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Synthesis of Eicosanyl (E)-Caffeate, a Metabolite of *Calystegia Soldanella*†

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Eicosanyl (E)-caffeate (**1**), isolated from the stems of *Calystegia soldanella* has been synthesized starting from 3,4-dihydroxybenzaldehyde (**2**) in four steps with an overall yield of 29%.

INTRODUCTION

Phenylpropanoids (C_6–C_3) are biosynthetic precursors for a variety of bio-active natural products, like flavonoids (C_6–C_3–C_6), lignans (C_6–C_3–C_3–C_6), coumarins (C_6–C_3), etc[1]. Phenylpropanoids also occur naturally and are reported to possess important biological activities like antioxidant[2,3], anthelmintic[4], plant growth inhibitor[5] etc. Cafieic acid and its derivatives have been reported as antioxidant compounds[2,3,6]. Eicosanyl (E)-caffeate (**1**) was isolated as one of the metabolities from the stems of *Calystegia soldanella* R. Br. (Convolvulaceae), a Japanese medicinal plant[7] and *Echinosophora koreensis*[8]. Due to our interest on phenylpropanoids[9,10], we have synthesized **1**, and the results are reported in this paper.

EXPERIMENTAL

Melting points were recorded in open capillaries and are not corrected. UV spectra were recorded on a Shimadzu UV-190 spectrophotometer, IR spectra were recorded on a Perkin-Elmer BX1 FT-IR spectrophotometer, ^{1}H NMR spectra were recorded on a Varian Gemini 400 MHz or Jeol JNM EX 90 MHz NMR spectrophotometer and mass spectra on VG micromass 70–70H mass spectrometer. Acme silica gel G and silica gel (100–200 mesh) were used for analytical TLC and column chromatography respectively.

3,4-Dibenzyloxybenzaldehyde (3)

A mixture of 3,4-dihydroxybenzaldehyde (**2**, 2 g, 14.5 mmol), benzylbromide (5.2 mL, 43.5 mmol), potassium carbonate (9 g, 65.6 mmol) and acetone (40 mL)

†Laila Impex Communication 10.

was heated under reflux for 4 h. After completion of reaction, the solid was filtered off and the solvent was evaporated. The residue obtained was chromatographed over silica gel column using mixtures of petroleum ether and ethyl acetate (95 : 5) as eluent to give **3** (4.1 g, 89%), m.p. 85–87°C (Lit.[11] m.p. 89–90°C); IR (KBr) ν_{max}: 2817, 2726, 1687 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ: 5.20 (2H, s), 5.25 (2H, s), 6.95 (1H, d, J = 8.5 Hz), 7.01–7.45 (12H, m) and 9.70 (1H, s).

3,4-Dibenzylcaffeic acid (4)

A mixture of **3** (2 g, 6.29 mmol), malonic acid (1.56 g, 15.0 mmol), pyridine (3.2 mL, 39.6 mmol) and piperidine (0.2 mL) was heated on a water bath (80–90°C) for 3 h. The reaction mixture was poured into excess dil. HCl (100 mL, 2 N). The solid was filtered, washed with cold water and dried to give **4** (2.1 g, 93%), m.p. 198–200°C (Lit.[12] m.p. 202°C); UV (MeOH) λ_{max} (log ε): 211 (4.40), 291 (4.21); IR (KBr) ν_{max}: 3060–2866 (br), 1670 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz): δ 5.22 (2H, s), 5.28 (2H, s), 6.26 (1H, d, J = 15.6 Hz), 7.70 (1H, d, J = 15.6 Hz) and 6.88–7.56 (13H, m).

1-Eicosanyl (E)-3,4-dibenzylcaffeate (5)

3,4-Dibenzyloxycinnamoyl chloride was prepared from **4** (0.5 g, 1.39 mmol) using thionyl chloride (0.22 mL, 2.9 mmol) by refluxing on a water bath for 30 min. and the excess thionyl chloride was removed under vacuum.

To a mixture of 1-eicosanol (0.42 g, 1.39 mmol), triethyl amine (1.2 mL, 8.5 mmol) and CH_2Cl_2 (5 mL) and a catalytic amount of DMAP at room temperature, was added the solution of 3,4-dibenzyloxycinnamoyl chloride in CH_2Cl_2 (5 mL) dropwise for about 20 min under stirring. After 2 h, the reaction mixture was diluted with ethyl acetate (50 mL) and washed with sodium bicarbonate, brine and dried over Na_2SO_4. The residue obtained after removal of the solvent was purified further by column chromatography over silica gel column using mixtures of petroleum ether and ethyl acetate (98 : 2) as eluent to give **5** (0.55 g, 62%), m.p. 62–64° C; UV (MeOH) λ_{max} (log ε): 212 (4.35), 320 (4.29); IR (KBr) ν_{max}: 2919, 2850, 1714, 1635, 1168, 933 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.00 (3H, t, J = 6.9 Hz), 1.34–1.55 (34H, m), 1.80–1.84 (2H, m), 4.30 (2H, t, J = 6.7 Hz), 5.30 (2H, s), 5.32 (2H, s), 6.37 (1H, d, J = 15.9 Hz), 7.04 (1H, d, J = 8.3 Hz), 7.19 (1H, dd, J = 8.3, 1.4 Hz), 7.25 (1H, d, J = 1.4 Hz), 7.43–7.59 (10H, m), 7.69 (1H, d, J = 15.9 Hz).

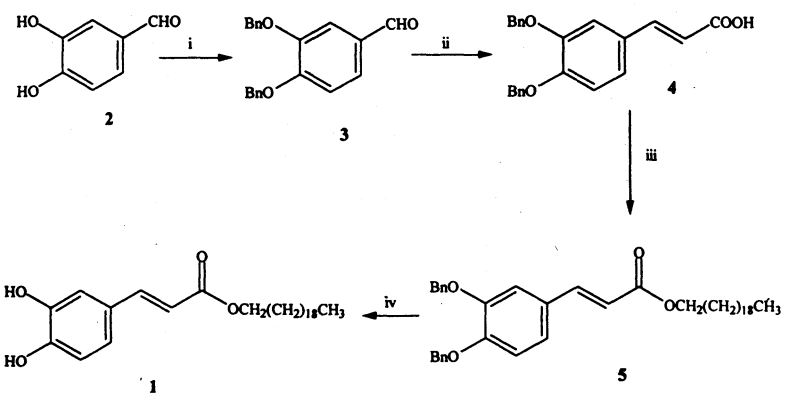
1-Eicosanyl (E)-caffeate (1)

To a mixture of **5** (0.25 g, 0.39 mmol), N,N-dimethyl aniline (0.3 mL, 2.37 mmol) and CH_2Cl_2 (25 mL), was added aluminium chloride (0.21 g, 1.56 mmol) at 0°C and the temperature was maintained at 0°C for further 30 min. The reaction mixture was then allowed to come to room temperature and continued stirring for 2 h. The reaction mixture was quenched with 1 N HCl (15 mL) and extracted with EtOAc (30 mL). The organic layer was washed with Na_2CO_3, brine and dried over Na_2SO_4. The residue obtained after removal of the solvent was purified further by column chromatography over silica gel column using mixtures of chloroform-methanol (98 : 2) as eluent to give **1** (0.1 g, 56%), m.p. 112–114°C

(Lit.[8] m.p. 109–110°C); UV (MeOH) λ_{max} (log ε): 219 (4.16), 328 (4.26); IR (KBr) ν_{max}: 3479, 3309, 2919, 2848, 1683, 1605, 1282, 1178 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.88 (3H, t, J = 6.8 Hz), 1.26–1.39 (34H, m), 1.68–1.71 (2H, m), 4.18 (2H, t, J = 6.7 Hz), 5.49 (1H, s), 5.63 (1H, s), 6.27 (1H, d, J = 15.9 Hz), 6.87 (1H, d, J = 8.2 Hz), 7.02 (1H, d, J = 8.2 Hz), 7.08 (1H, br, s), 7.56 (1H, d, J = 15.9 Hz); EIMS m/z: 461 (15%, M^{+1}), 460 (47, M^+), 181 (54), 180 (28), 179 (100), 163 (56), 135 (18), 134 (10) and 123 (17).

RESULTS AND DISCUSSION

Condensation of 3,4-dibenzyloxybenzaldehyde (**3**), obtained from 3,4-dihydroxybenzaldehyde (**2**), with malonic acid under Knoevenagel-Doebner conditions[13], gave 3,4-dibenzylcaffeic acid (**4**) in 93% yield. **4** was converted into the corresponding acid chloride with $SOCl_2$ and then esterified with 1-eicosanol to give 1-eicosanyl (E)-3,4-dibenzylcaffeate (**5**) in 62% yield. Debenzylation of **5** was carried out using $AlCl_3$ and N,N-dimethylaniline[14] to give the title compound **1** in 56% yield (Scheme-1). Thus, **1** was obtained starting from 3,4-dihydroxybenzaldehyde in four steps with an overall yield of 29%. The spectral data of synthetic **1** agree well with those of reported for natural **1**.



Scheme 1: (i) BnBr, acetone, K_2CO_3, reflux, 4 h, 89% (ii) $CH_2(COOH)_2$, pyridine, piperidine, 80–90°C, 3 h, 93% (iii) $SOCl_2$, 1-eicosanol, Et_3N, DMAP, 62% (iv) $AlCl_3$, N,N-dimethyl aniline, 56%.

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