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The Synthesis and Configuration of Fukiic Acid Derivatives[1]

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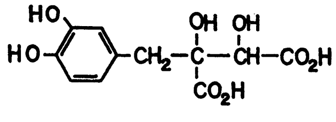
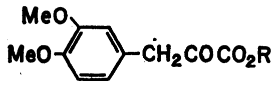
The methylation of 3,4-dimethoxyphenylpyruvic acid (II) gave the corresponding methyl ester (III), which was then subjected to a Wittig reaction with carbomethoxymethylenetriphenylphosphorane to give the corresponding fumaric (IVa) and maleic (IVb) acid derivatives in a 1: 3 ratio. The *cis*-hydroxylation of IVa and IVb with an aqueous solution of potassium permanganate and magnesium sulfate gave methyl (±)-*threo*-2,3-dihydroxy-4-(3,4-dimethoxyphenyl)-3-methoxycarbonylbutyrate (Va) and its (±)-*erythro*-isomer (Vb) respectively. The dimethyl esters, (±)-Va and (±)-Vb, were converted to the corresponding monomethyl esters, (±)-VIIa and (±)-VIIb respectively, *via* two dicarboxylic acid derivatives, (±)-VIa and (±)-VIb. The resolution of (±)-VIIb with brucine gave (+)-VIIb and (−)-VIIb, which were then converted to (+)-Vb and (+)-VIb and to (−)-Vb and (−)-VIb respectively. The synthetic (+)-Vb was shown to be identical with the natural *O,O′*-dimethylfukiic acid dimethyl ester by a mixed fusion and by comparisons of their IR and NMR spectra. From the present study it is evident that natural fukiic acid has an *erythro* configuration.

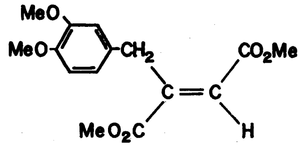
Recently a new polyphenol, fukinolic acid, was isolated from the leaves, leaf stems, and flower stalks of *Petasites japonicus* by Sakamura *et al.*[2] They have also been reported that the alkaline hydrolysis of fukinolic acid gave caffeic acid and a new acid, named fukiic acid, in a molar ratio of 1: 1. Although no physical properties of fukiic acid have been reported except the *Rf* value on paper chromatography, its structure was proposed to be 2,3-dihydroxy-4-(3,4-dihydroxyphenyl)-3-carboxybutyric acid (I) on the basis of the analytical and spectroscopic studies of its derivatives. Two racemic modifications (*threo* and *erythro*) are possible for I. However, since the stereochemistry of fukiic acid has not yet been reported, the present authors attempted a total synthesis of fukiic acid derivatives in order to confirm the proposed structure and to elucidate the stereochemistry of fukiic acid. The present paper will describe a stereospecific synthesis of fukiic acid derivatives and their stereochemistry. For their synthesis, 3, 4-dimethoxyphenylpyruvic acid (II) was chosen as the starting substance, and the acid (II) was methylated with one equivalent of diazomethane to give the corresponding methyl ester (III). The Wittig reaction[3] of III with carbomethoxymethylenetriphenylphosphorane afforded a 96% yield of a mixture of geometric isomers, which were then successfully separated, by means of column chromatography on silica gel, into two crystalline esters in a 1: 3 ratio. It is well known that the ylids stabilized by an adjacent carbonyl function yield, as the predominant product, the isomer in which the carbonyl function is *trans* to the larger group at the beta carbon atom. In the NMR spectra it is also known that the signal of a *cis*-vinyl proton to the methoxycarbonyl group is to be found at a field lower than that of the corresponding *trans*-vinyl proton. The chemical shifts of the olefinic protons in the above minor (mp 49—50°C) and major (mp 56.5—57°C) esters were observed at δ *ca.* 6.8 ppm and at δ 5.67 ppm respectively. Therefore, the structures of the minor and major esters were identified as the 1-(3,4-dimethoxybenzyl)fumaric acid dimethyl ester (IVa) and the 1-(3, 4-dimethoxybenzyl)maleic acid dimethyl ester (IVb) respectively. These assignments were further supported by the chemical shifts of the methylene protons in IVa and IVb. That is, IVa showed the signal of the methylene protons at δ 4.12 ppm, suggesting the presence of a *cis*-methoxycarbonyl group relative to the methylene protons, because IVb showed the corresponding signal at δ 3.61 ppm. The hydroxylation of IVa and IVb in methanol with an aqueous solution of potassium permanganate and magnesium sulfate at −20°C gave the corresponding diols, (±)-Va (mp 93—94°C) and (±)-Vb (mp 142°C) respectively. Since it is well



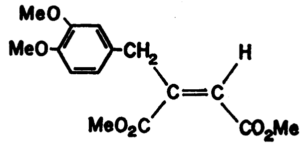
I



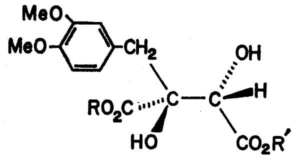
II R=H
III R=Me

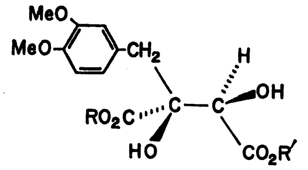


IVa



IVb





Va	R=R′=Me	Vb
VIa	R=R′=H	VIb
VIIa	R=H, R′=Me	VIIb

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[1] A preliminary communication concerning this work appeared in *Chem. Lett.*, **1972**, 1.

[2] S. Sakamura, T. Yoshihara, and K. Toyoda, *Agr. Biol. Chem.* (Tokyo), **33**, 1795 (1969).

[3] A. Maercker, "Organic Reactions," Vol. 14, Wiley, New York (1965), p. 270.

known that an aqueous solution of potassium permanganate reacts with olefins to add two hydroxyl functions to the double bond in a *cis* manner, the structures of the above diols were identified as methyl $(\pm)$-*threo*-2,3-dihydroxy-4-(3,4-dimethoxyphenyl)-3-methoxycarbonylbutyrate for Va and its $(\pm)$-*erythro*-isomer for Vb. The dimethyl esters, $(\pm)$-Va and $(\pm)$-Vb, were then hydrolyzed with aqueous potassium hydroxide to the corresponding dicarboxylic acid derivatives, $(\pm)$-VIa and $(\pm)$-VIb, which were subsequently methylated back into $(\pm)$-Va and $(\pm)$-Vb with diazomethane. This proved that there was no configurational change during the hydrolyses of $(\pm)$-Va and $(\pm)$-Vb. The NMR spectra of $(\pm)$-Vb in $CDCl_3$ and of $(\pm)$-VIb in $(CD_3)_2CO$ showed signals due to the methylene protons at δ 3.05 and 3.27 ppm, and at δ 3.06 and 3.26 ppm, respectively as well-defined AB-type quartets, while the spectra of $(\pm)$-Va in $CDCl_3$ and $(\pm)$-VIa in $(CD_3)_2CO$ showed the corresponding signals at δ 3.07 ppm as a singlet, and at δ 3.16 ppm as a slightly separated doublet, respectively. In the NMR spectrum of the natural fukiic acid monomethyl ester in $(CD_3)_2CO$, Sakamura *et al.*[2] had reported that the signal of the methylene protons was observed at δ 2.94 and 3.14 ppm as an AB-type quartet. From the similarity of these NMR spectra in the synthetic and natural compounds, it seemed that fukiic acid had an *erythro* configuration.

To obtain further confirmation by a direct comparison of the optically-active synthetic compound with the corresponding natural sample, the resolution of the synthetic racemate was carried out as follows. Since an attempt at the resolution of $(\pm)$-VIb was not encouraging, it was converted to the corresponding monomethyl ester, $(\pm)$-VIIb (mp 185—186°C), by treatment with methanol containing a small amount of concentrated hydrochloric acid. The $(\pm)$-VIIb acid in methanol was successfully resolved by means of brucine, and one of the diastereomeric salts (mp 185—186°C dec.) was decomposed with dilute hydrochloric acid to give $(+)$-VIIb, mp 138—139°C, $[\alpha]_D+40.8°$ (methanol). The mother liquor, after the separation of the above brucine salt, was also treated with dilute hydrochloric acid to give $(-)$-VIIb, mp 138—139°C, $[\alpha]_D-38.0°$ (methanol). The alkaline hydrolyses of $(+)$-VIIb and $(-)$-VIIb gave $(+)$-VIb, mp 104—106°C, $[\alpha]_D+40.3°$ (methanol) and $(-)$-VIb, mp 104—106°C, $[\alpha]_D-40.5°$ (methanol), respectively. The methylation of $(+)$-VIb or $(+)$-VIIb with diazomethane gave $(+)$-Vb, mp 116—117°C, $[\alpha]_D+40.5°$ (methanol), which was shown to be identical with the natural *O,O'*-dimethylfukiic acid dimethyl ester by a mixed-melting-point determination and by comparisons of their IR and NMR spectra. The acids, $(-)$-VIb, and $(-)$-VIIb, were also methylated with diazomethane to $(-)$-Vb, mp 116—117°C, $[\alpha]_D-39.7°$ (methanol). $(\pm)$-VIa was also converted to the corresponding monomethyl ester, $(\pm)$-VIIa, mp 159—160°C.

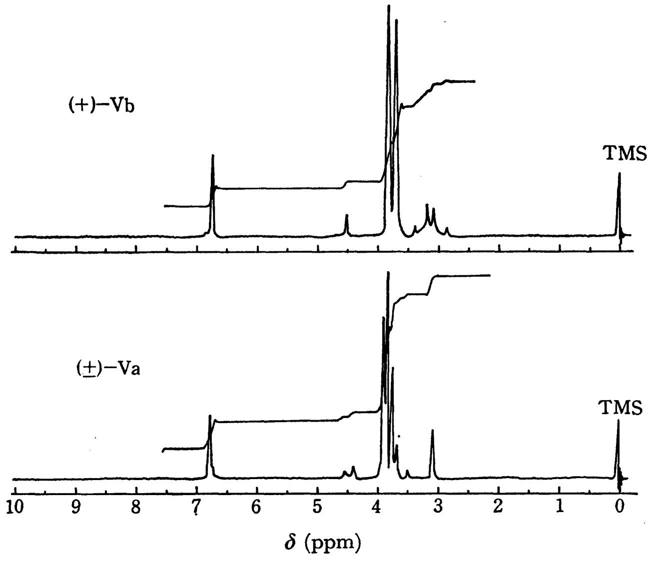

Fig. 1. NMR spectra of synthetic $(+)$-Vb and $(\pm)$-Va in $CDCl_3$.

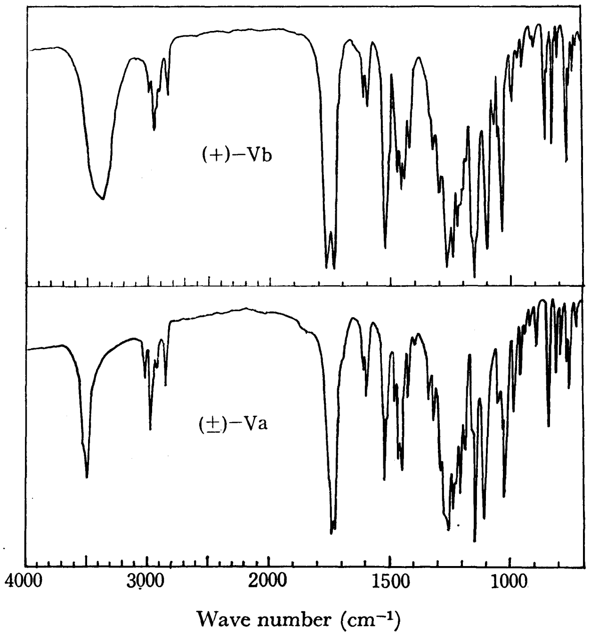

Fig. 2. IR spectra of synthetic $(+)$-Vb and $(\pm)$-Va in KBr.

From the present study, it is evident that natural fukiic acid has an *erythro* confiugration.[4]

Experimental

All the melting points are uncorrected. The NMR spectra were taken on a Hitachi Model R-20 NMR spectrometer (60 MHz), using tetramethylsilane as the internal standard. Their chemical shifts are presented in terms of δ values; s: singlet; d: doublet; dd: double doublet; t: triplet; m: multiplet. The optical rotation measurements were carried out by the use of a Yanagimoto OR-50 direct-reading polarimeter. The length of the cell used was 1 cm. The column chromatography was performed on Merck silica gel (0.08 mm).

Methyl 3,4-Dimethoxyphenylpyruvate (III). An ether solution (34 m*l*) containing diazomethane (0.56 g: 0.0134 mol) was stirred into a suspension of 3,4-dimethoxyphenylpyruvic

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[4] In a recent private communication from Professor S. Sakamura, he stated that his group also reached the same conclusion on the basis of a different synthesis of the (±)-*O,O'*-dimethylfukiic acid dimethyl ester, and that they also have identified the absolute configuration of fukiic acid; the details of their work were submitted to *Tetrahedron Lett.* and *Agr. Biol. Chem.* (Tokyo).

acid (II) (3.00 g: 0.0134 mol) in acetone (20 m*l*) with cooling in an ice–water bath. After the addition was complete, the mixture was filtered to remove a small amount of the starting acid (II), and then the filtrate was immediately evaporated under a vacuum. The residue was recrystallized from aqueous methanol to give pale yellow crystals (III); mp 99—102°C; yield, 2.10 g. NMR in $CDCl_3$: 3.89 (9H, s, 2-OC$\underline{H}_3$ and -CO$_2$C$\underline{H}_3$), 6.42 (2H, dd, J=1.5 and 8 Hz, -C$\underline{H}_2$-), 6.85 (1H, d, J=8 Hz), 7.28 (1H, dd, J=1.5 and 8 Hz), 7.49 (1H, d, J=1.5 Hz).

Found: C, 60.77; H, 5.93%. Calcd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92%.

1-(3,4-Dimethoxybenzyl)fumaric Acid Dimethyl Ester (IVa) and 1-(3,4-Dimethoxybenzyl)maleic Acid Dimethyl Ester (IVb). A mixture of the ester (III: 10.0 g), carbomethoxymethylenetriphenylphosphorane (14.6 g), and dry benzene (200 m*l*) was refluxed for 2 hr under a stream of nitrogen and then evaporated under a vacuum. The residue was extracted with ether, and the extract, after the removal of the ether, was chromatographed on silica gel, using benzene containing 7% and then 50% ether as the eluents. The first fraction gave IVa (2.943 g), which was recrystallized from ether containing petroleum ether to give pale yellow crystals; mp 49—50°C. NMR in $CDCl_3$: 3.74 and 3.79 (each 3H and s, 2-CO$_2$C$\underline{H}_3$), 3.82 (6H, s, 2-OC$\underline{H}_3$), 4.12 (2H, s, -C$\underline{H}_2$-), 6.78—6.95 (4H, m, aromatic (3H) and olefinic (1H) protons).

Found: C, 61.46; H, 6.35%. Calcd for $C_{15}H_{18}O_6$: C, 61.21; H, 6.17%.

The second fraction gave IVb (8.876 g) which was also recrystallized from ether containing petroleum ether to give colorless crystals; mp 56.5—57°C. A mixed-melting-point determination with the above IVa (mp 49—50°C) gave 34.5—36°C. NMR in $CDCl_3$: 3.61 (2H, d, J=1.5 Hz, -C$\underline{H}_2$-), 3.70 and 3.78 (each 3H and s, 2-CO$_2$C$\underline{H}_3$), 3.85 (6H, s, 2-OC$\underline{H}_3$), 5.67 (1H, t, J=1.5 Hz, =C$\underline{H}$CO$_2$CH$_3$), 6.68—6.83 (3H, m, aromatic protons).

Found: C, 61.16; H, 6.15%. Calcd for $C_{15}H_{18}O_6$: C, 61.21; H, 6.17%.

*Methyl (±)-*threo*- (Va) and Methyl (±)-*erythro*-2,3-Dihydroxy-4-(3,4-dimethoxyphenyl)-3-methoxycarbonylbutyrate (Vb).* *a)*: A solution of potassium permanganate (6.12 g) and magnesium sulfate heptahydrate (9.55 g) in water (270 m*l*) was stirred, drop by drop, into a solution of IVb (8.80 g) in methanol (255 m*l*) for 110 min at −20±2°C. The mixture was further stirred for 3 hr at this temperature, and then aqueous sodium bisulfite was added. The mixture was evaporated under a vacuum to remove the methanol, saturated with sodium chloride, and extracted with ethyl acetate, which was then washed with a saturated sodium chloride solution. After drying over sodium sulfate and removing the solvent, the residual solid was recrystallized from acetone to give methyl (±)-*erythro*-2,3-dihydroxy-4-(3,4-dimethoxyphenyl)-3-methoxycarbonylbutyrate (Vb) as colorless crystals; mp 142°C; yield, 4.17 g. NMR in $CDCl_3$: 3.28 (1H, s, -O$\underline{H}$), 3.28 (1H, d, J=8.5 Hz, -CH(O$\underline{H}$)-), 3.05 and 3.27 (2H, each d and J=14 Hz, -C$\underline{H}_2$-), 3.74 and 3.82 (each 6H and s, 2-CO$_2$C$\underline{H}_3$ and 2-OC$\underline{H}_3$), 4.54 (1H, d, J=8.5 Hz, -C$\underline{H}$(OH)-), 6.72 (3H, s, aromatic protons).

Found: C, 54.84; H, 6.10%. Calcd for $C_{15}H_{20}O_8$: C, 54.87; H, 6.14%.

b): A solution of IVa (1.09 g) in methanol was also hydroxylated with an aqueous potassium permanganate solution by a method similar to that used for (±)-Vb. The crude product was recrystallized from ether containing petroleum ether to give methyl (±)-*threo*-2,3-dihydroxy-4-(3,4-dimethoxyphenyl)-3-methoxycarbonylbutyrate (Va) as colorless crystals; mp 93—94°C; yield, 708 mg. NMR in $CDCl_3$: 3.07 (2H, s, -C$\underline{H}_2$-), 3.58 (1H, d, J=9 Hz, -CH(O$\underline{H}$)-), 3.71 (3H), 3.81 (6H), and 3.84 (3H) (each s, 2-CO$_2$C$\underline{H}_3$ and 2-OC$\underline{H}_3$), 4.43 (1H, d, J=9 Hz, -C$\underline{H}$(OH)-), 6.75 (3H, s, aromatic protons).

Found: C, 55.10; H, 6.16%. Calcd for $C_{15}H_{20}O_8$: C, 54.87; H, 6.14%.

*(±)-*threo*- (VIa) and (±)-*erythro*-2,3-Dihydroxy-4-(3,4-dimethoxyphenyl)-3-carboxybutyric Acid (VIb).* *a)*: A mixture of (±)-Vb (1.10 g) and aqueous potassium hydroxide (5%: 15 m*l*) was stirred on a steam bath for 40 min. After cooling, the mixture was acidified with dilute hydrochloric acid, saturated with sodium chloride, and then extracted with ethyl acetate. The extract, after having been washed with a saturated sodium chloride solution, was dried over sodium sulfate and then evaporated under a vacuum. The residue was recrystallized from acetone containing petroleum ether to give (±)-*erythro*-2,3-dihydroxy-4-(3,4-dimethoxyphenyl)-3-carboxybutyric acid (VIb) as colorless crystals; mp 179—180.5°C; yield, 830 mg. NMR in $(CD_3)_2CO$: 3.06 and 3.26 (2H, each d and J=13 Hz, -C$\underline{H}_2$-), 3.73 (6H, s, 2-OC$\underline{H}_3$), 4.57 (1H, s, -C$\underline{H}$(OH)-), 6.78 and 6.83 (3H, aromatic protons).

Found: C, 52.30; H, 5.54%. Calcd for $C_{13}H_{16}O_8$: C, 52.00; H, 5.37%.

The above (±)-VIb in acetone was methylated with diazomethane to give, after crystallization, colorless crystals (mp 142°C), which were shown to be identical with (±)-Vb by a mixed-melting-point determination and by a comparison of their IR spectra.

b): The dimethyl ester, (±)-Va, was also hydrolyzed with aqueous potassium hydroxide by a method similar to that used for (±)-VIb. The crude product was recrystallized from acetone to give (±)-*threo*-2,3-dihydroxy-4-(3,4-dimethoxyphenyl)-3-carboxybutyric acid (VIa) as colorless crystals; mp 112—115°C.

Found: C, 49.22; H, 5.81%. Calcd for $C_{13}H_{16}O_8 \cdot H_2O$: C, 49.06; H, 5.70%.

The above crystals were dissolved in acetone containing benzene, and the solution was then evaporated to dryness under a vacuum. The residue was recrystallized from acetone containing petroleum ether to give colorless crystals; mp 188—190°C. NMR in $(CD_3)_2CO$: 3.16 (2H, slightly separated d, -C$\underline{H}_2$-), 3.75 (6H, s, 2-OC$\underline{H}_3$), 4.43 (1H, s, -C$\underline{H}$(OH)-), 6.81 and 6.87 (3H, aromatic protons).

Found: C, 51.70; H, 5.37%. Calcd for $C_{13}H_{16}O_8$: C, 52.00; H, 5.37%.

The methylation of (±)-VIa with diazomethane gave (±)-Va.

*Methyl (±)-*threo*- (VIIa) and Methyl (±)-*erythro*-2,3-Dihydroxy-4-(3,4-dimethoxyphenyl)-3-carboxybutyrate (VIIb).* *a)*: A solution of (±)-VIb (200 mg) in methanol (3.0 m*l*) containing one drop of concentrated hydrochloric acid was allowed to stand at room temperature for 2 hr and then evaporated under a vacuum. The residue was recrystallized from a mixture of acetone and petroleum ether to give the corresponding monomethyl ester, (±)-VIIb (mp 185—186°C) as colorless crystals; yield, 110 mg. NMR in pyridine-d_5: 3.60 (9H, s, -CO$_2$C$\underline{H}_3$ and 2-OC$\underline{H}_3$), 3.62 and 3.83 (2H, each d, and J=14 Hz, -C$\underline{H}_2$-), 5.26 (1H, s, -C$\underline{H}$(OH)-).

Found: C, 53.52; H, 5.80%. Calcd for $C_{14}H_{18}O_8$: C, 53.50; H, 5.77%.

b): A mixture of (±)-VIa (1.20 g), concentrated hydrochloric acid (1.2 m*l*), and methanol (20 m*l*) was allowed to stand overnight at room temperature and was then evaporated under a vacuum. The residue was purified by means of column chromatography. A column was prepared from a suspension of silica gel (100 g) in a mixture of benzene (400 m*l*) and acetone (140 m*l*) containing dilute sulfuric acid (20%: 6.0 m*l*). Elution was carried out with benzene containing 30% acetone to give a solid (1.02 g), which was then recrystallized from a mixture of acetone and petroleum ether to give the monomethyl ester, (±)-VIIa, as colorless crystals; mp 159—160°C; yield, 863 mg. NMR in $(CD_3)_2CO$: 3.04 (2H, s, $-C\underline{H}_2-$), 3.71 (6H) and 3.76 (3H) (each s, $-CO_2C\underline{H}_3$ and $2-OC\underline{H}_3$), 4.40 (1H, s, $-C\underline{H}(OH)-$), 6.78 and 6.88 (3H, aromatic protons).

Found: C, 53.63; H, 5.73%. Calcd for $C_{14}H_{18}O_8$: C, 53.50; H, 5.77%.

Resolution of (±)-VIIb with Brucine. *a)*: Brucine dihydrate (595 mg) was dissolved in a hot solution of (±)-VIIb (433 mg) in methanol (8.0 m*l*), after which the solution was allowed to stand at room temperature. The precipitates were collected, washed with acetone, and then recrystallized from methanol to give colorless crystals; mp 185—186°C dec.; yield, 490 mg. A mixed-melting-point determination with (±)-VIIb (mp 185—186°C) showed 175—178°C.

Found: C, 61.15; H, 6.13; N, 3.81%. Calcd for $C_{37}H_{44}O_{12}N_2 \cdot H_2O$: C, 61.00; H, 6.38; N, 3.86%.

A suspension of the above brucine salt (255 mg) in dilute hydrochloric acid (2N: 5.0 m*l*) was extracted with ethyl acetate. The extract was washed with water, dried over sodium sulfate, and then evaporated under a vacuum. The residue (132 mg) was recrystallized from a mixture of acetone and petroleum ether to give (+)-VIIb as colorless crystals; mp 138—139°C, $[\alpha]_D^{28}+40.8°$ (*c* 1.25, methanol); yield, 114 mg.

Found: C, 50.82; H, 6.20%. Calcd for $C_{14}H_{18}O_8 \cdot H_2O$: C, 50.60; H, 6.07%.

b): The mother liquor in *a)*, after the separation of the brucine salt (490 mg: mp 185—186°C dec.), was evaporated under a vacuum. The residue was suspended in dilute hydrochloric acid (2N: 5.0 m*l*) and then treated by a method similar to that used for (+)-VIIb. The crude product was recrystallized from a mixture of acetone and petroleum ether to give (−)-VIIb as colorless crystals; mp 138—139°C, $[\alpha]_D^{28}-38.0°$ (*c* 0.72, methanol); yield, 104 mg.

Found: C, 50.68; H, 5.98%. Calcd for $C_{14}H_{18}O_8 \cdot H_2O$: C, 50.60; H, 6.07%.

Hydrolyses of (+)-VIIb and (−)-VIIb. *a)*: (+)-VIIb (245 mg) was hydrolyzed with aqueous potassium hydroxide (5%: 3.0 m*l*) by a method similar to that used for (±)-VIb. The crude product was recrystallized from a mixture of acetone and petroleum ether to give (+)-VIb as colorless crystals; mp 104—106°C, $[\alpha]_D^{28}+40.3°$ (*c* 0.72, methanol); yield, 124 mg.

Found: C, 49.18; H, 5.75%. Calcd for $C_{13}H_{16}O_8 \cdot H_2O$: C, 49.06; H, 5.70%.

b): Similarly, (−)-VIIb was also hydrolyzed to (−)-VIb; mp 104—106°C, $[\alpha]_D^{25}-40.5°$ (*c* 0.79, methanol).

Found: C, 49.27; H, 5.81%. Calcd for $C_{13}H_{16}O_8 \cdot H_2O$: C, 49.06; H, 5.70%.

*(+)- and (−)-*O,O′*-Dimethylfukiic Acid Dimethyl Ester (Vb).* *a)*: The treatment of (+)-VIb or (+)-VIIb with diazomethane gave (+)-Vb as colorless crystals; mp 116—117°C, $[\alpha]_D^{26}+40.5°$ (*c* 0.78, methanol).

Found: C, 54.89; H, 6.11%. Calcd for $C_{15}H_{20}O_8$: C, 54.87; H, 6.14%.

The synthetic (+)-Vb was shown to be identical with the natural *O,O′*-dimethylfukiic acid dimethyl ester (mp 117—118°C) by a mixed-melting-point determination and by comparisons of their IR and NMR spectra.

b): Similarly, (−)-VIb or (−)-VIIb was also methylated with diazomethane to (−)-Vb; mp 116—117°C, $[\alpha]_D^{26}-39.7°$ (*c* 0.78, methanol).

Found: C, 55.04; H, 6.08%. Calcd for $C_{15}H_{20}O_8$: C, 54.87; H, 6.14%.

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