 t (7.0)		
$OC\underline{H}_2CH_3$		4.22 q (7.0)		
$OC\underline{H}_2Ph$			5.24 s	
4′			7.30 t (7.0)	
3′, 5′			7.37 t (7.0)	
2, 6′			7.45 d (7.0)	
$-OCH_2O-$				6.0 s

deshielded by carbonyl at δ 7.53 (1H, s, H-2). Irradiation at δ 0.94 (H-9) caused the multiplet at δ 2.75 (H-8) to collapse to a doublet signal (J=12.6 Hz), and irradiation at δ 1.14 (H-9′) caused H-8′ to collapse to a doublet signal (J=10.8 Hz). Sodium borohydride reduced **11a** to an alcohol **11b** [mp 139—140 °C, ν_{max} 3367 cm^{-1}], which exhibits four methine protons at δ 1.89 (1H, m, H-8), 2.19 (1H, dd, J=11.2, 10.8 Hz, H-7′), 2.98 (1H, m, H-8′) and 4.37 (1H, d, J=6.7 Hz, H-7), and a H-2 signal shift to δ 7.15 (1H, s). From the coupling constants of methine protons in compounds **11a** and **11b**, the substituents are all considered to be in quasi-equatorial orientation. Based on the above evidence, **11a** was concluded to be the first example of a nonnatural lignan with an 8–7′, 6–8′ linkage. Compound **2a** was also reduced with sodium borohydride to give an alcohol **17** [mp 131—133 °C] which is different from **11b**. The coupling constants of four methine protons [δ 1.52 (1H, m, H-8), 1.63 (1H, m, H-8′), 3.47 (1H, d, J=10.4 Hz, H-7′), 4.11 (1H, d, J=9.0 Hz, H-7)] revealed that the substituted groups in the tetraline **17** are all in *trans* configuration. The signal of H-2 in **17** appeared at δ 7.12 (s). Compound **12** is an interesting product. It contains one methoxy group (δ 3.90), one ethoxy group [δ 1.58 (3H, t, J=6.5 Hz), 4.16 (2H, q, J=6.5 Hz)], and two singlet aromatic protons [δ 6.78 (s, H-3), 7.26 (s, H-6)]. Based on the elementary analysis, compound **12** was formulated as $C_{12}H_{14}O_4$. It was a monolignol derivative with four substituents located on aromatic C-1, C-2, C-4, and C-5. The UV spectrum (λ_{max} 273, 310 nm) and IR spectrum (ν_{max} 1737 cm^{-1}) indicated that the conjugated carbonyl is cyclopentanone. Further, there are two signals at δ 1.51 (3H, d, J=6.8 Hz) and 5.42 (1H, q, J=6.8 Hz, H-8). The structure of **12** was concluded to be as shown based on the above evidence. Compound **4** was identified as cagayanone by comparison of their physical data.[9]

We tried to prepare **1b** from 3,4,5-trimethoxybenzaldehyde and obtained an interesting result, as follows. Ethylmagnesium bromide was reacted with 3,4,5-trimethoxybenzaldehyde to yield an alcohol **18a** [ν_{max} 3430 cm^{-1}; δ 0.70 (3H, t, J=7.4 Hz), 1.52 (2H, m), 4.25 (1H, t,

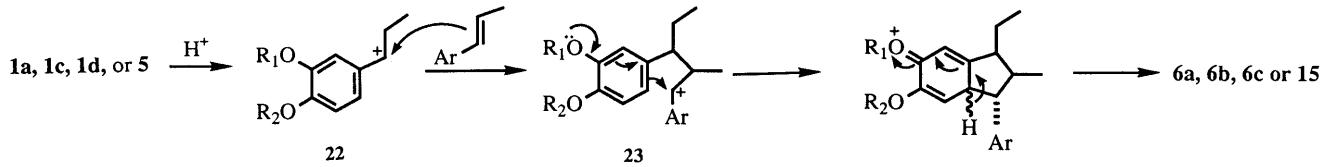

Chart 1

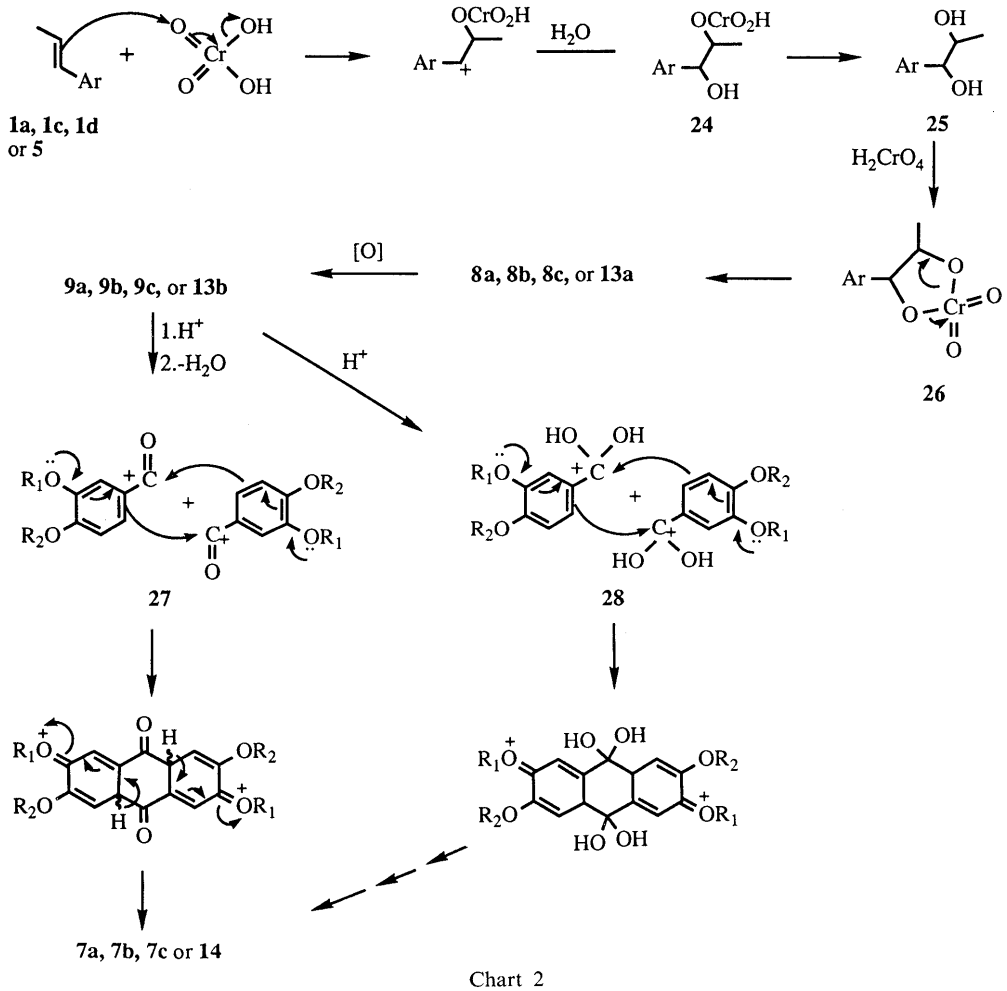

Chart 2

$J=6.5$ Hz)]. Compound **18a** and TsOH in acetone were heated under reflux, and four products, **19**, **1b**, **20**, and **21** were observed. When benzene was used as a solvent in place of acetone, it yielded the same four products with a different ratio. The reaction of **18a** with MsCl in triethylamine at 0 °C to room temperature also gave the same four products. The above three methods for preparation of **1b** from **18a** are not good, but the following pyrolysis method is an excellent and facile one. When **18b**, prepared from **18a**, was heated in dimethyl sulfonide (DMSO) at 190 °C, the only product obtained was found to be **1b** (95%). The structures of **19**, **20**, and **21** are supported by their physical data. The ^{1}H-NMR spectrum of **19** shows that the molecule is symmetric. The methyl proton signals of the ethyl group in **19**, seen at higher field [δ 0.13 (6H, t, $J=7.3$ Hz)], indicated that the ethyl group must be in quasi-axial orientation, being shielded by the anisotropic effect of the aromatic ring. Therefore, the two ethyl groups in **19** must be in *trans* diquasi-axial orientation.

The formation of the products by oxidative coupling of **1a**, **1c**, **1d**, and **5** may be rationalized in terms of the mechanisms in Charts 1—4. The formation of **6** and **15** is similar to the formation of diisoeugenol (**6d**) from isoeugenol by acidic coupling. The mechanism of this reaction is proposed to be as shown in Chart 1. Protonation on **1** or **5** would give the benzylic cation **22**, followed by coupling with **1** or **5** to form the other benzylic cation **23**. Cyclization and deprotonation provide **6** or **15**.

Oxidation of **1a**, **1c**, **1d**, or **5** with chromic acid provides the intermediate benzylic cation, which would add water to form **24**, followed by hydrolysis to yield the glycol **25**.[10] The cleavage of the cyclic chromate **26**, obtained from **25** and chromic acid, affords **8a**, **8b**, **8c**, or **13a**, respectively. Further oxidation with chromic acid gives the acids **9a**, **9d**, **9c**, or **13b** (Chart 2). The formation of four anthraquinones from **9a**, **9b**, **9c**, and **13b** is proposed. The protonation of **9a**, **9b**, **9c**, or **13b** may form the intermediate **27** or **28**. The intermediate **27** or **28** couples to itself then subsequently deprotonates to yield the anthraquinone, **7a**, **7b**, **7c**, or **14**. The pathway is also presented in Chart 2.

Compound **25** is oxidized to give the acyloin **29**, then protonated to form the oxonium ion **30**. After intramolecular cycloaddition and tautomerization, **30** is converted to **12** (Chart 3).

Coupling of **24** and 1-arylprop-1-ene would produce two intermediates **31** (major) and **32** (minor). Formation of **3** from **31** proceeds *via* an *O*-cycloaddition. *Via* *C*-cycloaddition then oxidation, **31** give **33**, which is transformed to **2a**, **2b**, or **4**. Compound **11a** is obtained from **34**, itself derived from a minor intermediate **32** *via* the same pathways (Chart 4).

The formation of **19**, **20**, and **21** from **18a** is proposed to

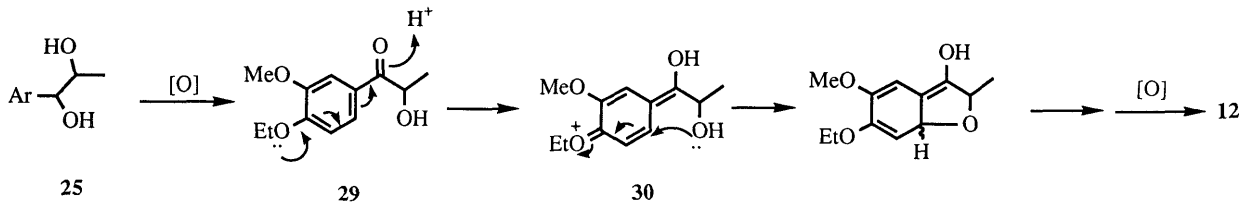

Chart 3

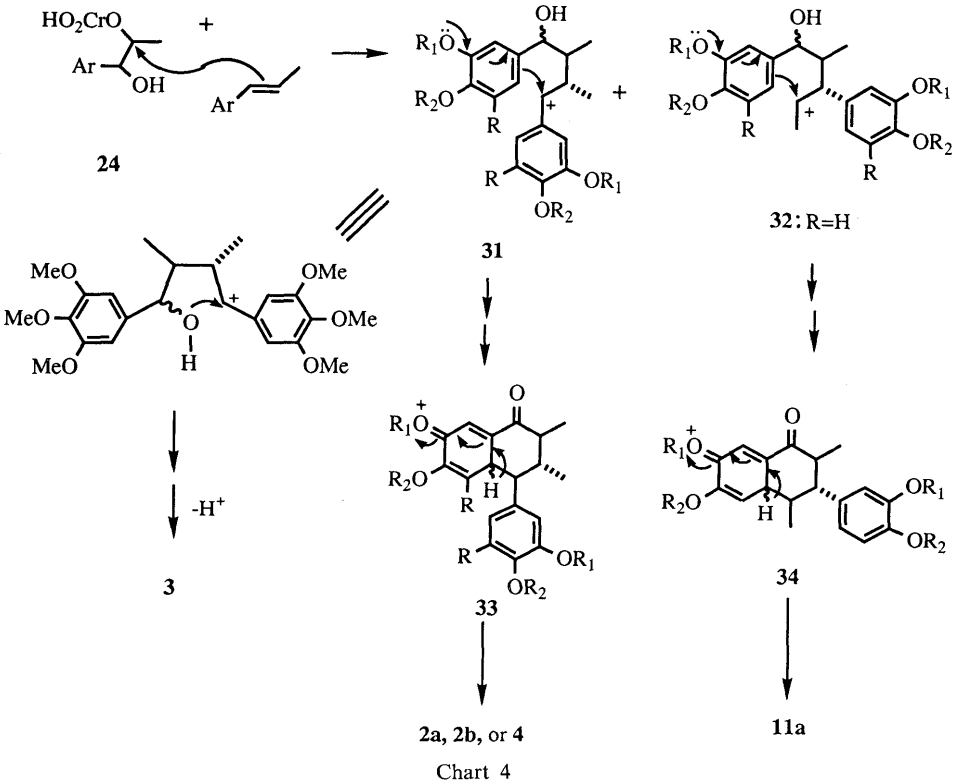

Chart 4

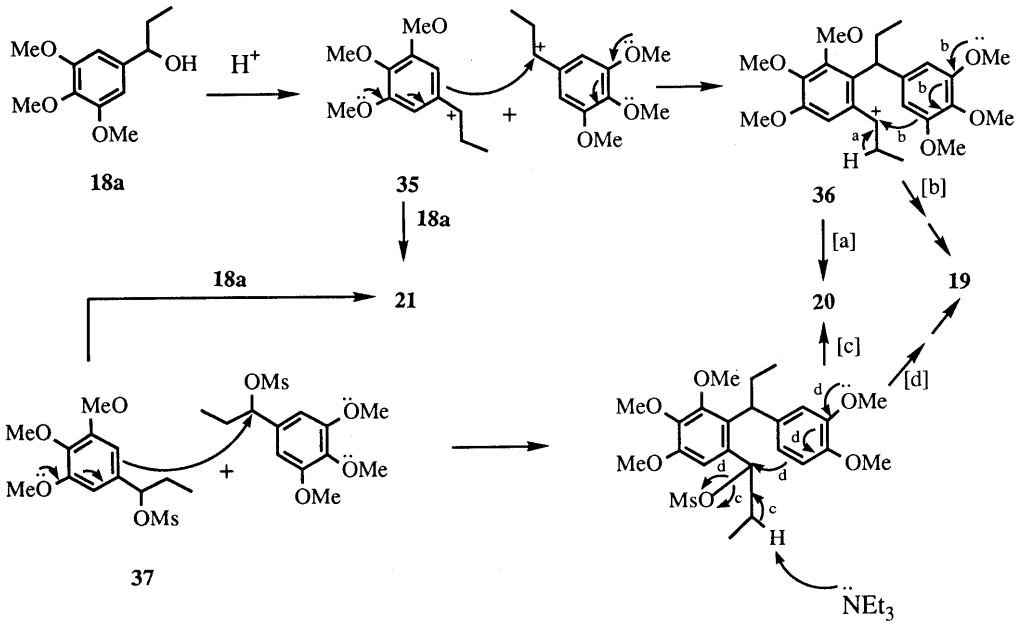

Chart 5

be as shown in Chart 5. Protonation and dehydration of **18a** form the intermediate **35**, which couples to itself to give the benzylic cation **36**. Intermediate **36** is deprotonated to give **20** (path a) and cyclized to **19** (path b). Coupling of **35** with **18a** would give compound **21**. The mechanisms of formation of **19**, **1b**, **20**, and **21** from the mesylate **37** in refluxing triethylamine are similar to that of **18a** with acid (Chart 5).

Experimental

Melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 781 spectrophotometer. ^{1}H and ^{13}C-NMR spectra were run on a Brucker AM 300 at 300 MHz and 75 MHz in the indicated solvent with tetramethylsilane (TMS) 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) and UV spectra were taken on JEOL JMS-100 and Hitachi U-3200 spectrometers, respectively.

General Procedure for Preparation of 1a, 1c, and 1d Isoeugenol (3 g), methyl iodide (3 ml), and potassium carbonate (510 mg) were added to dry acetone (30 ml). The reaction mixture was heated under reflux for 8 h. After evaporation of acetone and CH_3I, 50 ml of water was added to the residue, and the mixture was extracted with ether (30 ml) three times. Purification by silica gel chromatography gave **1a** (3.05 g). Under similar conditions, the use of ethyl iodide and benzyl bromide in place of methyl iodide yielded **1c** (3.06 g) [liquid; IR ν_{max}^{neat} cm^{-1}: 3050, 1595, 1580, 1235, 1225; ^{1}H-NMR ($CDCl_3$) δ: 1.42 (3H, t, J=6.9 Hz), 1.64 (3H, dd, J=6.4, 1.5 Hz), 3.85 (3H, s), 4.05 (2H, q, J=6.9 Hz), 6.06 (1H, dq, J=15.6, 6.4 Hz), 6.31 (1H, d, J=15.6 Hz), 6.75—6.87 (3H, m)] and **1d** (4.27 g) [liquid; IR ν_{max}^{neat} cm^{-1}: 3060, 1595, 1497, 1464, 1384, 1265: ^{1}H-NMR ($CDCl_3$) δ: 1.90 (3H, d, J=6.5 Hz), 3.81 (3H, s), 5.06 (2H, s), 6.14 (1H, dq, J=15.8, 6.5 Hz), 6.38 (1H, d, J=15.8 Hz), 6.80—6.95 (3H, m), 7.25—7.50 (5H, m)], respectively, from isoeugenol.

General Procedure for Oxidation of 1-Arylprop-1-ene by CrO_3–MeCN 1-Arylprop-1-ene was dissolved in MeCN (20 ml) at 0—5 °C under stirring. A solution of CrO_3 (7.5 g), H_2O (25 ml), and $HClO_4$ (20 ml) was added dropwise to the MeCN solution during 30 min, and the mixture was allowed to stand at 0—5 °C for 3 h under stirring. After purification by silica gel chromatography, compound **1a** (3.0 g) gave seven products **6a** (3.3%), **7a** (3.3%), **8a** (29%), **9a** (9.7%), **2a** (10%), **10** (3.4%), and **11** (1.5%), compound **1c** (3.25 g) afforded five products, **6b** (3.1%), **8b** (7%), **7b**(6%), **12** (20%), and **9b** (13%), compound **1d** (4.22 g) gave four products, **6c** (2.9%), **8c** (8%), **7c** (4%), and **9c** (32%), and compound **5** yielded five products **13a** (15%), **14** (10%), **15** (6%), **13b** (4%), and **4** (14%). Physical data of all products are given below.

4: mp 234—236 °C (lit. 236—238 °C).[9]

6a: mp 103—104 °C. IR ν_{max}^{KBr} cm^{-1}: 3050, 1595, 1513, 1416, 1229, 1152, 1095. ^{1}H-NMR ($CDCl_3$): Table I. *Anal.* Calcd for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 73.95; H, 7.98.

6b: mp 128—129 °C. IR ν_{max}^{KBr} cm^{-1}: 3040, 1610, 1505, 1389, 1259, 1210, 1156, 1139, 1094, 1060, 1037, 855, 774. ^{1}H-NMR ($CDCl_3$): Table I. *Anal.* Calcd for $C_{24}H_{32}O_4$: C, 74.97; H, 8.39. Found: C, 75.24; H, 8.32.

6c: Amorphous solid. IR ν_{max}^{KBr} cm^{-1}: 3040, 1600, 1504, 1488, 1248, 1145, 1032. ^{1}H-NMR ($CDCl_3$): Table I. *Anal.* Calcd for $C_{34}H_{36}O_4$: C, 80.28; H, 7.13. Found: C, 80.12; H, 7.18.

15: mp 90—91 °C. IR ν_{max}^{KBr} cm^{-1}: 3030, 2871, 2800, 1605, 1496, 1430, 1372, 1200, 1039, 940. MS *m/z*: 324 (M^+, 78), 295 (100), 205 (6), 202 (13), 181 (24). ^{1}H-NMR ($CDCl_3$): Table I. *Anal.* Calcd for $C_{20}H_{20}O_4$: C, 74.05; H, 6.22. Found: 74.31; H, 6.29.

7a: mp 194—196 °C (yellow crystals). IR ν_{max}^{KBr} cm^{-1}: 1677, 1639, 1581, 1509, 1449, 1369, 1328. MS *m/z*: 328 (M^+, 1), 246 (100), 218 (20), 203 (25), 187 (7), 147 (9). UV $\lambda_{max}^{CH_2Cl_2}$ nm (log ε): 270 (3.96), 290 (3.74), 346 (3.52), 406 (3.28). ^{1}H-NMR ($CDCl_3$): Table II. *Anal.* Calcd for $C_{18}H_{16}O_6$: C, 65.85; H, 4.91. Found: C, 65.51; H, 4.88.

7b: mp 135—136 °C (yellow crystals). IR ν_{max}^{KBr} cm^{-1}: 3030, 1643, 1619, 1578, 1510, 1314, 1242, 1128, 1097, 893, 788, 722. MS *m/z*: 356 (M^+, 1), 260 (100), 232 (48), 204 (60), 189 (55), 161 (13), 91 (5), 77 (11). UV $\lambda_{max}^{CH_2Cl_2}$ nm (log ε): 270 (4.37), 292 (4.21), 348 (3.69), 410 (3.43). ^{1}H-NMR ($CDCl_3$): Table II. *Anal.* Calcd for $C_{20}H_{20}O_6$: C, 67.40; H, 5.66. Found: C, 67.62; H, 5.61.

7c: mp 158—160 °C (yellow crystals). IR ν_{max}^{KBr} cm^{-1}: 3060, 1640, 1617, 1578, 1508, 1461, 1369, 1325, 1222, 1187. MS *m/z*: 480 (M^+, 0.9), 322 (31), 294 (25). UV $\lambda_{max}^{CH_2Cl_2}$ nm (log ε): 270 (3.92), 288 (3.82), 344 (3.35), 408 (3.04). ^{1}H-NMR ($CDCl_3$): Table II. *Anal.* Calcd for $C_{30}H_{24}O_6$: C, 74.99; H, 5.03. Found: C, 74.76; H, 5.09.

14: mp 159—161 °C (yellow crystals). IR ν_{max}^{KBr} cm^{-1}: 1658, 1585, 1480, 1394, 1377, 1323, 1245. MS *m/z*: 296 (M^+, 0.8), 230 (100), 204 (17), 187 (3). ^{1}H-NMR ($CDCl_3$): Table II. *Anal.* Calcd for $C_{16}H_8O_6$: C, 64.87; H, 2.72. Found: C, 64.65; H, 2.69.

8a: 3,4-Dimethoxybenzaldehyde (mp 42—44 °C; lit. 42—45 °C).[11]

8b: 4-Ethoxy-3-methoxybenzaldehyde (mp 58—60 °C; lit. 59—60 °C).[11]

8c: Liquid. IR ν_{max}^{neat} cm^{-1}: 2713, 1684, 1599, 1498, 1445, 1484, 1354, 1259. ^{1}H-NMR ($CDCl_3$) δ: 3.92 (3H, s), 5.22 (2H, s), 6.97 (1H, d, J=7.1 Hz), 7.24—7.66 (7H, m), 9.81 (1H, s).

13a: Piperonal (mp 36—37 °C; lit. 35—37.5 °C).[11]

9a: 3,4-Dimethoxybenzoic acid (mp 179—181 °C; lit. 179—182 °C).[11]

9b: mp 170—172 °C. IR ν_{max}^{KBr} cm^{-1}: 3300—2660, 1683, 1598, 1585, 1511, 1464, 1305, 1273, 1230. ^{1}H-NMR ($CDCl_3$) δ: 1.49 (3H, t, J=7.1 Hz), 3.92 (3H, s), 4.16 (2H, q, J=7.1 Hz), 6.89 (1H, d, J=8.5 Hz), 7.58 (1H, d, J=2.0 Hz), 7.73 (1H, dd, J=8.5, 2.0 Hz). *Anal.* Calcd for $C_{10}H_{12}O_4$: C, 61.21; H, 6.71. Found: C, 61.46; H, 6.14.

9c: Amorphous solid. IR ν_{max}^{KBr} cm^{-1}: 3060—2540, 1674, 1598, 1585,

1516, 1424, 1274, 1135. ^{1}H-NMR ($CDCl_3$) δ: 3.92 (3H, s), 5.19 (2H, s), 6.86 (1H, d, J=8.2 Hz), 7.21—7.48 (7H, m). *Anal.* Calcd for $C_{15}H_{14}O_4$: C, 69.75; H, 5.46. Found: C, 69.87; H, 5.51.

13b: Piperonylic acid (mp 228—230 °C; lit. 229—231 °C).[11]

10: mp 98—100 °C. IR ν_{max}^{KBr} cm^{-1}: 1767, 1608, 1593, 1517, 1451, 1421, 1382, 1235, 1200, 1178. MS *m/z*: 250 (M^+, 30), 191 (9), 175 (7), 166 (100), 151 (14), 91 (14), 77 (26). ^{1}H-NMR ($CDCl_3$) δ: 1.11 (3H, d, J=6.3 Hz, H-12), 1.28 (3H, d, J=6.8 Hz, H-11), 1.99 (1H, m, H-8), 2.34 (1H, m, H-9), 3.86, 3.87 (each 3H, s), 4.74 (1H, d, J=10.0 Hz), 6.84 (3H, m, H-2, H-5, H-6). H-12 shows NOE with H-8 (12.6% enhancement), H-9 (9.4% enhancement), H-7 (8.8% enhancement), and H-2, H-6 (3.7% enhancement), and H-11 exhibits NOE with H-8 (10.6% enhancement) and H-9 (11.8% enhancement). *Anal.* Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.31; H, 7.31.

11a: mp 121—123 °C. IR ν_{max}^{KBr} cm^{-1}: 1664, 1597, 1510, 1460, 1400, 1357, 1266, 1233, 1215. MS *m/z*: 370 (M^+, 100), 355 (11), 327 (5), 314 (22), 299 (11), 283 (14), 263 (14). *Anal.* Calcd for $C_{22}H_{26}O_5$: C, 71.33; H, 7.08. Found: C, 71.12; H, 7.12.

12: mp 125—126 °C. IR ν_{max}^{KBr} cm^{-1}: 1737, 1599, 1498, 1364, 1337, 1279, 1223. UV $\nu_{max}^{CH_2Cl_2}$ nm (log ε): 273 (4.02), 310 (3.87). ^{13}C-NMR ($CDCl_3$) δ: 14.4 (C-9), 20.4 ($OCH_2\underline{C}H_3$), 56.2 (OCH_3), 64.9 ($O\underline{C}H_2CH_3$), 77.0 (C-8), 103.7 (C-3), 106.2 (C-6), 117 (C-1), 145.7 (C-5), 150.6 (C-4), 154.2 (C-2), 170.7 (C-7). *Anal.* Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.56; H, 6.28.

Preparation of 6a, 6b, and 6c from Diisoeugenol (6d) Diisoeugenol (**6d**) (100 mg), methyl iodide, ethyl iodide, or benzyl bromide (0.2 ml each) and potassium carbonate (250 mg) were added to dry acetone (20 ml). The reaction mixture was heated under reflux for 8 h. Purification gave **6a**, **6b**, or **6c** (each 90% yield).

Acid Coupling of Isosafrole (5) Isosafrole (**5**) (210 mg), dissolved in formic acid (2 ml), was heated under reflux for 1 h. An excess of water (50 ml) was added and the whole was extracted with ether (30 ml) three times. The ether layer was washed with sodium bicarbonate aqueous solution and gave **15** (125 mg) after purification by silica gel chromatography.

Preparation of 15 from 6a Boron tribromide (0.5 ml) was poured into a solution of **6a** (80 mg) in dry CH_2Cl_2 (5 ml) under an argon atmosphere at −10 °C. The reaction mixture was stirred for 3 h at the same temperature. Then 50 ml of 3% sodium bicarbonate aqueous solution was added slowly. The solution was extracted with CH_2Cl_2 three times. The organic layer yielded **16** [74%; mp 133—135 °C. IR ν_{max}^{KBr} cm^{-1}: 3282, 1607, 1523, 1449, 1523, 1269, 1233. ^{1}H-NMR (CD_3COCD_3) δ: 0.92 (3H, t, J=7.3 Hz), 0.97 (3H, d, J=6.9 Hz), 1.32, 1.64 (each 1H, m), 2.35, 2.83 (each 1H, m), 3.62 (1H, d, J=9.3 Hz), 6.30, 6.73 (each 1H, s), 6.49—6.76 (3H, m, Ar-H), 7.51, 7.55, 7.68, 7.71 (each 1H, br s, Ar-OH, disappeared on D_2O exchange)] after purification by silica gel chromatography. Compound **16** (45 mg), K_2CO_3 (70 mg), and CH_2I_2 (1 ml) were added to 30 ml of dry acetone, and the mixture was heated under reflux in argon for 10 h. After purification, compound **15** (91%) was obtained from the reaction mixture.

Oxidation of 8a, 8b, 8c, and CrO_3 in AcOH A solution of 60 mg of CrO_3 in 1 ml of AcOH containing a few drops of water was added dropwise to a solution of 50 mg of **8a**, **8b**, **8c**, or **13a** in 1 ml of AcOH. The mixture was left at room temperature for 1 h, then poured into water (50 ml) and extracted with ether. The extract was treated by the usual method to give **9a**, **9b**, **9c**, or **13b**, respectively (85% yield).

Reduction of 11a by Sodium Borohydride Excess $NaBH_4$ was added in small portions to a solution of **11a** (120 mg) in 1 ml of MeOH, and the mixture was stirred for 30 min, then poured into 50 ml of water. The precipitates were crystallized: mp 139—140 °C, **11b** (104 mg). IR ν_{max}^{KBr} cm^{-1}: 3367, 1604, 1510, 1326, 1255, 1241. ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, d, J=6.5 Hz), 1.11 (3H, d, J=6.7 Hz), 1.89 (1H, m), 2.19 (1H, dd, J=11.2, 10.8 Hz, H-7'), 2.98 (1H, m), 3.85, 3.85, 3.87, 3.89 (each 3H, s), 4.37 (1H, d, J=6.7 Hz, H-7), 6.51—6.83 (4H, m), 7.15 (1H, s).

Reduction of 2a by Sodium Borohydride Compound **2a** (75 mg) was reduced by $NaBH_4$ under similar conditions to the above, giving **17** (68 mg) [mp 131—133 °C. IR ν_{max}^{KBr} cm^{-1}: 3323, 3055, 1589, 1510, 1257, 1220, 1140, 1117, 1104, 1026, 832, 768. ^{1}H-NMR ($CDCl_3$) δ: 0.86 (3H, d, J=6.3 Hz), 1.21 (3H, d, J=6.3 Hz), 1.52 (1H, m), 1.63 (1H, m), 3.47 (1H, d, J=10.4 Hz), 3.55, 3.78, 3.87, 3.88 (each 3H, s), 4.11 (1H, d, J=9.0 Hz), 6.11 (1H, s), 6.51—6.80 (3H, m), 7.12 (1H, s)].

Preparation of 18a and 18b from 3,4,5-Trimethoxybenzaldehyde Small pieces of magnesium metal (0.6 g), were placed in dry ether (30 ml) and then ethyl bromide (2.0 g) was added slowly. The reaction mixture was stirred at ambient temperature for 8 h until the magnesium metal had dissolved completely. 3,4,5-Trimethoxybenzaldehyde (2.0 g) dissolved in dry ether (25 ml) was poured into the Grignard reagent solution at 0—5 °C. After 1 h, the reaction mixture was stirred at ambient temperature for 4 h, and then saturated ammonium chloride aqueous solution was added to quench the reaction. After purification by silica gel chromatography, the reaction mixture afforded the alcohol **18a** (1.91 g) [liquid. IR ν_{max}^{neat} cm^{-1}: 3430, 1589, 1501, 1457, 1416, 1324, 1231, 1132, 1125, 1045, 1005. ^{1}H-NMR ($CDCl_3$) δ: 0.70 (3H, t, J=7.4 Hz), 1.52 (2H, m), 3.36 (1H, br s, –OH), disappeared on D_2O exchange), 3.59, 3.61, 3.61 (each 3H, s), 4.25 (1H, t, J=6.5 Hz), 6.34 (2H, s)]. Compound **18a** (1.1 g) was allowed to react with Ac_2O (3 ml) in pyridine (2 ml) at room temperature overnight. Usual work-up gave the monoacetate **18b** (1.1 g) [liquid. IR ν_{max}^{neat} cm^{-1}: 1730, 1587, 1501, 1457, 1417, 1367, 1234, 1123. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J=7.4 Hz), 1.85 (2H, m), 2.09, 3.83, 3.85, 3.85 (each 3H, s), 5.58 (1H, t, J=7.9 Hz), 6.55 (2H, s)].

Reaction of 18a with TsOH in Acetone or Benzene Compound **18a** (1.0 g) and TsOH (50 mg) were heated in acetone (50 ml) under reflux for 3 h. The reaction mixture was purified by silica gel chromatography, and gave four products, **19** (70 mg) [mp 102—103 °C. IR ν_{max}^{KBr} cm^{-1}: 1595, 1485, 1443, 1396, 1348, 1245, 1200, 1110. MS *m/z*: 416 (M^+, 3), 387 (100), 358 (25), 197 (12). ^{1}H-NMR ($CDCl_3$) δ: 0.13 (6H, t, J=7.3 Hz), 1.68 (2H, m), 2.08 (2H, m), 3.85, 3.86, 3.91 (each 6H, s), 4.30 (2H, dd, J=3.5, 3.0 Hz), 6.56 (2H, s)], **1b** (150 mg) [liquid. IR ν_{max}^{neat} cm^{-1}: 1577, 1498, 1457, 1411, 1335, 1237, 1182, 1126. ^{1}H-NMR ($CDCl_3$) δ: 1.79 (3H, dd, J=6.6, 1.2 Hz), 3.76, 3.78, 3.78 (each 3H, s), 6.06 (1H, dq, J=15.9, 6.6 Hz), 6.25 (1H, d, J=15.9 Hz), 6.48 (2H, s)], **20** (405 mg) [amorphous. IR ν_{max}^{KBr} cm^{-1}: 2831, 1587, 1504, 1485, 1402, 1328, 1237, 1126, 1058, 921, 843, 807. ^{1}H-NMR ($CDCl_3$) δ: 0.82 (3H, t, J=7.4 Hz), 1.79 (3H, dd, J=6.6, 1.1 Hz), 2.14 (2H, m), 3.50, 3.75, 3.75, 3.79, 3.81, 3.85 (each 3H, s), 4.27 (1H, t, J=6.3 Hz), 5.86 (1H, dq, J=15.3, 6.6 Hz), 6.43 (2H, s), 6.56 (1H, br d, J=15.3 Hz), 6.63 (1H, s)], and **21** (251 mg) [mp 64—64.5 °C. IR ν_{max}^{KBr} cm^{-1}: 1589, 1500, 1458, 1419, 1323, 1234, 1127, 1045. MS *m/z*: 434 (M^+, 14), 210 (100). ^{1}H-NMR ($CDCl_3$) δ: 0.85 (6H, t, J=7.2 Hz), 1.57 (2H, m), 1.76 (2H, m), 3.82 (12H, s), 3.84 (6H, s), 3.90 (2H, dd, J=7.6, 5.7 Hz), 6.46 (4H, s)]. Under similar conditions, but with benzene as the solvent instead of acetone, the reaction also gave four products, **19** (5%), **1b** (10%), **10** (30%), and **21** (40%).

Reaction 18a with MsCl in Triethyl Amine Methanesulfonyl chloride (0.6 g) was slowly added to a solution of **18a** (1.0 g) in dry triethylamine at 0 °C. The reaction mixture was stirred at room temperature for 6 h, and then was heated under reflux overnight. Usual work-up gave four products, **19** (trace), **1b** (30%), **20** (40%) and **21** (13%).

Pyrolysis of 18b in DMSO at 190 °C The monoacetate **18b** (1.0 g) was dissolved in DMSO (15 ml) and heated at 190 °C for 6 h. The solvent was evaporated *in vacuo* to give a residue, to which water (50 ml) was added. The aqueous solution was extracted with ether (50 ml) three times. The combined ether extracts were washed with water and purified by silica gel chromatography. Compound **1b** was obtained in high yield (95%).

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