# Reaction of Methyl 4,5-Epoxy-(2*E*)-pentenoate with Arenes. I. A Facile Synthesis of 4-Aryl-5-hydroxy-(2*E*)-pentenoate Derivatives[1)]

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**The reactivity of methyl 4,5-epoxy-(2*E*)-pentenoate (2) toward various aromatic nucleophiles in the presence of boron trifluoride etherate was examined. When benzene derivatives possessing an electron-donating substituent were employed, *meta*-substituted benzenes attacked only the 4-position of 2, while *ortho*- or *para*-substituted benzenes simultaneously attacked the 4- and 2-positions of 2.**

**Keywords** methyl 4,5-epoxy-(2*E*)-pentenoate; benzene derivative; boron trifluoride etherate; regioselectivity; Friedel–Crafts reaction; 4-aryl-5-hydroxypentenoate

Conjugated oxiranes which are directly bonded to a π-electron system and/or conjugated esters, are synthetically important because they are able to sustain regioselective reactions depending on the reactant or the conditions. The reactions of various kinds of nucleophiles with methyl 4,5-epoxy-(2*E*)-hexenoate (**1**), possessing both a conjugated oxirane and a conjugated ester function, have been reported. The reaction of **1** and methyl acetoacetate in the presence of palladium complex in dimethylsulfoxide gave the 4,5-disubstituted hexenoate (1,4-adduct) and 2,5-disubstituted hexenoate (1,2-adduct) (9 : 1),[2)] while the reactions of **1** and various kinds of methyl-metal reagents were reported to provide the 1,4-adduct and 1,2-adduct with varying product ratios.[3)] Further, treatment of **1** with various kinds of nucleophiles such as phenol, thiophenol, polymethoxybenzene and indole in the presence of a Lewis acid afforded the 4,5-*anti*-disubstituted 2-hexenoate and/or 2,5-*anti*-disubstituted 3-hexenoate.[4)]

In this paper, we report the relative reactivity of methyl 4,5-epoxy-(2*E*)-pentenoate (**2**) toward aromatic nucleophiles in the presence of boron trifluoride etherate from the viewpoint of the reaction site of the attacking arenes in comparison with that of **1**.

The substrate **2** was obtained in 63% yield by epoxidation of methyl (2*E*),4-pentadienoate[5)] with *m*-chloroperbenzoic acid. As a preliminary experiment, when **2** was treated with benzene in the presence of boron trifluoride etherate in dichloromethane for 10 min at −20 °C, most of it was decomposed and other products could not be obtained. In the reaction of **2** in toluene under the same conditions, an inseparable mixture of three types of 4-aryl-2-pentenoates was obtained in 55% yield. However, the reaction of **2** and anisole proceeded under the same reaction conditions to yield methyl 4-(4-methoxyphenyl)-5-hydroxy-(2*E*)-pentenoate (**3**) (71% yield) and methyl 4-(2-methoxyphenyl)-5-hydroxy-(2*E*)-pentenoate (**4**) (10% yield) (Chart 1).

In the Friedel–Crafts reaction of a simple epoxide, 1,2-epoxypropane, with benzene or anisole, 2-phenyl-1-propanol was obtained as a main product in the former reaction[6)] while the latter reaction[7)] gave 1,1-dianisylpropane as a predominant product when nitromethane was employed as a solvent. The conversion of epoxide to aldehydes in the presence of a mild acid catalyst such as boron trifluoride etherate at low temperature is known.[8)] The formation of 1,1-dianisylpropane can be explained in term of rearrangement of epoxide to aldehyde and the subsequent condensation with the arene. However, this type of rearrangement was not observed in the case of **2**.

**Reaction of 2 and *ortho*-, *meta*- and *para*-Methoxytoluenes** The reaction of **2** and *ortho*-methoxytoluene in the presence of boron trifluoride etherate in dichloromethane for 1 h at −78 °C gave methyl 4-(3-methyl-4-methoxyphenyl)-5-hydroxy-(2*E*)-pentenoate (**5**) in 86% yield. The substitution pattern of the aromatic ring in **5** was determined by a nuclear Overhauser effect (NOE) experiment (400 MHz) as shown in Chart 1.

Next, the reaction of **2** with *meta*-methoxytoluene was carried out under the same conditions to provide two kinds of isomeric compounds, methyl 4-(2-methyl-4-methoxyphenyl)-5-hydroxy-(2*E*)-pentenoate (**6**) (49% yield) and methyl 4-(4-methyl-2-methoxyphenyl)-5-hydroxy-(2*E*)-pentenoate (**7**) (23% yield) (Chart 2). The structures of **6** and **7** were determined as follows. Compound **7** was treated with aluminum chloride in ethanethiol for 30 min at 0 °C to give the demethylated compound **8** (23% yield) along with the lactone **9** (25% yield). Compound **8** underwent an intramolecular Michael reaction on standing in methanol containing a small amount of triethylamine at room temperature to afford the dihydrobenzofuran

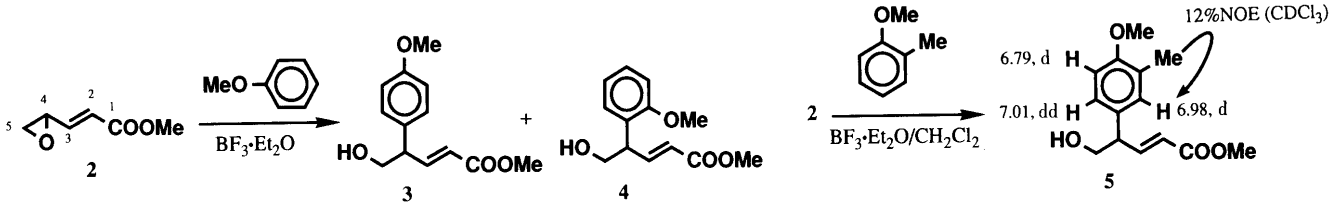


Chart 1

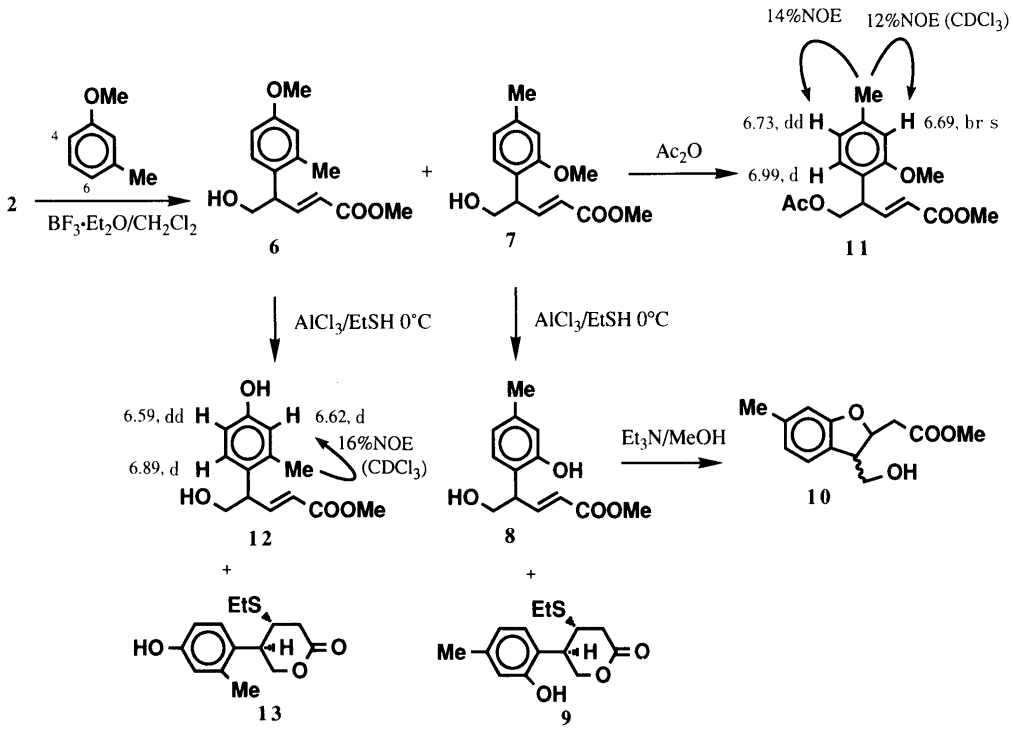


Chart 2

derivative **10**.

This cyclization indicates that the methoxyl group of **7** exists in the *ortho*-position to the incoming substituent. In addition, an NOE experiment (400 MHz, Chart 2) on the acetate **11** supports the assignment of the substitution pattern of the aromatic ring. The same treatment of another isomer **6** afforded the demethylated compound **12** (55% yield) and the lactone **13** (34% yield). The substitution pattern on the aromatic ring of **12** was confirmed by NOE experiments as shown in Chart 2. Both methyl and methoxyl groups serve as electron donors that activate the *ortho*- and *para*-positions and stabilize the transition state leading to $\sigma$-complex formation. The methoxyl group is a stronger *ortho*- and *para*-orienting substituent than the methyl group. In addition, the former has a larger steric effect. Therefore, it is reasonable that the formation of **6** exceeds that of isomer **7** in this case. The product ratio of **6**/**7** upon the reaction of **2** and *meta*-methoxytoluene in dichloromethane at various temperatures or with various catalysts was evaluated by $^1$H-NMR analysis of the reaction mixture as shown in Table I. The temperature and catalyst employed had relatively little effect on the ratio.

Furthermore, when **2** and *para*-methoxytoluene were reacted in the presence of boron trifluoride etherate under the same conditions, two compounds possessing the same substitution pattern on the aromatic ring were isolated (Chart 3), *i.e.*, methyl 4-(5-methyl-2-methoxyphenyl)-5-hydroxy-(2*E*)-pentenoate (**14**) (43% yield) and the other one is methyl 2-(5-methyl-2-methoxyphenyl)-5-hydroxy-(3*E*)-pentenoate (**15**) (25% yield). The product ratio of **14**/**15** evaluated by $^1$H-NMR analysis was 70/30. The structures of both products were confirmed by chemical correlation: diisobulylaluminum hydride (DIBAL-H) reduction of **14** and **15** gave the same diol **16**. The reaction site (3-position) of *para*-methoxytoluene is located at the *ortho*-position of the methoxyl group and corresponds to the *meta*-position of the methyl group, which only affects the reactivity by electronic interaction. As described later, when the reaction site of the aromatic ring is located at the *meta*-position with respect to at least one *ortho*-and *para*-directing substituent, both 4-aryl- and 2-arylpentenoate derivatives are obtained.

**Reaction of 2 and *ortho*-, *meta*- and *para*-Dimethoxybenzenes** The reaction of **2** and *ortho*-dimethoxybenzene in the presence of boron trifluoride etherate in dichloromethane at $-78$ °C gave two regioisomers, methyl 4-(3,4-dimethoxyphenyl)-5-hydroxy-(2*E*)-pentenoate (**17**) (73% yield) and methyl 2-(3,4-dimethoxyphenyl)-5-hydroxy-(3*E*)-pentenoate (**18**) (5% yield) (Chart 4). The reaction of **2** and *para*-dimethoxybenzene under the same conditions afforded methyl 4-(2,5-dimethoxyphenyl)-5-hydroxy-(2*E*)-pentenoate (**19**) (50% yield) and methyl 2-(2,5-dimethoxyphenyl)-5-hydroxy-(3*E*)-pentenoate (**20**) (6% yield) (Chart 4). For the purpose of establishing the ratio of regioisomers, a separate experiment was carried out under the same conditions and the product ratio was calculated by $^1$H-NMR analysis of the reaction mixture. In the case of the reaction of *ortho*-dimethoxybenzene, the ratio of **17**/**18** was found to be 91/9 . In the case of the reaction of *para*-dimethoxybenzene, that of **19**/**20** was found to be 79/21. The 4-position of *ortho*-dimethoxybenzene is activated by one methoxyl substituent but is slightly deactivated by the other one. *para*-Dimethoxybenzene possesses the same electronic system. The finding that two regioisomers (*i.e.* **17** and **18** or **19** and **20**) were obtained is consistent with the previous case (the formation of **14** and **15**) for the above-mentioned reason.

On the other hand, when **2** was treated with *meta*-dimethoxybenzene in dichloromethane in the presence

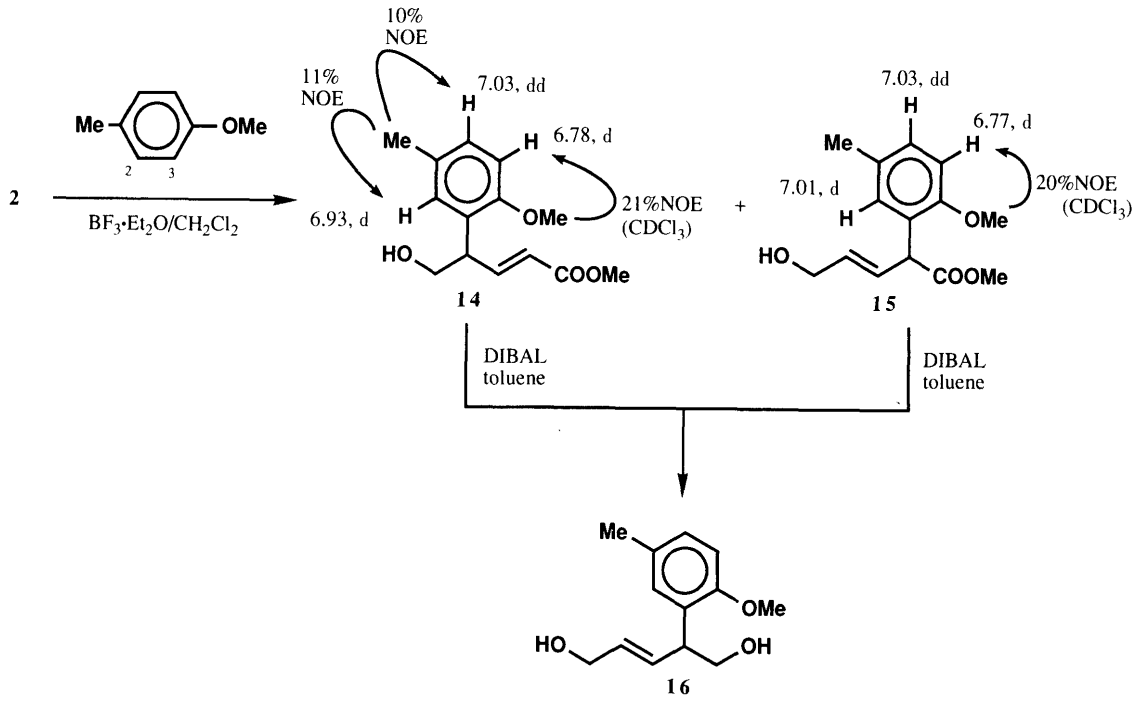


Chart 3

TABLE I. Product Ratio of **6** and **7** on the Reaction of **2** and *m*-Methoxytoluene in Dichloromethane

| Catalyst | Temperature (°C) | Time (h) | 6 | 7 |
|---|---|---|---|---|
| $BF_3 \cdot Et_2O$ | −78 | 1 | 68 | 32 |
| $BF_3 \cdot Et_2O$ | −20 | 0.5 | 70 | 30 |
| $BF_3 \cdot Et_2O$ | 0 | 0.5 | 69 | 31 |
| $SnCl_4$ | −78 | 1 | 76 | 24 |
| $CF_3SO_3H$ | −78 | 1 | 61 | 39 |

The reaction of *m*-methoxytoluene (1 mmol) and **2** (1.5 mmol) was carried out in the presence of 0.5 mmol of catalyst in dichloromethane (2 ml).

of boron trifluoride etherate at −78 °C, methyl 4-(2,4-dimethoxyphenyl)-5-hydroxy-(2*E*)-pentenoate (**21**) (70% yield) was obtained as the sole product (Chart 4). This result can be explained by the fact that the 4-position of *meta*-dimethoxybenzene is activated by mesomeric effect.

**Reaction of 2 and Trisubstituted Benzenes Possessing Methyl and Methoxyl Groups** The reaction of **2** and trisubstituted benzenes under the same conditions was also examined. In the reaction of 5-methyl-1,3-dimethoxybenzene, the 4-arylpentenoate derivative (**22**) (82% yield) was predominantly obtained along with the 4-arylpentenoate derivative (**23**) (0.4% yield) (Chart 5). Regioselective substitution on the benzene ring can be explained by the fact that the 4-position of 5-methyl-1,3-dimethoxybenzene is more susceptible than the in 2-position from a steric hindrance point of view. However, in the reaction of **2** and 4-methyl-1,2-dimethoxybenzene, and the reaction of **2** and 2-methyl-1,4-dimethoxybenzene, the 4-arylpentenoate derivative [**24** (46% yield) and **26** (68% yield)] was obtained as a main product along with the 2-arylpentenoate derivative [**25** (18% yield) and **27** (11% yield)] under the same reaction conditions as in the previous case (Chart 5).

The reactivity of trisubstituted benzenes having electron-donating groups toward **2** was found to be similar to that of disubstituted benzenes toward **2**. When the nucleophilic center of the benzene ring (as in 5-methyl-1,3-dimethoxybenzene) is located at the *ortho*- or *para*-position to three substituents, the nucleophile attacks only the 4-position of the electrophile **2**. However, when the nucleophilic center is located at the *meta*-position to at least one substituent, the nucleophile attacks the 4- and 2-positions of **2** simultaneously. In the reaction of **2** and poly-substituted benzene derivatives, it appears that the contribution of each substituent is constant and that the influence of the substituents is simply additive. But it is difficult to explain the regio-selectivity toward electrophile **2** in the present case.

The behavior of **1** toward nucleophiles has been rationalized by means of CNDO/2 calculations.[3] That is to say, the harder nucleophiles attack predominantly the 4-position of **1** under charge control while the softer ones attack predominantly the 2-position of **1** under orbital control. The preferred site of **2** attacked by nucleophiles seems to be similar to that of **1** because of the structural similarity of **1** and **2**.

In the forthcoming paper, we will describe the application of 4-arylpentenoate derivatives to the syntheses of bisabolane-type sesquiterpenes.

## Experimental

The melting points were determined on a Yanaco MP-S3 micro melting point apparatus and are uncorrected. IR spectra were recorded on a Hitachi 260-30 spectrometer. $^1$H-NMR spectra were recorded on a JEOL EX-400 (400 MHz) spectrometer with tetramethylsilane as an internal standard. The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), double doublet (dd), double triplet (dt), multiplet (m) and broad (br). High-resolution mass spectra (HRMS) were obtained with a JEOL JMX-DX 303 spectrometer. In general, reactions were carried out in dry solvents under an argon atmosphere unless otherwise mentioned. For column chromatography, Silica gel 60 (Merck 7734) was employed.

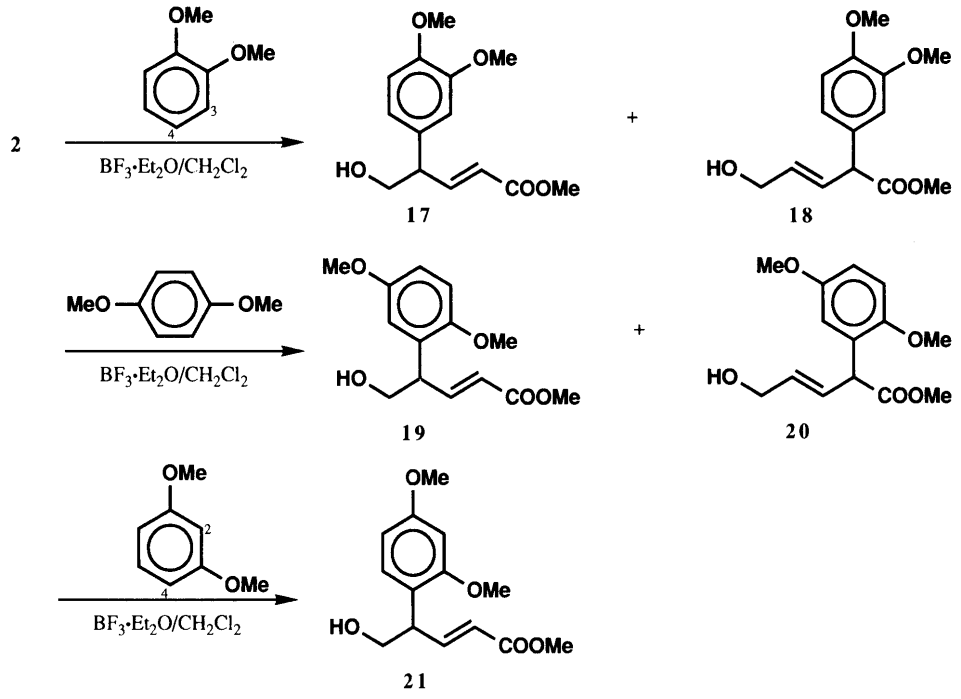


Chart 4

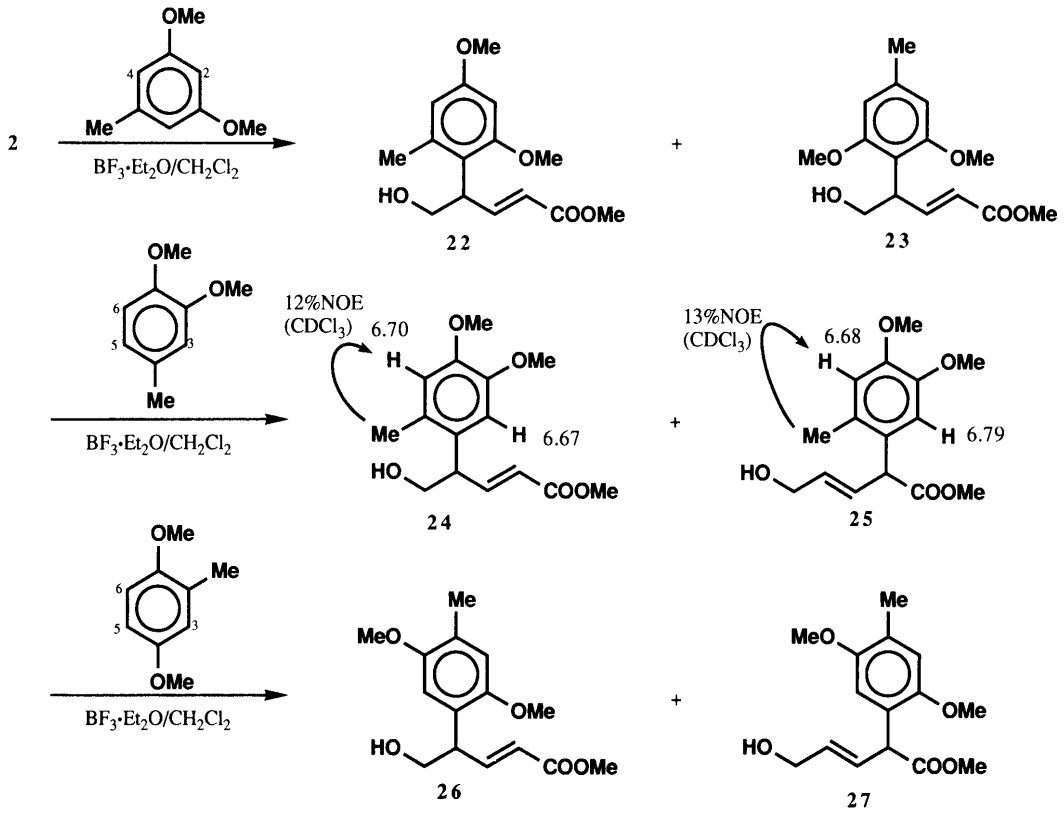


Chart 5

**Methyl 4,5-Epoxy-(2*E*)-pentenoate (2)** A solution of methyl (2*E*),4-pentadienoate[5] (22.40 g, 0.20 mol) and *m*-chloroperbenzoic acid (43.14 g, 0.25 mol) in $CH_2Cl_2$ (500 ml) was stirred for 3 d at room temperature. The precipitated *m*-chlorobenzoic acid was filtered off and the filtrate was washed with 7% aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$. After removal of $CH_2Cl_2$, the residue was distilled to give a colorless oil **2** (16.20 g, 63%), bp 90—91 °C/18 mmHg. *Anal.* Calcd for $C_6H_8O_3 \cdot 1/10H_2O$: C, 55.47; H, 6.36. Found: C, 55.63; H, 6.32. IR ($CCl_4$): 2980, 2940, 1715, 1650 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 2.72 (1H, dd, $J_{4,5}$ = 2.0 Hz, $J_{gem}$ = 6.0 Hz, 5-H), 3.07 (1H, dd, $J_{4,5}$ = 5.0 Hz, $J_{gem}$ = 6.0 Hz, 5-H), 3.46 (1H, ddd, $J_{4,5}$ = 2.0, 5.0 Hz, $J_{3,4}$ = 7.0 Hz, 4-H), 3.75 (3H, s, COOMe), 6.19 (1H, d, $J_{2,3}$ = 16.0 Hz, 2-H), 6.64 (1H, dd, $J_{2,3}$ = 16.0 Hz, $J_{3,4}$ = 7.0 Hz, 3H).

**General Procedure of the Reaction of 2 and Nucleophiles in the Presence of $BF_3 \cdot Et_2O$** Under dry ice/acetone cooling, $BF_3 \cdot Et_2O$ (5 mmol) was added slowly to a solution of **2** (15 mmol) and a nucleophile (10 mmol) in $CH_2Cl_2$ (20 ml). The reaction mixture was stirred for 1 h at −78 °C, then gradually warmed to −20 °C. After addition of saturated brine at −20 °C, the whole was extracted with $CH_2Cl_2$. The organic layer was washed with 7% aqueous $NaHCO_3$ and dried over $MgSO_4$. Evaporation of $CH_2Cl_2$ gave an oily product, which was chromatographed on silica gel (60 g) to afford a homogeneous oil from the hexane–AcOEt (5 : 1—1 : 1,

v/v) eluate. The chemical yield of each product was calculated based on the nucleophile used unless otherwise mentioned.

Compound **3**: The second elution with hexane : AcOEt (3 : 1) gave a pale yellow oil **3** (71% yield, calculated based on **2**). HRMS *Anal.* Calcd for $C_{13}H_{16}O_4$ ($M^+$, *m/z*): 236.1049. Found: 236.1048. IR ($CCl_4$): 3430, 1700, 1650 $cm^{-1}$. $^1$H-NMR($CDCl_3$) $\delta$: 3.59 (1H, br q, $J$=7.0 Hz, 4-H), 3.69 (3H, s, COOMe), 3.76 (3H, s, OMe), 3.81 (2H, d, $J$=7.0 Hz, 5-H), 5.85 (1H, dd, $J_{2,3}$=16.0 Hz, $J_{2,4}$=1.5 Hz, 2-H), 6.86 (2H, d, $J$=9.0 Hz, *o*-position of OMe), 7.11 (1H, dd, $J_{2,3}$=16.0 Hz, $J_{3,4}$=7.0 Hz, 3-H), 7.11 (2H, d, $J$=9.0 Hz, *m*-position of OMe).

Compound **4**: The first elution with hexane : AcOEt (3 : 1) gave a pale yellow oil **4** (10% yield, calculated based on **2**). HRMS *Anal.* Calcd for $C_{13}H_{16}O_4$ ($M^+$, *m/z*): 236.1049. Found: 236.1061. IR ($CCl_4$): 3440, 1700, 1650 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 3.72 (3H, s, COOMe), 3.83 (3H, s, OMe), 3.92 (2H, br d, $J$=6.0 Hz, 5-H), 4.13 (1H, m, 4-H), 5.92 (1H, dd, $J_{2,3}$=16.0 Hz, $J_{2,4}$=2.0 Hz, 2-H), 6.90 (1H, br d, $J$=8.0 Hz, *o*-position of OMe), 6.94 (1H, dt, $J$=1.5, 7.5 Hz, *p*-position of OMe), 7.15 (1H, dd, $J$=7.5, 2.0 Hz, *o*-position of R$^{9)}$), 7.19 (1H, dd, $J_{2,3}$=16.0 Hz, $J_{3,4}$=8.0 Hz, 3-H), 7.25 (1H, ddd, $J$=8.0, 7.5, 2.0 Hz, *p*-position of R$^{9)}$).

Compound **5**: Pale yellow oil, 86% yield. HRMS *Anal.* Calcd for $C_{14}H_{18}O_4$ ($M^+$, *m/z*): 250.1205. Found: 250.1186. IR ($CHCl_3$): 3420, 1700, 1650 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 2.20 (3H, s, Me), 3.59 (1H, dq, $J_{2,4}$=1.5 Hz, $J_{3,4}$=7.0 Hz, $J_{4,5}$=7.0 Hz, 4-H), 3.71 (3H, s, COOMe), 3.81 (3H, s, OMe), 3.85 (2H, d, $J$=7.0 Hz, 5-H), 5.88 (1H, dd, $J_{2,3}$=16.0 Hz, $J_{2,4}$=1.5 Hz, 2-H), 6.79 (1H, d, $J$=8.0 Hz, *o*-position of OMe), 6.98 (1H, d, $J$=2.0 Hz, *o*-position of Me), 7.01 (1H, dd, $J$=8.0, 2.0 Hz, *p*-position of Me), 7.12 (1H, dd, $J_{2,3}$=16.0 Hz, $J_{3,4}$=7.0 Hz, 3-H).

Compound **6**: The second elution with hexane : AcOEt (2 : 1) gave a pale yellow oil **6** (49% yield). HRMS *Anal.* Calcd for $C_{14}H_{18}O_4$ ($M^+$, *m/z*): 250.1205. Found: 250.1213. IR ($CCl_4$): 3420, 2930, 1700, 1650 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 2.31 (3H, s, Me), 3.70 (3H, s, COOMe), 3.78 (3H, s, OMe), 3.88 (3H, m, 4-H and 5-H), 5.83 (1H, d, $J$=16.0 Hz, 2-H), 6.74 (2H, m, two *o*-positions of OMe), 7.06 (1H, d, $J$=9.0 Hz, *m*-position of OMe), 7.09 (1H, dd, $J_{2,3}$=16.0 Hz, $J_{3,4}$=7.0 Hz, 3-H).

Compound **7**: The first elution with hexane : AcOEt (2 : 1) gave a pale yellow oil **7** (23% yield). HRMS *Anal.* Calcd for $C_{14}H_{18}O_4$ ($M^+$, *m/z*): 250.1205. Found: 250.1217. IR ($CCl_4$): 3440, 2940, 1700, 1650 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.99 (1H, br s, OH), 2.33 (3H, s, Me), 3.70 (3H, s, COOMe), 3.80 (3H, s, OMe), 3.87 (2H, d, $J$=7.0 Hz, 5-H), 4.07 (1H, dq, $J_{2,4}$=1.5 Hz, $J$=7.0 Hz, 4-H), 5.89 (1H, dd, $J_{2,3}$=16.0 Hz, $J_{2,4}$=1.5 Hz, 2-H), 6.70 (1H, br s, *o*-position of OMe), 6.74 (1H, br d, $J$=8.0 Hz, *p*-position of OMe), 7.01 (1H, d, $J$=8.0 Hz, *m*-position of OMe), 7.17 (1H, dd, $J_{2,3}$=16.0 Hz, $J_{3,4}$=7.0 Hz, 3-H).

Compound **14**: The first elution with hexane : AcOEt (5 : 1) gave a pale yellow oil **14** (43% yield). HRMS *Anal.* Calcd for $C_{14}H_{18}O_4$ ($M^+$, *m/z*): 250.1205. Found: 250.1207. IR ($CHCl_3$): 3430, 1700, 1650 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.88 (1H, br s, OH), 2.27 (3H, s, Me), 3.71 (3H, s, COOMe), 3.78 (3H, s, OMe), 3.89 (2H, d, $J$=7.0 Hz, 5-H), 4.08 (1H, dq, $J_{2,4}$=1.5 Hz, $J$=7.0 Hz, 4-H), 5.91 (1H, dd, $J_{2,3}$=16.0 Hz, $J_{2,4}$=1.5 Hz, 2-H), 6.78 (1H, d, $J$=8.0 Hz, *o*-position of OMe), 6.93 (1H, d, $J$=2.0 Hz, *o*-position of R$^{9)}$), 7.03 (1H, dd, $J$=8.0, 2.0 Hz, *p*-position of R$^{9)}$), 7.18 (1H, dd, $J_{2,3}$=16.0 Hz, $J_{3,4}$=7.0 Hz, 3-H).

Compound **15**: The second elution with hexane: AcOEt (5 : 1) gave a pale yellow oil **15** (25% yield). HRMS *Anal.* Calcd for $C_{14}H_{18}O_4$ ($M^+$, *m/z*): 250.1205. Found: 250.1186. IR ($CCl_4$): 3430, 2900, 1710 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.80 (1H, s, OH), 2.27 (3H, s, Me), 3.67 (3H, s, COOMe), 3.78 (3H, s, OMe), 4.12 (2H, d, $J$=5.0 Hz, 5-H), 4.58 (1H, d, $J$=8.0 Hz, 2-H), 5.70 (1H, dt, $J_{3,4}$=16.0 Hz, $J_{4,5}$=5.0 Hz, 4-H), 6.06 (1H, dd, $J_{2,3}$=8.0 Hz, $J_{3,4}$=16.0 Hz, 3-H), 6.77 (1H, d, $J$=8.0 Hz, *o*-position of OMe), 7.01 (1H, d, $J$=2.0 Hz, *o*-position of R$^{9)}$), 7.03 (1H, dd, $J$=8.0, 2.0 Hz, *p*-position of R$^{9)}$).

Compound **17**: The first elution with hexane : AcOEt (2 : 1) gave a pale yellow oil **17** (73% yield). HRMS *Anal* Calcd for $C_{14}H_{18}O_5$ ($M^+$, *m/z*): 266.1154. Found: 266.1134. IR ($CHCl_3$): 3430, 1700 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.91 (1H, br s, OH), 3.62 (1H, br q, $J$=7.0 Hz, 4-H), 3.72 (3H, s, COOMe), 3.86, 3.87 (each 3H, s, OMe), 3.87 (2H, d, $J$=7.0 Hz, 5-H), 5.90 (1H, dd, $J_{2,3}$=16.0 Hz, $J_{2,4}$=1.5 Hz, 2-H), 6.72 (1H, d, $J$=2.0 Hz, *o*-position of one OMe and *o*-position of R$^{9)}$), 6.77 (1H, dd, $J$=8.0, 2.0 Hz, *m*-position of one OMe and the *p*-position of other OMe), 6.85 (1H, d, $J$=8.0 Hz, *m*-position of R$^{9)}$), 7.12 (1H, dd, $J_{2,3}$=16.0 Hz, $J_{3,4}$=7.0 Hz, 3-H).

Compound **18**: The second elution with hexane : AcOEt (2 : 1) gave a pale yellow oil **18** (5% yield). HRMS *Anal.* Calcd for $C_{14}H_{18}O_5$ ($M^+$, *m/z*): 266.1154. Found: 266.1126. IR($CHCl_3$): 3430, 1710 $cm^{-1}$. $^1$H-NMR (benzene-$d_6$) $\delta$: 3.33, 3.35, 3.40 (each 3H, s, COOMe, OMe), 3.79 (2H, d, $J$=5.0 Hz, 5-H), 4.29 (1H, d, $J$=8.0 Hz, 2H), 5.57 (1H, dt, $J_{3,4}$=15.0 Hz, $J_{4,5}$=5.0 Hz, 4-H), 6.22 (1H, dd, $J_{2,3}$=8.0 Hz, $J_{3,4}$=15.0 Hz, 3-H), 6.58 (1H, d, $J$=8.0 Hz, *m*-position of R$^{9)}$), 6.91 (1H, br d, $J$=8.0 Hz, *m*-position of one OMe and *p*-position of other OMe), 6.92 (1H, br s, *o*-position of one OMe and *o*-position of R$^{9)}$).

Compound **19**: The first elution with hexane: AcOEt (5 : 1) gave a pale yellow oil **19** (50% yield). HRMS *Anal.* Calcd for $C_{14}H_{18}O_5$ ($M^+$, *m/z*): 266.1154. Found: 266.1126. IR ($CCl_4$): 3440, 2930, 1700 $cm^{-1}$. $^1$H-NMR($CDCl_3$) $\delta$: 2.00 (1H, s, OH), 3.70 (3H, s, COOMe), 3.75, 3.77 (each 3H, s, OMe), 3.88 (2H, d, $J$=7.0 Hz, 5-H), 4.09 (1H, br q, $J$=7.0 Hz, 4-H), 5.90 (1H, dd, $J_{2,3}$=16.0 Hz, $J_{2,4}$=1.5 Hz, 2-H), 6.73 (1H, d, $J$=2.0 Hz, *o*-position of R$^{9)}$), 6.75 (1H, dd, $J$=9.0, 2.0 Hz, *p*-position of R$^{9)}$), 6.82 (1H, d, $J$=9.0 Hz, *m*-position of R$^{9)}$), 7.16 (1H, dd, $J_{2,3}$=16.0 Hz, $J_{3,4}$=7.0 Hz, 3-H).

Compound **20**: The second elution with hexane: AcOEt (5 : 1) gave a pale yellow oil **20** (6% yield). HRMS *Anal.* Calcd for $C_{14}H_{18}O_5$ ($M^+$, *m/z*): 266.1154. Found: 266.1131. IR ($CCl_4$): 3440, 2900, 1720 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.65 (1H, s, OH), 3.69 (3H, s, COOMe), 3.77, 3.78 (each 3H, s, OMe), 4.15 (2H, d, $J$=5.0 Hz, 5-H), 4.62 (1H, d, $J$=8.0 Hz, 2-H), 5.72 (1H, dt, $J_{3,4}$=15.0 Hz, $J_{4,5}$=5.0 Hz, 4-H), 6.07 (1H, dd, $J_{2,3}$=8.0 Hz, $J_{3,4}$=15.0 Hz, 3-H), 6.78 (1H, dd, $J$=9.0, 2.0 Hz, *p*-position of R$^{9)}$), 6.82 (1H, d, $J$=9.0 Hz, *m*-position of R$^{9)}$), 6.82 (1H, d, $J$=2.0 Hz, *o*-position of R$^{9)}$).

Compound **21**: Pale yellow oil, 70% yield. *Anal.* HRMS Calcd for $C_{14}H_{18}O_5$ ($M^+$, *m/z*): 266.1154. Found: 266.1120. IR ($CCl_4$): 3440, 2910, 1700, 1645, 1600 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.92 (1H, s, OH), 3.71 (3H, s, COOMe), 3.80 (3H × 2, s, OMe), 3.87 (2H, br d, $J$=7.0 Hz, 5-H), 4.03 (1H, q, $J$=7.0 Hz, 4-H), 5.89 (1H, dd, $J_{2,3}$=16.0 Hz, $J_{2,4}$=1.5 Hz, 2-H), 6.46 (1H, br d, $J$=9.0 Hz, *m*-position of R$^{9)}$ and *p*-position of one OMe), 6.47 (1H, br s, *o*-position of two OMe), 7.03 (1H, d, $J$=9.0 Hz, *o*-position of R$^{9)}$), 7.16 (1H, dd, $J_{2,3}$=16.0 Hz, $J_{3,4}$=7.0 Hz, 3-H).

Compound **22**: The second elution with hexane: AcOEt (2 : 1) gave a colorless powder **22** (82% yield), mp 75 °C (hexane). MS *m/z*: 280 ($M^+$). *Anal.* Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.32; H, 7.32. IR ($CHCl_3$): 3500, 2940, 1700 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.84 (1H, br s, OH), 2.30 (3H, s, Me), 3.70 (3H, s, COOMe), 3.76, 3.78 (each 3H, s, OMe), 3.93, 4.05 (each 1H, dd, $J_{gem}$=9.0 Hz, $J_{4,5}$=7.0 Hz, 5-H), 4.00 (1H, br q, $J$=7.0 Hz, 4-H), 5.80 (1H, dd, $J_{2,3}$=16.0 Hz, $J_{2,4}$=1.5 Hz, 2-H), 6.33, 6.35 (each 1H, d, $J$=2.0 Hz, phenyl signal), 7.31 (1H, dd, $J_{2,3}$=16.0 Hz, $J_{3,4}$=7.0 Hz, 3-H).

Coupound **23**: The first elution with hexane : AcOEt (2 : 1) gave a colorless powder **23** (0.4% yield), mp 79—80 °C ($Et_2O$–hexane). MS *m/z*: 280 ($M^+$). *Anal.* Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.11; H, 7.20. IR ($CHCl_3$): 3460, 2940, 1700, 1640 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.90 (1H, s, OH), 2.33 (3H, s, Me), 3.69 (3H, s, COOMe), 3.77 (3H × 2, s, OMe), 3.91, 4.02 (each 1H, dd, $J_{gem}$=10.0 Hz, $J_{4,5}$= 7.0 Hz, 5-H), 4.36 (1H, br q, $J$=7.0 Hz, 4-H), 5.82 (1H, dd, $J_{2,3}$= 16.0 Hz, $J_{2,4}$=1.5 Hz, 2-H), 6.38 (2H, s, phenyl signals), 7.32 (1H, dd, $J_{2,3}$=16.0 Hz, $J_{3,4}$=7.0 Hz, 3-H).

Compound **24**: The first elution with hexane : AcOEt (2 : 1) gave a pale yellow oil **24** (46% yield). HRMS *Anal.* Calcd for $C_{15}H_{20}O_5$ ($M^+$, *m/z*): 280.1311. Found: 280.1305. IR ($CCl_4$): 3460, 2920, 1700, 1650 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.90 (1H, s, OH), 2.27 (3H, s, Me), 3.72 (3H, s, COOMe), 3.84, 3.85 (each 3H, s, OMe), 3.90 (3H, m, 4- and 5-H), 5.85 (1H, dd, $J_{2,3}$=16.0 Hz, $J_{2,4}$=1.5 Hz, 2-H), 6.67 (1H, s, *m*-position of Me), 6.70 (1H, s, *o*-position of Me), 7.10 (1H, dd, $J_{2,3}$=16.0 Hz, $J_{3,4}$=6.0 Hz, 3-H).

Compound **25**: The second elution with hexane : AcOEt (2 : 1) gave a pale yellow oil **25** (18% yield). HRMS *Anal.* Calcd for $C_{15}H_{20}O_5$ ($M^+$, *m/z*): 280.1311. Found: 280.1298. IR ($CCl_4$): 3450, 2910, 1740 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 2.29 (3H, s, Me), 3.69 (3H, s, COOMe), 3.84, 3.85 (each 3H, s, OMe), 4.14 (2H, br d, $J$=5.0 Hz, 5-H), 4.49 (1H, d, $J$=8.0 Hz, 2-H), 5.65 (1H, dt, $J_{3,4}$=15.0 Hz, $J_{4,5}$=5.0 Hz, 4-H), 6.07 (1H, dd, $J_{2,3}$=8.0 Hz, $J_{3,4}$=15.0 Hz, 3-H), 6.68 (1H, s, *o*-position of Me), 6.79 (1H, s, *m*-position of Me).

Compound **26**: The first elution with hexane : AcOEt (1 : 1) gave a pale yellow oil **26** (68% yield). HRMS *Anal.* Calcd for $C_{15}H_{20}O_5$ ($M^+$, *m/z*): 280.1311. Found: 280.1308. IR ($CCl_4$): 3440, 2920, 1700, 1650 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.73 (1H, br d, $J$=7.0 Hz, OH), 2.21 (3H, s, Me), 3.72 (3H, s, COOMe), 3.77 (3H × 2, s, OMe), 3.91 (2H, t, $J$=7.0 Hz, 5-H), 4.07 (1H, br q, $J$=7.0 Hz, 4-H), 5.92 (1H, dd, $J_{2,3}$=16.0 Hz, $J_{2,4}$=1.5 Hz, 2-H), 6.62 (1H, s, *m*-position of Me), 6.72 (1H, s, *o*-position of Me), 7.19 (1H, dd, $J_{2,3}$=16.0 Hz, $J_{3,4}$=7.0 Hz, 3-H).

Compound **27**: The second elution with hexane : AcOEt (1 : 1) gave a pale yellow oil **27** (11% yield). HRMS *Anal.* Calcd for $C_{15}H_{20}O_5$ ($M^+$, *m/z*): 280.1311. Found: 280.1320. IR ($CCl_4$): 3450, 2920, 1740 $cm^{-1}$. $^1$H-NMR (benzene-$d_6$) $\delta$: 2.10 (1H, br s, OH), 2.26 (3H, s, Me), 3.37, 3.39, 3.44 (each 3H, s, OMe), 3.90 (2H, d, $J$ = 5.0 Hz, 5-H), 4.90 (1H, d, $J$ = 8.0 Hz, 2-H), 5.71 (1H, dt, $J_{3,4}$ = 15.0 Hz, $J_{4,5}$ = 5.0 Hz, 4-H), 6.30 (1H, dd, $J_{2,3}$ = 8.0 Hz, $J_{3,4}$ = 15.0 Hz, 3-H), 6.54 (1H, s, *o*-position of Me), 6.95 (1H, s, *m*-position of Me).

**Demethylation of 7** A solution of anhydrous $AlCl_3$ (680 mg, 5 mmol) in ethanethiol (2 ml) was added to the mixture of **7** (257 mg, 1 mmol) and ethanethiol (2 ml) at 0 °C. The whole was stirred for 30 min at 0 °C, then ether and 2 N HCl were added to the reaction mixture. The whole was extracted with ether, and the ehereal solution was washed with saturated brine and dried over $MgSO_4$. The filtrate was evaporated under reduced pressure. The residue was subjected to column chromatography with hexane–AcOEt (4 : 1) . The first fraction afforded the lactone **9** (68 mg, 25%) as a colorless crystal, mp 130 °C (benzene). MS *m/z*: 266 ($M^+$). *Anal.* Calcd for $C_{14}H_{18}O_3S$: C, 63.13; H, 6.81. Found: C, 63.06; H, 6.87. $^1$H-NMR ($CDCl_3$) $\delta$: 1.17 (3H, t, $J$ = 7.0 Hz, $CH_2\underline{CH_3}$), 2.27 (3H, s, Me), 2.50 (2H, m, $CH_2\underline{CH_3}$), 2.71 (1H, dd, $J$ = 17.0, 7.0 Hz, 2-H), 3.18 (1H, dd, $J$ = 17.0, 7.0 Hz, 2-H), 3.33 (1H, ddd, $J_{3,4}$ = 8.0 Hz, $J_{4,5}$ = 5.0, 9.0 Hz, 4-H), 3.68 (1H, dt, $J_{3,4}$ = 8.0 Hz, $J_{2,3}$ = 7.0 Hz, 3-H), 4.48 (1H, dd, $J$ = 11.0, 5.0 Hz, 5-H), 4.58 (1H, dd, $J$ = 11.0, 9.0 Hz, 5-H), 6.67 (1H, br s, *o*-position of OH), 6.70 (1H, br d, $J$ = 8.0 Hz, *p*-position of OH), 6.80 (1H, br s, phenol-OH), 7.04 (1H, d, $J$ = 8.0 Hz, *m*-position of OH). The substituents at the 3-position (EtS-) and 4-position (Ar-) should be in *trans*-configuration as judged from the coupling constant (8.0 Hz). The second fraction afforded **8** (57 mg, 23%) as a pale yellow oil. HRMS *Anal.* Calcd for $C_{13}H_{16}O_4$ ($M^+$, *m/z*): 236.1049. Found: 236.1059. IR ($CHCl_3$): 3320, 1700 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 2.25 (3H, s, Me), 3.55 (1H, s, OH), 3.70 (3H, s, COOMe), 3.85 (1H, m, 4-H), 3.98 (2H, m, 5-H), 5.85 (1H, dd, $J_{2,3}$ = 16.0 Hz, $J_{2,4}$ = 1.5 Hz, 2-H), 6.66 (1H, br s, *o*-position of OH), 6.66 (1H, br d, $J$ = 9.0 Hz, *p*-position of OH), 6.90 (1H, d, $J$ = 9.0 Hz, *m*-position of OH), 7.22 (1H, dd, $J_{2,3}$ = 16.0 Hz, $J_{3,4}$ = 7.0 Hz, 3-H), 7.88 (1H, br s, phenol-OH).

**Demethylation of 6** Compound **6** (272 mg, 1 mmol) was treated in the same manner as described for the demethylation of **7**. The first fraction afforded the lactone **13** (98 mg, 34%) as colorless crystals, mp 179 °C (benzene). MS *m/z*: 266 ($M^+$). *Anal.* Calcd for $C_{14}H_{18}O_3S$: C, 63.13; H, 6.81. Found: C, 63.04; H, 6.87. $^1$H-NMR ($CDCl_3$) $\delta$: 1.15 (3H, t, $J$ = 7.0 Hz, $CH_2\underline{CH_3}$), 2.36 (3H, s, Me), 2.42 (2H, q, $J$ = 7.0 Hz, $CH_2\underline{CH_3}$), 2.74 (1H, dd, $J$ = 17.0, 8.0 Hz, 2-H), 3.15 (1H, dd, $J$ = 17.0, 6.0 Hz, 2-H), 3.30 (1H, dt, $J_{3,4}$ = 9.0 Hz, $J_{4,5}$ = 9.0, 5.0 Hz, 4-H), 3.34 (1H, m, 3-H), 4.25 (1H, dd, $J$ = 12.0, 9.0 Hz, 5-H), 4.40 (1H, dd, $J$ = 12.0, 5.0 Hz, 5-H), 4.90 (1H, br s, phenol-OH), 6.70 (1H, br d, $J$ = 9.0 Hz, *p*-position of Me), 6.71 (1H, br s, *o*-position of Me), 7.05 (1H, d, $J$ = 9.0 Hz, *m*-position of Me). The two substituents at the 3-position (EtS-) and 4-position (Ar-) should be in *trans*-configuration as judged from the coupling constant (9.0 Hz). The second fraction afforded **12** (141 mg, 55%) as a pale yellow oil. HRMS *Anal.* Calcd for $C_{13}H_{16}O_4$ ($M^+$, *m/z*): 236.1049. Found: 236.1062. IR ($CHCl_3$): 3380, 1700, 1650 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 2.18 (3H, s, Me), 2.63 (1H, s, OH), 3.68 (3H, s, COOMe), 3.82 (3H, m, 4- and 5-H), 5.79 (1H, d, $J$ = 16.0 Hz, 2-H), 6.59 (1H, dd, $J$ = 9.0, 2.0 Hz, *p*-position of Me), 6.62 (1H, d, $J$ = 2.0 Hz, *o*-position of Me), 6.89 (1H, d, $J$ = 9.0 Hz, *m*-position of Me), 7.04 (1H, dd, $J_{2,3}$ = 16.0 Hz, $J_{3,4}$ = 7.0 Hz, 3-H), 7.21 (1H, br s, phenol-OH).

**Cyclization of 8 to 10** A methanol (1 ml) solution of **8** (20 mg, 0.09 mmol) containing $Et_3N$ (1 drop) was kept for 1 h at room temperature and concentrated under reduced pressure. The residue was purified by column chromatography to give almost diastereomerically pure compound **10** (19 mg, 94%), but the stereochemistry could not be determined. Pale yellow oil. HRMS *Anal.* Calcd for $C_{13}H_{16}O_4$ ($M^+$, *m/z*): 236.1049. Found: 236.1047. IR ($CCl_4$): 3460, 2920, 1730 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 2.30 (3H, s, Me), 2.70, 2.85 (each 1H, dd, $J$ = 16.0, 7.0 Hz, $CH_2\underline{COOMe}$), 3.32 (1H, m, 3-H), 3.73 (3H, s, COOMe), 3.77, 3.85 (each 1H, dd, $J$ = 11.0, 5.5 Hz, $CH_2\underline{OH}$), 5.02 (1H, dt, $J$ = 5.0, 7.0 Hz, 2-H), 6.63 (1H, br s, 7-H), 6.70 (1H, br d, $J$ = 8.0 Hz, 5-H), 7.05 (1H, d, $J$ = 8.0 Hz, 4-H).

Compound **12** was treated in the same manner as described for **8**, but was completely recovered.

**Acetylation of 6 or 7** Compound **6** or **7** was acetylated in a usual manner using $Ac_2O$ in pyridine to give acetylated **6** or acetylated **7(11)** respectively.

Compound Ac-**6**: Pale yellow oil. HRMS *Anal.* Calcd for $C_{16}H_{20}O_5$ ($M^+$, *m/z*): 292.1311. Found: 292.1292. IR ($CCl_4$): 2940, 1730, 1650 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 2.04 (3H, s, acetyl-Me), 2.32 (3H, s, Me), 3.72 (3H, s, COOMe), 3.78 (3H, s, OMe), 4.01 (1H, q, $J$ = 7.0 Hz, 4-H), 4.29, 4.32 (each 1H, dd, $J$ = 11.0, 7.0 Hz, 5-H), 5.82 (1H, dd, $J_{2,3}$ = 16.0 Hz, $J_{2,4}$ = 1.5 Hz, 2-H), 6.73 (1H, br d, $J$ = 9.0 Hz, *p*-position of Me), 6.74 (1H, br s, *o*-position of Me), 7.03 (1H, d, $J$ = 9.0 Hz, *m*-position of Me), 7.08 (1H, dd, $J_{2,3}$ = 16.0 Hz, $J_{3,4}$ = 7.0 Hz, 3-H).

Compound **11**: Pale yellow oil. HRMS *Anal.* Calcd for $C_{16}H_{20}O_5$ ($M^+$, *m/z*): 292.1311. Found: 292.1309. IR ($CCl_4$): 2940, 1725, 1650 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 2.02 (3H, s, acetyl-Me), 2.33 (3H, s, Me), 3.71 (3H, s, COOMe), 3.80 (3H, s, OMe), 4.18 (1H, m, 4-H), 4.30 (1H, dd, $J$ = 11.0, 7.0 Hz, 5-H), 4.38 (1H, dd, $J$ = 11.0, 8.0 Hz, 5-H), 5.85 (1H, dd, $J_{2,3}$ = 16.0 Hz, $J_{2,4}$ = 1.5 Hz, 2-H), 6.69 (1H, br s, *o*-position of OMe), 6.73 (1H, br d, $J$ = 8.0 Hz, *p*-position of OMe), 6.99 (1H, d, $J$ = 8.0 Hz, *m*-position of OMe), 7.14 (1H, dd, $J_{2,3}$ = 16.0 Hz, $J_{3,4}$ = 7.0 Hz, 3-H).

**Reduction of 14 or 15 with DIBAL-H** A solution of **14** (50 mg, 0.2 mmol) in dry toluene (1 ml) was treated dropwise with 1.5 M DIBAL-H toluene solution (0.5 ml) at 0 °C and the whole was stirred at room temperature for a further 1 h. The reaction was quenched by adding ether and 2 N HCl. The whole was extracted with ether and the ethereal solution was washed with saturated brine and dried over $MgSO_4$. The filtrate was evaporated under reduced pressure to give crude **16**, which was purified by column chromatography to afford pure **16** (17 mg, 38%).

Reduction of **15** (50 mg, 0.2 mmol) was carried out as the same manner to give **16** (18 g, 39%).

**4-(2-Methoxy-5-methylphenyl)-(2*E*)-penten-1,5-diol (16)** Colorless oil. HRMS *Anal.* Calcd for $C_{13}H_{18}O_3$ ($M^+$, *m/z*): 222.1256. Found: 222.1244. IR ($CHCl_3$): 3380, 2920, 1490, 1460 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 2.17 (2H, br s, OH), 2.27 (3H, s, Me), 3.78 (5H, m, OMe and 5-H), 3.93 (1H, q, $J$ = 7.0 Hz, 4-H), 4.13 (2H, d, $J$ = 5.0 Hz, 1H), 5.79 (1H, dt, $J_{2,3}$ = 16.0 Hz, $J_{1,2}$ = 5.0 Hz, 2-H), 5.94 (1H, dd, $J_{2,3}$ = 16.0 Hz, $J_{3,4}$ = 7.0 Hz, 3-H), 6.77 (1H, d, $J$ = 8.0 Hz, *o*-position of OMe), 6.96 (1H, d, $J$ = 2.0 Hz, *o*-position of R[9]), 7.00 (1H, dd, $J$ = 8.0, 2.0 Hz, *p*-position of R[9]).

## References and Notes


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