Synthesis of caffeic acid esters

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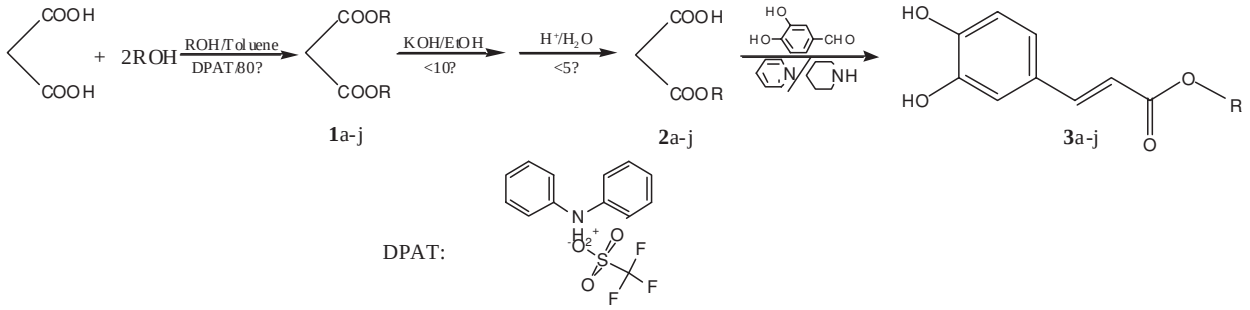
A new method for the preparation of caffeic acid esters was investigated. Ten caffeic acid esters were prepared by condensation of protocatechualdehyde with malonic acid mono-esters in moderate yield. Malonic acid mono-esters were prepared from the corresponding malonate di-esters. The conformations of compounds are *trans* (*E*) form.

Keywords: protocatechualdehyde, Knoevenagel–Doebner condensation, caffeic acid ester

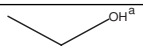
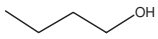
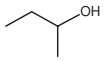
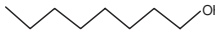
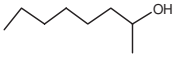
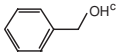
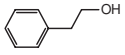
Caffeic acid 3-(3,4-dihydroxyphenyl)propenoic acid esters have been separated from propolis, fruits and vegetables.[1,2] Most of them have bioactivities such as antibacterial,[3] antiviral,[4] anti-inflammatory,[5] antiatherosclerotic.[6] Caffeic acid phenylethyl ester (CAPE) has been identified as one of the major biologically active compounds.[7] Caffeic acid esters have been synthesised previously by: acid-catalysed esterification,[8] alkylation of caffeic acid with β-bromoethylbenzene,[9] esterification *via* acyl chlorides,[10] and by Wittig reactions.[11] These methods have some disadvantages. For example, the yields are lower; the raw material used is the caffeic acid which is more expensive; purification is not easy, and some need to use preparative chromatography.

A convenient method is shown in Scheme 1. Firstly, using Wakasugi method, [12] the malonate di-esters **1** were prepared. Then, the malonic acid mono-esters **2** were obtained by saponification of the malonate di-esters with one equivalent of potassium hydroxide. Finally, the caffeic acid esters **3** were prepared by condensation reaction. Ten compounds including 5 new compounds were synthesised by this method. The results are summarised in Table 1.



Scheme 1

Table 1 Synthesis of caffeic acid esters

Entry	ROH	Reaction time/h		Yield/%			M.p./ °C/ (Lit.)
		1	3	1	2	3	
a		–	17	–	75.6	71.1	149–151 (149–151)[13]
b		18	24	94.3	35.8	67.8	109–111 (110–111)[13]
c		23	23	90.1	67.6	58.5	124–127[d]
d		13	18	78.2	43.0	64.3	110–113 (111–112)[13]
e		22	29	81.2	81.2	65.2	132–135[d]
f		–	26	–	13.7	46.9	151–155[d]
g		11	21	58.3	37.1	87.1	150–152 (151–154)[13]
h		16	16	96.8	73.5	82.6	126–129 (126–128)[8]
i		28	24	81.2	80.8	67.2	150–151[d]
j		22	48	90.8	82.5	71.6	148–151[d]

[a]Diethyl malonate is commercially available.
[b]Directly synthesise malonic acid mono-ester according literature.[14]
[c]Concentrated H_2SO_4 instead of DPAT and at reflux temperature to prepare the di-ester.[15]
[d]New compounds.

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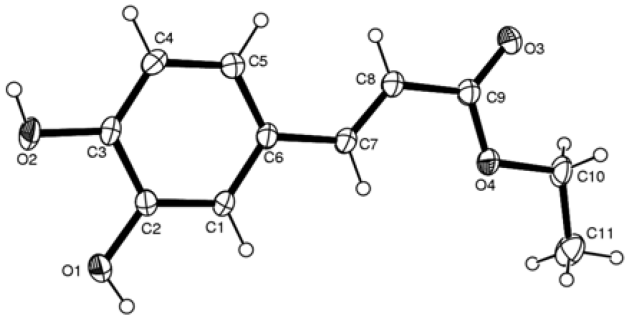

Fig. 1 X-ray crystal structure of 3a.

The coupling constants (J=15.9 or 16.0Hz) between the α-H and β-H of the products **3** indicate that caffeic acid esters prepared by this method are *trans* (*E*) form. The *trans* (*E*) form of **3a** is further confirmed by X-ray crystallography.[16]

Experimental

Melting points were taken on XRC-1 apparatus and are uncorrected. The MS spectra were run on HP5989B instrument. The IR spectra were recorded on Nicolet ET-50DX spectrophotometer (KBr).^{1}H NMR spectra were determined in DMSO-d_6 on Brucker AC-80 operating at 400MHz using TMS as the internal standard. The elemental analysis were obtained on a Carlo Erba 1106 instrument.

General procedure

Preparation of the malonic acid di-ester: Malonic acid (10.4g, 0.1mol), alcohol (0.2mol) and diphenylamine trifluoromethane sulfonate (DPAT) (0.64g, 0.002mol) were heated to 80°C in toluene. The reaction was monitired by TLC. After evaporation of the toluene under reduced pressure, the crude material was washed with diluted HCl solution, saturated $NaHCO_3$ solution and water respectively to afford the malonate di-ester.

Preparation of the malonic acid mono-ester: KOH (5.6g, 0.1mol) in ethanol (64 ml) was added to a solution of malonate di-ester (0.1 mol) and absolute ethanol (64 ml) below 10°C over 0.5 h, and stirred an additional 0.5 h. The white precipitate of mono-potassium malonate was collected by suction filtration. The potassium salt was dissolved in water 20 ml cooled to 0°C, concentrated hydrochloric acid was added till pH 2. The malonic acid mono-ester was extracted by ether. After removal of the ether, the malonic acid mono-ester was obtained.

Preparation of caffeic acid ester: Malonic acid mono-ester (25mmol) and protocatechualdehyde (1.4g, 10mmol) were dissolved in pyridine (8ml) and piperidine (0.25ml). The solution was stirred at room temperature and monitored by TLC. The solvent was removed below 80°C in reduced pressure; and residue the remainder was dissolved in 30ml ether, washed with dilute hydrochloric acid solution, saturated $NaHCO_3$ solution and water respectively. The solvent was evaporated and the crude product was recrystallised from benzene to give the pure product.

Compound (**3a**): Light brown crystalline. ^{1}H NMR (DMSO-d_6,400MHz) δ 9.56 (s,1H,OH), 9.11 (s,1H, OH), 7.47 (d,J=15.9Hz,1H, α-H), 7.04 (d,1H,ArH), 7.00 (d,J=8.1Hz,1H,ArH), 6.76 (d,J=8.1Hz,1H, ArH), 6.25 (d,J=15.9Hz, 1H,β-H), 4.15 (dd,2H,CH_2), 1.24 (t,3H,CH_3). IR(KBr) ν_{max}/cm^{-1} 3436, 3183, 1658, 1609, 1454, 1282. EIMS *m/z* (%): 208(M^+,67), 163(100), 145(33), 135(30), 134(31), 117(30), 89(43).

Compound (**3b**): Light yellow solid. ^{1}H NMR (DMSO-d_6,400MHz) δ 9.59 (s,1H,OH), 9.15 (s,1H,OH), 7.46 (d,1H,J=15.9Hz,α-H), 7.05 (d,J=2.0Hz,1H,ArH), 7.01 (dd,J=2.0,8.1Hz,1H,ArH), 6.76 (1H,d,J= 8.1Hz,ArH), 6.25 (d,1H,J=15.9Hz,β-H), 4.11 (t,2H,CH_2), 1.61 (m,2H,CH_2), 1.37 (m,2H,CH_2), 0.91 (t,3H, CH_3). IR (KBr) ν_{max}/cm^{-1} 3488, 3343, 1684, 1603, 1278, 1185. EIMS *m/z* (%): 237(M^++1,33), 236(M^+,43), 180(77), 163(100), 136(32), 134(38), 89(49), 41(41).

Compound (**3c**): Light yellow crystalline. ^{1}H NMR (DMSO-d_6,400MHz) δ 9.56 (s,1H,OH), 9.10 (s,1H, OH), 7.44 (d,J=15.9Hz,1H,α-H), 7.03 (d,J=2.0Hz,1H,ArH), 7.00 (dd,J=2.0,8.1Hz,1H,ArH), 6.75 (d,J= 8.1Hz,1H,ArH), 6.23 (d,J=15.9Hz,1H,β-H), 4.83 (m,1H,CH), 1.58 (m,2H,CH_2), 1.20 (d,3H,CH_3), 0.88 (t, 3H,CH_3). IR(KBr) ν_{max}/cm^{-1} 3446, 2970, 1664, 1605, 1442, 1281. EIMS *m/z* (%) 236[M^+](32), 180(80), 163(100), 136(45), 135(28), 134(61), 89(49), 79(26). Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.01; H, 7.03%.

Compound (**3d**): Yellow solid. ^{1}H NMR (DMSO-d_6,400MHz) δ 9.58 (s,1H,OH), 9.11 (s,1H,OH), 7.45 (d,J=15.9Hz,1H,α-H), 7.03 (d,1H,ArH), 7.00 (d,J=8.1Hz,1H,ArH), 6.75 (d,J=8.1Hz,1H,ArH), 6.25 (d, J=15.9Hz,1H,β-H), 4.10 (t,2H,CH_2), 1.61 (m,2H,CH_2), 1.26 (broad m,10H,5CH_2), 0.86 (t,3H,CH_3). IR (KBr) ν_{max}/cm^{-1} 3489, 3317, 2919, 1682, 1441, 1282. EIMS *m/z* (%) 292(M^+,14), 181(48), 180(100), 163(29), 136(18), 134(40), 89(42), 55(25).

Compound (**3e**): Pale yellow crystalline. ^{1}H NMR (DMSO-d_6,400MHz) δ 9.56 (s,1H,OH), 9.11 (s,1H,OH), 7.44 (d,J=15.9Hz,1H,α-H), 7.03 (d,J=1.9Hz,1H,ArH), 7.00 (dd,J=1.9,8.1Hz,1H,ArH), 6.75 (1H, J=8.1Hz,d,ArH), 6.22 (d,1H,J=15.9Hz,β-H), 4.99 (m,1H,CH), 1.54 (broad s,2H,CH_2), 1.25 (broad s,8H, 4CH_2), 1.20 (d,3H, CH_3), 0.85 (t,3H,CH_3). IR(KBr) ν_{max}/cm^{-1} 3494, 3336, 1684, 1602, 1278, 1183. EIMS *m/z* : 292(M^+,1), 208(69), 180(32), 163(100), 136(36), 145(31), 135(26), 134(26), 89(29). Anal. Calcd for $C_{17}H_{24}O_4$: C,69.84; H,8.27. Found: C,69.66; H,8.18%.

Compound (**3f**): Tellow crystalline. ^{1}H NMR (DMSO-d_6,400MHz) δ 9.70 (s,1H,OH), 9.19 (s,1H,OH), 7.68 (d,J=15.9Hz,1H,α-H), 7.45 (1H,J=2.1Hz,d,ArH), 7.43 (dd,1H,J=2.1,8.1Hz,ArH), 7.11–7.29 (m, 5H,ArH), 6.79 (d,J=8.1Hz,1H,ArH), 6.49 (d,J=15.9Hz,1H, β-H). IR(KBr) ν_{max}/cm^{-1} 3503, 3366, 1708, 1603, 1264, 1201. EIMS *m/z* (%): 256(M^+,3), 163(100), 145(15), 136(33), 135(13), 117(13), 89(23), 7(11), 65(12). Anal. Calcd for $C_{15}H_{12}O_4$: C,70.31; H,4.72. Found: C,69.98; H,4.85%.

Compound (**3g**): Pale yellow solid. ^{1}H NMR (DMSO-d_6,400MHz) δ 9.59 (s,1H,OH), 9.20 (s,1H,OH), 7.52 (d,J=15.9Hz,1H,α-H), 7.34–7.41 (m,5H,ArH), 7.05 (d,J=2.0Hz,1H,Ph-H), 7.02 (dd,J=2.0,8.1Hz, 1H,ArH), 6.75 (d,J=8.1Hz,1H,ArH), 6.32 (d,J=15.9Hz,1H,β-H), 5.19 (s,2H,CH_2). IR(KBr) ν_{max}/cm^{-1} 3464, 3327, 1689, 1600, 1277, 1185. EIMS *m/z* (%): 270(M^+,9), 208(19), 163(50), 136(33), 91(100), 89(32), 77(19), 65(20), 51(18).

Compound (**3h**): Pale white needle crystalline. ^{1}H NMR (DMSO-d_6,400MHz) δ 9.59 (s,1H,OH), 9.12 (s,1H,OH), 7.45 (d,J=15.9Hz,1H,α-H),7.22–7.33 (m,5H,ArH), 7.04 (d,2.4Hz,1H, ArH), 7.00 (dd, J=2.4,8.0Hz,1H,ArH), 6.76 (1H,d,J=8.0Hz, ArH), 6.23 (d,J=15.9Hz,1H,β-H), 4.32 (t,J=14.0Hz,2H, CH_2), 2.95 (t,J=14.0Hz,2H,CH_2). IR(KBr) ν_{max}/cm^{-1} 3481, 3329, 1683, 1601, 1279, 1181. EIMS *m/z* (%): 284(M^+,3), 180(100), 163(61), 134(34), 105(50), 104(66), 89(53), 77(49), 51(33).

Compound (**3i**): Pale white needle solid. ^{1}H NMR (DMSO-d_6,400MHz) δ 9.56 (s,1H,OH), 9.10 (s,1H, OH), 7.44 (d,J=15.9Hz,1H,α-H), 7.03 (s,1H,ArH), 7.00 (d,J=8.1Hz,1H,ArH), 6.74 (d,J=8.1Hz,1H, ArH), 6.23 (d,J=15.9Hz,1H,β-H), 4.75 (m,1H,CH), 1.82 (broad m,2H,CH_2), 1.69 (broad m,2H,CH_2), 1.33–1.43 (broad m,6H, 3CH_2). IR(KBr) ν_{max}/cm^{-1} 3446, 3275, 1685, 1600, 1273, 1179. EIMS *m/z*(%): 262(M^+,27), 181(75), 180(100), 163(97), 136(33), 134(50), 89(50), 5(66), 41(71). Anal. Calcd for $C_{15}H_{18}O_4$: C,68.68; H,6.92. Found: C,68.38; H,6.88%.

Compound (**3j**): Pale yellow solid. ^{1}H NMR (DMSO-d_6,400MHz) δ 9.58 (s,1H,OH), 9.18 (s,1H, OH), 7.41 (d,J=15.9Hz,1H,α-H), 6.99 (d,J=2.0Hz,1H,ArH), 6.99 (dd,J=2.0,8.1Hz,1H,ArH), 6.75 (d, J= 8.1Hz,1H,ArH), 6.20 (d,J=15.9Hz,1H,β-H), 4.66 (m,1H,CH), 1.73–1.76 (m,5H,2CH_2,CH), 1.04–1.24 (m, 2H,CH_2), 2.03 (s, 3H,CH_3), 0.83 (s,6H,2CH_3). IR(KBr) ν_{max}/cm^{-1} 3327, 2929, 1682, 1626, 1244, 1069. EIMS *m/z* (%): 316(M^+,4), 180(16), 164(13), 163(100), 81(15), 69(10), 5(10), 3(14), 41(17). Anal. Calcd for $C_{19}H_{24}O_4$: C,72.13; H,7.65. Found: C,72.42; H,7.74%.

The authors thank the Organic Chemistry Group in Zhejiang University for MS, ^{1}H NMR and Elemental analysis and Prof. Min-Qin Chen for crystal structure analysis.

Received 17 January 2005; accepted 24 February 2005
Paper 05/3023

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