The Synthesis of Dimethyl Esters of *dl*-O,O'-Dimethylfukiic Acid and *dl*-O,O'-Dimethylepifukiic Acid

Teruhiko YOSHIHARA, Akitami ICHIHARA and Sadao SAKAMURA

Department of Agricultural Chemistry, Faculty of Agriculture,
Hokkaido University, Sapporo, Japan

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The synthesis of dimethyl esters of *dl*-O,O'-dimethylfukiic acid (11) and *dl*-O,O'-dimethylepifukiic acid (12) are described.

Fukiic acid (1) is a component of fukinolic acid isolated from leaves, leaf stems and flower stalks of *Petasites japonicus* (japanese name, fuki). The chemical structure^{1,2)} and stereochemistry^{3,4)} were established by us. About the synthesis of dimethyl *dl*-O,O'-dimethylfukiiate (11) and dimethyl *dl*-O,O'-dimethylepifukiiate (12), we have already reported in a paper of short communication.⁵⁾ Meanwhile, Matsumoto *et al.* also reported the synthesis of dimethyl O,O'-dimethylfukiiate by an alternative route.^{6,7)} This report deals with details of the synthetic studies of fukiic acid derivatives.

Caffeic acid was adopted as our starting materials, and ethyl α -keto- β -carbethoxy- γ -(3,4-dimethoxyphenyl)butyrate (3) was prepared through four steps which were hydrogenation, methylation, esterification and condensation with diethyl oxalate according to the known procedure.⁸⁾ The ketoester 3 was reduced with five moles of NaBH₄ and the crystalline lactone 6 was obtained. The molecular formula, C₁₃H₁₈O₅, was assigned on the basis of mass spectrometry and elemental analysis. The infrared band at 1768 cm⁻¹ suggested the presence of γ -lactone. These results indicated that ketoester 3 was reduced to hydroxyester 4 and then to γ -lactone 6. To prevent excessive reduction, 0.3 mole of NaBH₄ was allowed to react with 3. The main distillate of reduction product, C₁₇H₂₄O₇, MS: *m/e* 340 (M⁺) had peaks of a hydroxy group (3500 cm⁻¹) and ester group (1730 cm⁻¹)

in IR and signals due to -CH₂-O- and $\begin{array}{c} \text{O} \\ | \\ -\text{CH} \end{array}$ (3.95~4.45) in PMR. These data unequivocally proved the structure of the hydroxyester 4.

The hydroxyester 4 could not be dehydrated by means of heating and with *p*-toluenesulfonic acid or mesyl chloride. Therefore dehydration was carried out with POCl₃⁹⁾ in pyridine at 104~106°C for 30 min. The reaction products were placed on the column of silica gel and eluted with 90% chloroform in cyclohexane. Three compounds, which were named as A-F₁, A-F₂ and A-F₃ in their order of elution, were obtained. The ratio of each products was 1:2:1. The IR spectra of A-F₂ revealed the absence of OH band at

near 3500 cm⁻¹ and $\begin{array}{c} \text{H} \\ | \\ >\text{C}=\text{C}< \end{array}$ at near 1650 cm⁻¹. Since the band ascribable to ester group appeared too higher wave number at 1744 cm⁻¹ as ordinary ester, the structure of A-F₂ was assigned as ethyl α -chloro- β -carbethoxy- γ -(3,4-dimethoxyphenyl) butyrate (5) together with other spectral data. As the patterns of MS peaks of A-F₁ and A-F₃ were similar mutually and M⁺ ion peaks were observed at *m/e* 322, it was elucidated that the both compounds were stereoisomers of dehydrated products. The structure of the stereoisomers was supported by the presence of the peaks at 1640 cm⁻¹ and 1650 cm⁻¹ assigned to $\begin{array}{c} \text{H} \\ | \\ >\text{C}=\text{C}< \end{array}$ in the IR spectrum.

FIG. 1.

The determination of the geometry of these isomers was carried out by means of IR and PMR spectra. Felton *et al.*¹⁰⁾ have reported that diethylfumarate was found to give an ester band at a position lower (1727 cm^{-1}) than that in diethylmaleate, viz., at 1734 cm^{-1} , (both in carbon tetrachloride solution). So it was decided that A-F₁ (1723 cm^{-1}) had CO_2Et/CO_2Et *trans*-geometry 7 and A-F₃ (1729 cm^{-1}) had *cis*-one 8. This result was also confirmed by PMR. Thus, A-F₁ showed olefinic proton at δ 6.87 in the PMR spectrum and A-F₃ did it at δ 5.59. The higher shift in A-F₃ is explained by the shielding effect by phenyl group.

In order to obtain the *trans*-isomer 7 in better yield, following conditions for dehydration were devised. Thus, the hydroxyester 4 was heated at more higher temperature and for longer reaction time, viz., at 129°C and for 60 min, and three compounds, B-F₁, B-F₂ and B-F₃, were obtained in a ratio of about 10:3:1. Because IR and UV spectra and behavior on TLC of B-F₁, were identical with A-F₁, B-F₁ was assigned as diethyl α -(3,4-dimethoxybenzyl) fumarate (7). As

B-F₂ and B-F₃ showed signals of $>C=C<$ at 1633 and 1635 cm^{-1} in the IR spectrum respectively, both products were regarded to be the dehydrated. The M^+ ion peak in B-F₂

and B-F₃ was observed at m/e 322, but the

peak assigned to (m/e 151)

was not present. These data indicate that a benzyl moiety in these compounds was no longer present and it was considered that double bond in 7 or 8 was rearranged. The rearrangement products must exist in the form of two geometrical isomers, diethyl 3,4-dimethoxyphenylitaconate (9) and diethyl 3,4-dimethoxyphenylaticonate (10). The

PMR signal assigned to $>C=C<$ was observed at δ 7.84 in B-F₂, while it was observed at δ 6.96 in B-F₃. Since the vinylic proton of 9 is deshielded by the ester carbonyl group, the chemical shift appears at lower ppm than that of 10. As a result the structures of B-F₂ and B-F₃ were demonstrated to be 9 and 10. An attempt to convert 9 and 10 to 7 or 8 failed in the use of *p*-toluenesulfonic acid or lithium diethylamide. Subsequently *trans*-ester 7 was prepared by heating the chloroester 5 with LiCl in moderate yield.

cis-Ester 8 was oxidized with OsO_4 , and then methylated with diazomethane. The resultant *cis*-oxidizing product 11 must be an *erythro* isomer. It had a melting point of $140.5\sim 141.0^\circ\text{C}$ and was formulated $C_{15}H_{20}O_8$. Comparison of synthetic products of *erythro*

isomer 11 with that of natural ester 2 established the identity in behaviors on TLC and the physical data. But slight differences were observed in IR measured as KBr tablets. It is reasonable more likely that this differences result from the nature of the crystal structure derived from *dl*-compound. However being recorded the IR spectrum in chloroform, the spectral pattern of 11 was completely identical with those of 2. On the other hand, *trans*-ester 7 was treated in a similar manner described above to obtain the *threo* compound 12. It had a melting point of 88.5~89.5°C and manifested the formula $C_{15}H_{20}O_8$, whose signals of MS were almost identical with those of natural ester 2. But the *Rf* value on TLC and IR and PMR data were not the same as those of 2. Therefore the oxidized product 12 was concluded to be dimethyl *dl*-O, O'-dimethylepifukiite.

We have already assigned the stereochemistry of fukiic acid as *S*-configuration at C-2 and *R*-configuration at C-3. The *erythro* configuration was further confirmed by this synthesis. And recently it was noted that dimethyl fukiite will serve as an important intermediate of synthesis of natural products, *e. g.* cephalotaxine.¹³⁾

EXPERIMENTAL

Infrared spectra were determined on a Hitachi EPI-S2 spectrometer. Ultraviolet spectra were measured using a Hitachi Perkin-Elmer 139 UV-VIS spectrophotometer. Proton magnetic resonance spectra were measured on a Hitachi H-60 spectrometer (60 MHz) and JEOL JNM-PS-100 spectrometer (100 MHz). Mass spectra were determined on a Hitachi RMS-4 spectrometer.

Ethyl α-hydroxy-β-carbethoxy-γ-(3,4-dimethoxyphenyl)-butyrate (4)

A mixture of 9.0 g (26.6 mmole) of 3 and 302 mg (8.0 mmole) of $NaBH_4$ in 200 ml of ethanol was stirred at room temperature for 15 min. Reaction mixture was evaporated to nearly dryness under reduced pressure. To a residue 200 ml of water was added and the aqueous solution was extracted with 200 ml each of ether for five times. The ether extract was washed with water and dried over Na_2SO_4 . After evaporation of the ether, the residue (8.1 g) was distilled under reduced pressure. Hydroxyester 4 was negative for $FeCl_3$ reagent. bp 197~8°C (0.75 mmHg). Yield 4.3 g (48%). Found: C, 59.82; H, 7.32. Calcd. for $C_{17}H_{24}O_7$: C, 60.00; H, 7.06%. IR ν_{max}^{film} cm^{-1} : 3500 (OH), 1730

(ester, $-\overset{\overset{O}{\parallel}}{C}-O-$), 1110 (secondary alcohol, $-\overset{\overset{H}{\mid}}{C}-OH$).

PMR $\delta_{Me_4Si}^{d_6\text{-acetone}}$ (60 MHz): 1.15 (3H, t, $J=7$ Hz, $-\text{CH}_3$), 1.24 (3H, t, $J=7$ Hz, $-\text{CH}_3$), 2.75 (1H, s, $-\text{OH}$), 2.85~3.20 (3H, m, $-\overset{\overset{O}{\mid}}{CH}$ and $-\text{CH}_2-$), 3.79 (6H, s, $2 \times \text{CH}_3O-$), 3.95~4.45 (5H, m, $-\overset{\overset{O}{\mid}}{CH}$ and $2 \times -\text{CH}_2-O-$), 6.84 (3H, s, Ar-H). MS m/e : 340 (M^+), 151 (base

FIG. 2. IR-Spectra of 2, 11 and 12. (KBr Tablet)

peak,).

Diethyl α-(3,4-dimethoxybenzyl)maleate (8) and diethyl α-(3,4-dimethoxybenzyl)fumarate (7)

a) To 60 ml of dry pyridine, which was heated at 106°C in silicon bath, 2.0 g of POCl₃ was added. Then 1.0 g (2.94 mmole) of hydroxyester 4 dissolved in 5 ml of pyridine was added and the reaction mixture was stirred at 104~106°C for 30 min. After cooling, the mixture was poured into 600 ml of ice water and extracted with 500 ml each of ether for four times. The ether layer was washed successively with 4 N HCl and water and dried over anhyd. Na₂SO₄. Evaporation of the solvent gave 1.1 g of syrup, which was chromatographed on silica gel. Elution with 90% chloroform in cyclohexane gave three compounds, 7, 5 and 8, in their order of elution.

Diethyl α-(3,4-dimethoxybenzyl)maleate (8). Yield 255 mg (27%). IR $\nu_{\text{max}}^{\text{CCl}_4}$ cm⁻¹: 1729 (α,β-unsaturated ester, , 1650 (trisubstituted double bond,). PMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$ (100 MHz): 1.16 (3H, t, *J*=7 Hz, -CH₃), 1.30 (3H, t, *J*=7 Hz, -CH₃), 3.58 (2H, d, *J*=2 Hz, -CH₂-), 3.84 (6H, s, 2×CH₃O-), 3.94~4.46 (4H, m, 2×-CH₂-), 5.59 (1H, t, *J*=2 Hz, -CH), 6.64~6.80 (3H, m, Ar-H). MS *m/e*: 322 (M⁺), 276 (base peak), 151. UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ε): 277 (sh) (5192), 282 (2043).

Diethyl α-(3,4-dimethoxybenzyl)fumarate (7). Yield 236 mg (24%). IR $\nu_{\text{max}}^{\text{CCl}_4}$: 1723 (α,β-unsaturated ester,). PMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$ (100 MHz): 1.18 (3H, t, *J*=7 Hz, -CH₃), 1.32 (3H, t, *J*=7 Hz, -CH₃), 3.84 (6H, s, 2×CH₃O-), 4.0~4.46 (6H, m, 3×-CH₂-), 6.67~6.84 (3H, m, Ar-H), 6.87 (1H, s, -CH). MS *m/e*: 322 (M⁺), 276 (base peak), 151. UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ε): 2225 (19611), 279 (3391).

Ethyl α-chloro-β-carbethoxy-γ-(3,4-dimethoxyphenyl)-butyrate (5). Yield 465 mg (44%). IR $\nu_{\text{max}}^{\text{CCl}_4}$ cm⁻¹: 1744 (α-chloroester, -CO-O-). PMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$ (100 MHz): 1.16 (3H, t, *J*=7 Hz, -CH₃), 1.25 (3H, t, *J*=7 Hz, -CH₃), 2.9~3.5 (3H, m, -CH and -CH₂-), 3.84 (6H, s, 2×CH₃O-), 3.94~4.46 (5H, m, Cl-CH and 2×-CH₂-), 6.67~6.84 (3H, m, Ar-H). MS *m/e*: 361 (M⁺+3, 11% of M⁺), 360 (M⁺+2, 44% of M⁺), 359 (M⁺+1, 25% of M⁺), 358 (M⁺), 313, 236, 191, 175, 151 (base peak). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ε): 232 (8162), 281 (3089).

b) Hydroxyester (4), 1.0 g, was dehydrated in a similar manner described above except the temperature

(129°C) and the reaction time (60 min). Three compounds, 7 (592 mg, yield 62%), 9 (180 mg, yield 19%) and 10 (66 mg, yield 7%), were obtained in their order of elution.

Diethyl 3,4-dimethoxyphenylitaconate (9). IR $\nu_{\text{max}}^{\text{film}}$ cm⁻¹: 1730, 1705 (ester, -CO-O-), 1633 (>C=C<), 1095 (ester, -C=C-COOEt), PMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$ (100 MHz): 1.25 (3H, t, *J*=7 Hz, -CH₃), 1.34 (3H, t, *J*=7 Hz, -CH₃), 3.57 (2H, s, -CH₂-), 3.85 (3H, s, -OCH₃), 3.89 (3H, s, -OCH₃), 4.15 (2H, q, *J*=7 Hz, -CH₂-O-), 4.24 (2H, q, *J*=7 Hz, -CH₂-O-), 6.90 (1H, s, Ar-H), 6.94 (2H, s, Ar-H), 7.84 (1H, s, HC-). MS *m/e*: 322 (M⁺, base peak). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ε): 217 (sh) (12867), 236 (13843), 294 (14198), 312 (15121).

Diethyl 3,4-dimethoxyphenylitaconate (10). IR $\nu_{\text{max}}^{\text{film}}$ cm⁻¹: 1735, 1705 (ester, -CO-O-), 1635 (>C=C<). PMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$ (100 MHz): 1.15 (3H, t, *J*=7 Hz, -CH₃), 1.25 (3H, t, *J*=7 Hz, -CH₃), 3.43 (2H, s, -CH₂-), 3.85 (3H, s, -OCH₃), 3.88 (3H, s, -OCH₃), 4.15 (4H, q, *J*=7 Hz, 2×-CH₂-O-), 6.77 (1H, d, *J*=2 Hz, Ar-H), 6.83 (1H, s, Ar-H), 6.89 (1H, d, *J*=2 Hz, Ar-H), 6.98 (1H, s, -CH). MS *m/e*: 322 (M⁺, base peak). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ε): 229 (15605), 292 (sh) (12075), 307 (12447).

Dehydrochlorination of ethyl α-chloro-β-carbethoxy-γ-(3,4-dimethoxyphenyl)butyrate (5)

A mixture of 1.0 g of chloroester (5) and 1.0 g of LiCl was heated at 132~137°C for 2 hr, in 20 ml of dimethylformamide. After cooling, 40 ml of water was added and the product was extracted with 50 ml of ether, and examined on TLC with 50% CHCl₃ in water (chloroform layer). The product (302 mg, yield 43.7%) was identical with diethyl α-(3,4-dimethoxybenzyl) fumarate (7).

Dimethyl dl-O,O'-dimethylfukuiate (11)

To a solution of 600 mg (1.86 mmoles) of diethyl α-(3,4-dimethoxybenzyl) maleate (8) in 5.0 ml of ether, was added a solution of 778 mg (3.07 mmoles) of OsO₄ in 30 ml of ether and then 3.0 ml of pyridine. The mixture was allowed to stand at room temperature for four days. The reaction mixture was filtered and filtrate was evaporated under reduced pressure. The obtained residue was dissolved in a solution of 25 ml of ethanol and 16 ml of water. To this mixture the above mentioned residue and then 4 g of Na₂SO₃ was added, and the mixture was refluxed at 85°C for 1 hr. After centrifuging, the supernatant was evaporated to about 15 ml *in vacuo*, and to which 15 ml of 2 N KOH was added. After allowing to stand at room temp. for 15 hr, the mixture was extracted twice with 100 ml of ether. The water layer was dried over Na₂SO₄, evaporated to dryness *in vacuo* and methylated with diazomethane in

ether. After evaporation of the ether, the residue was chromatographed on silica gel. Elution with 60% CHCl_3 in cyclohexane gave 64.8 mg (yield 9.8%) of 11 as crystalline material, mp $140.5 \sim 141^\circ\text{C}$. *Anal.* Found: C, 55.13; H, 6.27. Calcd. for $\text{C}_{15}\text{H}_{20}\text{O}_8$: C, 54.88; H, 6.10%. TLC on silica gel; *Rf* 0.46 (reference compound, natural dimethyl O,O'-dimethylfukiiate (2), 0.46) in ethylacetate-cyclohexane (9: 1). MS *m/e*:

328 (M^+), 151 (base peak,). PMR

$\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$ (100 MHz): 2.4~3.4 (2H, br, $2 \times -\text{OH}$), 3.00 (1H, d, $J=14$ Hz, $-\text{CH}_2-$), 3.28 (1H, d, $J=14$ Hz, $-\text{CH}_2-$), 3.72 (6H, s, $-\text{COOMe}$), 3.82 (6H, s, Ar-OMe), 4.52 (1H, s, $-\text{CH}$), 6.63 (1H, dd, $J=3$ and 10 Hz, Ar-H), 6.70 (1H, d, $J=3$ Hz, Ar-H), 6.75 (1H, d, $J=10$ Hz, Ar-H). IR data is shown in Fig. 2.

Dimethyl *dl*-O,O'-dimethylepifukiiate (12)

Using the same experimental conditions as in dimethyl *dl*-O,O'-dimethylfukiiate, *cis*-oxidation of 102 mg of diethyl α -(3,4-dimethoxybenzyl)fumarate (7) gave 39 mg (yield 34.5%) of 12 as crystalline material, mp $88.5 \sim 89.5^\circ\text{C}$. *Anal.* Found: C, 55.10; H, 6.22%. Calcd. for $\text{C}_{15}\text{H}_{20}\text{O}_8$: C, 54.88; H, 6.10%. TLC on silica gel; *Rf* 0.48 (reference compound, natural dimethyl O,O'-dimethylfukiiate (2), 0.46) in ethyl acetate-cyclohexane (9: 1) and 0.51 (0.48) in methanol-benzene (1: 3). MS *m/e*: 328 (M^+), 151 (base peak,

). PMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$ (100 MHz): 2.6~3.5

(2H, br, $-\text{OH}$), 3.05 (2H, s, $-\text{CH}_2-$), 3.72 (3H, s, $-\text{COOMe}$), 3.80 (3H, s, $-\text{COOMe}$), 3.81 (3H, s, $-\text{OMe}$),

3.83 (3H, s, Ar-OMe), 4.40 (1H, s, $-\text{CH}$), 6.57~6.80 (3H, br, $3 \times \text{Ar-H}$). IR data are shown in Fig. 2.

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