Preparation of a (±)-1,6-Di-*O*-feruloyl-*myo*-inositol Derivative: An Efficient Method for Introduction of Ferulic Acid to 1,6-Vicinal Hydroxyl Groups of *myo*-Inositol

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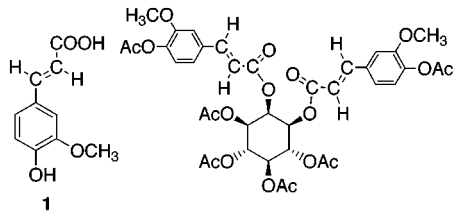
Ferulic acid (**1**) can be synthesized by the reaction of vanillin with malonic acid in the presence of an amine.[1] However, this reaction requires a long reaction time for completion and, hence, is impractical as a method for a large scale preparation of **1**.[1] On the other hand, **1** is known to occur in large amounts in various renewable resources such as rice, wheat, and corn. Recently, we have developed an efficient and practical method for the mass production of **1** from the oily component of rice bran.[2] Since then, the synthetic applications of **1** and related compounds have attracted considerable attention, especially in the field of chemoprevention study. For example, the ferulic acid derivative, ethyl 3-(4′-geranyloxy-3′-methoxyphenyl)-2-propenoate,[2b] in which the geranyl group is attached to the phenolic hydroxyl group of ethyl ferulate, was shown to have a suppressive effect on the formation of a colonic tumor marker in rats.[3] *O*-Tocopheryl succinyl *O*-ethyl ferulate was found to reduce the replication rate of the HIV-1 virus in infected cells in vitro by 80%.[4]

myo-Inositol is also obtained from rice bran, and it plays an important role in biological systems. D-*myo*-Inositol-1,4,5-trisphosphate was found to act as an intracellular second messenger for calcium mobilization.[5,6] *myo*-Inositol hexaphosphate (IP_6) was shown to have an anticancer action in a variety of experimental tumor models.[7]

Ferulic acid occurs usually as various ester or amide derivatives in natural products,[8] but the ester compounds containing ferulic acid and *myo*-inositol as components have not yet been discovered in nature.



In a previous paper, we reported the synthesis of seven ester compounds consisting of ferulic acid and *myo*-inositol and their inhibitory effect on 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced superoxide (O_2^-) generation by the use of differentiated HL-60 cells.[9] In this study, we found that only 3,4,5,6-tetra-*O*-acetyl-1,2-di-*O*-[3-(4′-acetoxy-3′-methoxyphenyl)-2-propenoyl]-*myo*-inositol (**2**) showed a distinct inhibitory activity. This result suggests that the architecture having two feruloyl groups at the vicinal positions of *myo*-inositol is essential for the inhibitory activity.

In the present paper, we report an efficient method for the introduction of ferulic acid to the 1,6-vicinal hydroxyl groups of (±)-3,4-*O*-(1,1,3,3-tetraisopropyldisiloxanedi-1,3-yl)-*myo*-inositol (TIPDS-*myo*-inositol, **4**) and the effect of intermolecular hydrogen bonding of **4** on the esterification reaction.

The introduction of functional groups to the 1,6-vicinal hydroxyl groups of *myo*-inositol has been performed through 2,3:4,5-di-*O*-cyclohexlidene-*myo*-inositol as an intermediate.[10] However, the synthesis of this diketal intermediate was difficult and troublesome: the reaction of *myo*-inositol with cyclohexanone gave 1,2-*O*-cyclohexylidene-*myo*-inositol and three diketals (1,2:3,4-, 1,2:4,5-, and 2,3:4,5-di-*O*-cyclohexylidene-*myo*-inositol).[11] The reaction of *myo*-inositol with 1-ethoxycyclohexene in DMF also gave the three diketals.[12] In these reactions, the yield of the 2,3:4,5-diketal was low, and the isolation of this ester from the reaction mixture was tedious.

In contrast, the disiloxanyl derivative **3** can readily be obtained from *myo*-inositol by consecutive regioselective cyclohexylidenation and silylation reactions.[13,14] The reaction of **3** with 1 equiv of ethylene glycol in the presence of a catalytic amount of *p*-toluenesulfonic acid in $CHCl_3$ at room temperature gave **4** as a white powder in an 86% yield (Scheme 1). We then examined the introduction of ferulic acid to the 1,6-vicinal hydroxyl groups of **4**.

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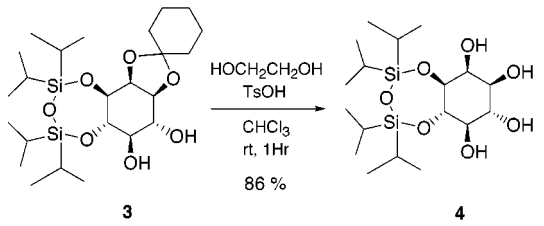
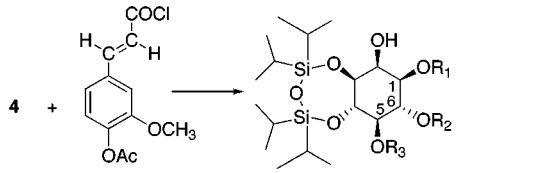
Scheme 1



Scheme 2[a]



	R1	R2	R3	
6a	Ac-Feru	H	H	trace
6b	H	Ac-Feru	H	ND
6c	Ac-Feru	Ac-Feru	H	trace
6d	Ac-Feru	Ac-Feru	Ac-Feru	trace

[a] Reagents and conditions: Et_3N, DMAP, and CH_2Cl_2, room temperature, 12 h.

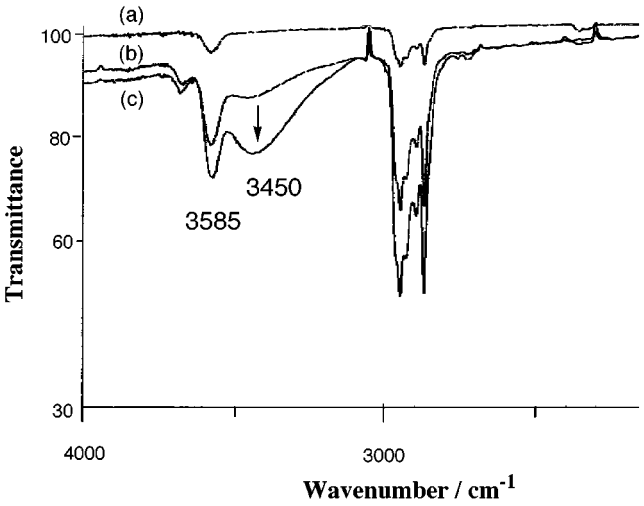


Figure 1. IR absorption spectra of **4** in CH_2Cl_2: (a) 2.5 mM, (b) 10 mM, and (c) 50 mM.

Ferulic acid was converted into 3-(4′-acetoxy-3′-methoxyphenyl)-2-propenoyl chloride (**5**) via two steps. The reaction of **4** with **5** was carried out in the presence of a mixture of triethylamine and 4-(dimethylamino)pyridine (DMAP) in CH_2Cl_2 (Scheme 2). However, the yield of the desired ester was very low.

The acid chloride **5** usually has sufficient reactivity in the ester formation with an alcohol.[9] Therefore, we studied the reason for the poor reactivity of **4** in this reaction. The solubility experiment revealed the unexpected fact that **4** was soluble in hydrophobic solvents. This fact implies that intramolecular and/or intermolecular hydrogen bonding exists in **4** in hydrophobic solvents such as CH_2Cl_2.

The FT-IR spectra of **4** in a 50 mM CH_2Cl_2 solution showed three peaks at 3688, 3585, and 3450 cm^{-1} in the OH-stretching region (Figure 1). The absorption peaks at 3688 and 3585 cm^{-1} can be assigned to the free OH group and the intramolecularly hydrogen-bonded OH group, respectively.[15−17] The absorption band centered at 3450 cm^{-1} can be assigned to the intermolecularly hydrogen-bonded OH group, because the absorbance of the band increased with increases in the concentration of **4**.

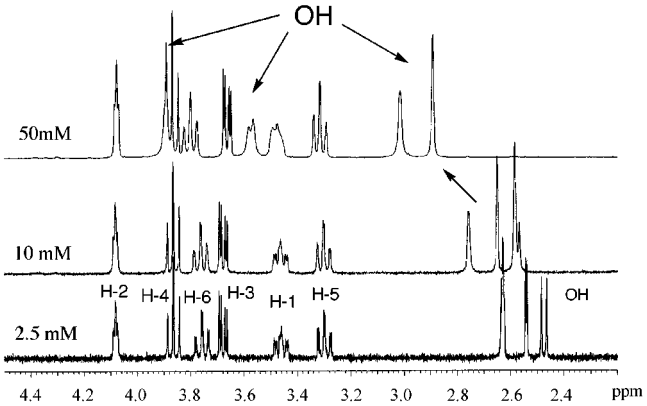


Figure 2. ^1H NMR spectra (400 MHz) of **4** in CD_2Cl_2 at various concentrations.

The formation of intermolecular hydrogen bonding was also confirmed by measuring the ^1H NMR spectrum of **4** in CD_2Cl_2 at various concentrations (Figure 2). The OH proton signals appeared at 2.4−2.7 ppm in the 2.5 mM solution, and these signals shifted downfield with increases in the concentration of **4**. These results strongly suggest that the OH groups of **4** form intermolecular hydrogen bonds in the real reaction mixture, and this intermolecular hydrogen bonding results in the poor reactivity in the esterification reaction of **4** with **5** in CH_2Cl_2 solution.

In general, intermolecular hydrogen bonding can be dissociated by raising the temperature or by the addition of a cosolvent such as DMF, THF, or pyridine; in fact, it is well-known that the esterification of an acid chloride by an alcohol proceeds efficiently in pyridine.[18]

We also found that the reaction of **4** with **5** in pyridine proceeded smoothly, and the ester compounds **6a**−**d** were obtained in moderate yields. When the reaction was carried out in pyridine in the presence of DMAP at 70 °C using **4** and **5** in a molar ratio of 1:5, **6c** was selectively obtained in an 81% yield. This regioselectivity is also compatible with the facts that (1) the hydroxyl group at the 2-position of **4** has a poor reactivity due to a hindered axial bond[19] and (2) the hydroxyl group at the 5-position of **4** is protected by bulky silyl substituents.[14,20]

Experimental Section

General Methods. The ^1H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Varian unity-plus 400 spectrometer. FT-IR spectra were recorded on a Shimazu FTIR 8200D instrument. The solutions were measured between NaCl windows. Solid samples were measured as KBr pellets using a JASCO IR-810 instrument. Melting points were measured in capillary tubes with a Yanagimoto micro melting point apparatus and are uncorrected. Elemental analyses were performed on a Perkin-Elmer 2400II instrument. Compound purity

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was checked by TLC on Silica Gel 60 F254 (E. Merck) with detection by charring with phosphomolybdic acid (10% in EtOH solution). Column chromatography was performed on Silica Gel, Wakogel C-200 (Wako Pure Chemical Industry).

Materials. Ferulic acid and *myo*-inositol were provided by Tsuno Food Industrial Co., Ltd. Ferulic acid was recrystallized from ethanol. *myo*-Inositol was dried under reduced pressure in a drying oven. (±)-1,2-*O*-Cyclohexylidene-3,4-*O*-(1,1,3,3-tetraisopropyldisiloxanedi-1,3-yl)-*myo*-inositol (**3**) was prepared according to literature.[13,14] Other chemicals were commercial products and were used without further purification. Solvents were reagent grade and, in most cases, dried prior to use.

(±)-3,4-*O*-(1,1,3,3-Tetraisopropyldisiloxanedi-1,3-yl)-*myo*-inositol (4). A mixture of a catalytic amount of *p*-toluenesulfonic acid and ethylene glycol (0.74 g, 12.0 mmol) was added to a solution of **3** (5.48 g, 10.9 mmol) in $CHCl_3$ (50 mL). The mixture was stirred at room temperature for 1 h. The organic layer was washed with saturated aqueous $NaHCO_3$ and water, and dried over Na_2SO_4. The solvent was evaporated to dryness under reduced pressure by an aspirator. The residue was chromatographed (silica gel, $CHCl_3$) to give **4** as a white solid (3.97 g, 86%): mp 118−121 °C; ^{1}H NMR (DMSO-d_6) δ 4.45−4.65 (m, 4H), 3.68−3.75 (m, 2H), 3.51 (dd, 1H, J = 2.4, 9.2 Hz), 3.39 (m, 1H), 3.19 (m, 1H), 3.02 (m, 1H), 0.86−1.10 (m, 28H); ^{13}C NMR (DMSO-d_6) δ 77.00, 75.61, 75.08, 72.97, 72.38, 71.51, 17.61, 17.57, 17.50, 17.39, 17.22, 12.54, 12.00, 11.87. Anal. Calcd for $C_{18}H_{38}O_7Si_2$: C, 51.15; H, 9.06. Found: C, 51.12; H, 9.21.

3-(4′-Acetyloxy-3′-methoxyphenyl)-2-propenoic Acid Chloride (5). Ferulic acid (**1**) (38.8 g, 0.2 mol) was added to a solution of NaOH (25.4 g, 0.52 mol) in water (200 mL), and the mixture was cooled to below 10 °C. Acetic anhydride (25.4 g, 0.25 mol) was then added to the cold solution. The solution was stirred at 20 °C for 10 min and then at room temperature for 20 min. Then, the pH of the solution was adjusted to 4−5 by adding dilute sulfuric acid. The resulting white precipitate was filtered and washed with water. Recrystallization from EtOH gave colorless needles (37.7 g, 77%): mp 197−200 °C; ^{1}H NMR (DMSO-d_6) δ 12.45 (s, 1H), 7.61 (d, 1H, J = 15.6 Hz), 7.12−7.49 (m, 3H), 6.61 (d, 1H, J = 15.6 Hz), 3.84 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 168.6, 167.8, 151.3, 143.5, 141.0, 133.4, 123.4, 121.5, 119.7, 112.0, 56.2, 20.6.

Thionyl chloride (8.5 mL, 0.12 mol) was added to a suspension of 3-(4′-acetyloxy-3′-methoxyphenyl)-2-propenoic acid (23.6 g, 0.1 mol) in $CHCl_3$ (100 mL) containing a catalytic amount of DMF. The mixture was stirred for 4 h at the reflux temperature. After the solvent and excess thionyl chloride were removed under reduced pressure, the acid chloride **5** was obtained as pale yellow crystals (25.0 g, 98%). This material was used without further purification: mp 129−131 °C; ^{1}H NMR ($CDCl_3$) δ 7.79 (d, 1H, J = 15.6 Hz), 7.09−7.12 (m, 3H), 6.59 (d, 1H, J = 15.6 Hz), 3.88 (s, 3H), 2.35 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 168.5, 165.9, 151.7, 149.8, 142.8, 131.8, 123.6, 122.5, 122.4, 111.9, 56.0, 20.6. Anal. Calcd for $C_{12}H_{11}ClO_4$: C, 56.60; H, 4.35. Found: C, 56.56; H, 4.28.

(±)-1-*O*-[3-(4′-Acetyloxy-3′-methoxyphenyl)-2-propenoyl]-3,4-*O*-(1,1,3,3-tetraisopropyldisiloxanedi-1,3-yl)-*myo*-inositol (6a) and (±)-6-*O*-[3-(4′-Acetyloxy-3′-methoxyphenyl)-2-propenoyl]-3,4-*O*-(1,1,3,3-tetraisopropyldisiloxanedi-1,3-yl)-*myo*-inositol (6b). The acid chloride **5** (159 mg, 0.625 mmol) was added to a solution of **4** (106 mg, 0.25 mmol) in anhydrous pyridine (10 mL). The mixture was stirred for 14 h at room temperature, and the reaction was quenched by adding water. Ethyl acetate was added, and the mixture was washed successively with saturated aqueous $KHSO_4$, saturated aqueous $NaHCO_3$, and brine. After the organic layer was dried over Na_2SO_4, the solvent was removed under reduced pressure. The residue was chromatographed on preparative TLC (1 mm thickness of silica gel, 3:2 *n*-hexane/ethyl acetate) to give **6a** (52.8 mg, 33%) and **6b** (10.5 mg, 6.6%) as white solids, respectively.

6a: TLC (1:1 *n*-hexane/ethyl acetate) R_f = 0.35; mp 163−165 °C; ^{1}H NMR ($CDCl_3$) δ 7.72 (d, 1H, J = 16.0 Hz), 7.04−7.13 (m, 3H), 6.54 (d, 1H, J = 16.0 Hz), 4.97 (dd, 1H, J = 2.8, 10.0 Hz), 4.25 (t, 1H, J = 2.8 Hz), 4.18 (m, 1H), 3.95 (t, 1H, J = 8.8 Hz), 3.86 (s, 3H), 3.79 (dd, 1H, J = 2.8, 8.8 Hz), 3.45 (m, 1H), 2.59−2.62 (m, 2H), 2.51 (d, 1H, J = 3.2 Hz), 2.33 (s, 3H), 1.00−1.11 (m, 28H); ^{13}C NMR ($CDCl_3$) δ 168.76, 166.51, 151.36, 145.23, 141.57, 133.17, 123.24, 121.61, 117.60, 111.08, 76.15, 75.06, 74.76, 73.06, 71.00, 69.59, 55.88, 20.65, 17.44, 17.30, 17.20, 17.12, 12.81, 12.76, 12.06, 12.03. Anal. Calcd for $C_{30}H_{48}O_{11}Si_2$: C, 56.22; H, 7.55. Found: C, 56.19; H, 7.60.

6b: TLC (1:1 *n*-hexane/ethyl acetate) R_f = 0.49; mp 102−104 °C; ^{1}H NMR ($CDCl_3$) δ 7.71 (d, 1H, J = 16.0 Hz), 7.04−7.13 (m, 3H), 6.47 (d, 1H, J = 16.0 Hz), 5.40 (t, 1H, J = 10.0 Hz), 4.14 (t, 1H, J = 2.8 Hz), 3.98 (t, 1H, J = 8.8 Hz), 3.86 (s, 3H), 3.53−3.73 (m, 3H), 2.70−2.78 (m, 2H), 2.45 (d, 1H, J = 3.2 Hz), 2.33 (s, 3H), 1.00−1.11 (m, 28H); ^{13}C NMR ($CDCl_3$) δ 168.76, 167.18, 151.32, 144.92, 141.42, 133.35, 123.21, 121.36, 117.80, 111.23, 74.67, 74.10, 73.06, 72.77, 70.92, 55.88, 20.66, 17.41, 17.32, 17.27, 17.20, 17.11, 12.78, 12.05, 12.02. Anal. Calcd for $C_{30}H_{48}O_{11}Si_2$: C, 56.22; H, 7.55. Found: C, 56.17; H, 7.63.

(±)-1,6-*O*-Bis[3-(4′-acetyloxy-3′-methoxyphenyl)-2-propenoyl]-3,4-*O*-(1,1,3,3-tetraisopropyldisiloxanedi-1,3-yl)-*myo*-inositol (6c) and (±)-1,5,6-*O*-Tris[3-(4′-acetyloxy-3′-methoxyphenyl)-2-propenoyl]-3,4-*O*-(1,1,3,3-tetraisopropyldisiloxanedi-1,3-yl)-*myo*-inositol (6d). A mixture of a catalytic amount of 4-(dimethylamino)pyridine and **5** (318 mg, 1.25 mmol) was added to a solution of **4** (106 mg, 0.25 mmol) in anhydrous pyridine (10 mL). The mixture was stirred at 70 °C for 1.5 h, and the reaction was quenched by adding water. Ethyl acetate was added, and the mixture was washed successively with saturated aqueous $KHSO_4$, saturated aqueous $NaHCO_3$, and brine. After the organic layer was dried over Na_2SO_4, the solvent was removed under reduced pressure. The residue was chromatographed (silica gel, 3:2 *n*-hexane/ethyl acetate) to give **6c** as a white solid (174 mg, 81%): TLC (1:1 *n*-hexane/ethyl acetate) R_f = 0.57; mp 198−200 °C; ^{1}H NMR ($CDCl_3$) δ 7.57−7.63 (m, 2H), 6.97−7.04 (m, 6H), 6.30−6.40 (m, 2H), 5.72 (t, 1H, J = 10.0 Hz), 5.35−5.38 (m, 2H), 4.99 (dd, 1H, J = 2.4, 10.0 Hz), 4.06 (m, 1H), 3.91 (m, 1H), 3.77−3.84 (m, 7H), 3.55 (m, 1H), 2.24 (s, 6H), 0.85−1.10 (m, 28H); ^{13}C NMR ($CDCl_3$) δ 168.69, 166.18, 166.12, 151.37, 151.31, 145.48, 144.95, 141.64, 141.48, 133.20, 133.02, 123.17, 123.20, 121.76, 121.45, 117.59, 117.21, 111.17, 111.06, 74.61, 73.41, 71.10, 70.97, 70.80, 55.92, 55.87, 20.61, 17.46, 17.35, 17.32, 17.26, 17.21, 17.13, 12.79, 12.06. Anal. Calcd for $C_{42}H_{58}O_{15}Si_2$: C, 58.72; H, 6.81. Found: C, 58.67; H, 6.94.

Further elution gave **6d** as a white solid (29.6 mg, 11%): TLC (1:1 *n*-hexane/ethyl acetate) R_f = 0.47; mp 191−194 °C; ^{1}H NMR ($CDCl_3$) δ 7.52−7.67 (m, 3H), 7.00−7.08 (m, 9H), 6.24−6.43 (m, 3H), 5.91 (t, 1H, J = 10.4 Hz), 5.37 (t, 1H, J = 10.0 Hz), 5.27 (dd, 1H, J = 2.4, 10.0 Hz), 4.33 (t, 1H, J = 2.8 Hz), 4.26 (t, 1H, J = 9.2 Hz), 3.95 (dd, 1H, J = 2.8, 8.4 Hz), 3.84 (s, 6H), 3.81 (s, 3H), 2.31 (s, 6H), 2.29 (s, 3H), 0.90−1.12 (m, 28H); ^{13}C NMR ($CDCl_3$) δ 168.77, 168.68, 166.00, 165.77, 165.53, 151.36, 151.30, 145.61, 145.19, 144.93, 141.67, 141.54, 141.49, 133.21, 133.03, 123.21, 123.15, 121.80, 121.64, 121.39, 117.36, 117.12, 111.17, 111.09, 75.12, 74.27, 72.74, 71.00, 70.89, 69.22, 55.94, 55.91, 20.64, 17.45, 17.34, 17.24, 17.14, 17.08, 12.79, 12.09, 12.03. Anal. Calcd for $C_{54}H_{68}O_{19}Si_2$: C, 60.21; H, 6.36. Found: C, 60.18; H, 6.44.

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