SUPPORTING INFORMATION

Synthesis and tyrosinase inhibitory activities of 4-oxobutanoate derivatives of carvacrol and thymol

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Experimental

General

All reagents used were of analytical grade and the solvents were dried according to standard procedures. Column chromatography was performed using Teledyne Isco Rf-Gold prepacked silica gel columns or standard silica gel (230-400 mesh). Melting point data were obtained on a Thomas-Hoover capillary melting point apparatus. Infrared spectra were recorded on a Thermo Scientific Nicolet iS50 FT-IR spectrometer. NMR data were acquired on a JEOL ECZ 400S spectrometer, using chloroform-d as solvent (^{1}H NMR, 400 MHz; ^{13}C NMR, 100 MHz). HR-ESIMS data were acquired on a Waters SYNAPT G2-S QTOFMS system.

Synthesis of ethyl carvacrol (3) and ethyl thymol (4)

A mixture of carvacrol, **1**, (20.0 g, 0.13 mol), bromoethane (19.5 mL, 0.27 mol), and sodium methoxide (10.7 g, 0.20 mol) in anhydrous acetonitrile (250 mL) was heated under reflux for 22 h and then cooled to room temperature. The mixture was filtered to remove the precipitated sodium bromide, and the filtrate was concentrated under reduced pressure. The mixture was diluted with ethyl acetate (75 mL), washed with saturated NaCl (50 mL), and dried over anhydrous Na_2SO_4. Removal of the solvent afforded the product as a pale yellow oil, **3**, (14.3 g, 60%). For thymol, **2**, the same procedure was used with an increase in the scale of the experiment by a factor of 2.5. The product was obtained as a pale yellow oil, **4**, (55.1 g, 93%). The NMR data for compounds **3** and **4** were in agreement with literature data.[18]

Synthesis of carvacrol 4-oxobutanoic acid (5) and thymol 4-oxobutanoic acid (6)

A mixture of ethyl carvacrol, **3**, (10 g, 56 mmol) and aluminum chloride (11.2 g, 84.2 mmol) in anhydrous CH_2Cl_2 (100 mL) was cooled in an ice-bath and stirred under N_2. Succinoyl chloride (9.3 mL, 84.2 mmol) was added to the reaction mixture over a period of 1 h. The mixture was allowed to warm to room temperature, and stirring was continued at room temperature for 26 h. The reaction mixture was slowly poured into a mixture of 50% aq. HCl (50 mL) and crushed ice (~50 mL) and stirred for 10 min. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (50 mL). The combined CH_2Cl_2 solution was washed with saturated NaCl (2 × 50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography, eluting with a solvent gradient of 10-40% ethyl acetate-hexanes to afford carvacrol 4-oxobutanoic acid (**5**).
Thymol 4-oxobutanoic acid (**6**) was prepared using a similar procedure, with 8.6 g (48 mmol) of ethyl thymol, **4**, as starting material.

Synthesis of alkyl 4-oxobutanoate derivatives of carvacrol (7-13) and thymol (14-20)

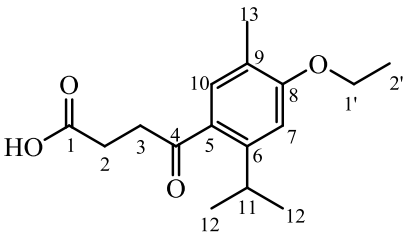
Carvacrol esters: A mixture of ethyl carvacrol 4-oxobutanoic acid, **5** (0.30 g, 1.1 mmol) and Cs_2CO_3 (0.53 g, 1.6 mmol) in anhydrous acetonitrile (20 mL) was stirred for 10 min at room temperature,

followed by the addition of the alkyl halide (1.6 mmol). The reaction mixture was heated under reflux, and the progress of the reaction was monitored by TLC analysis. After completion of the reaction (2 h to 24 h), the acetonitrile was removed *in vacuo*. Saturated NaCl (40 mL) was added to the mixture, followed extraction with CH_2Cl_2 (2 × 10 mL). The CH_2Cl_2 solution was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography, eluting with 5-10% ethyl acetate-hexanes. For synthesis of **13**, 0.50 g (1.8 mmol) of **5** was used.
Thymol esters: Thymol alkyl 4-oxobutanoates were prepared using the same procedure, except that the amounts of ethyl thymol 4-oxobutanoic acid, **6**, ranged from 0.30 g to 1.0 g (1.1 to 3.6 mmol).

Tyrosinase inhibition assay
The tyrosinase inhibitory effects were evaluated according to our previously reported methods with minor modifications.[20] The tyrosinase inhibition assay was conducted in a 96-well microplate format using a SpectraMax M2 microplate reader (Molecular Devices, Sunnyvale, CA, USA). Briefly, the test samples were dissolved in 10% DMSO at a concentration of 8.0 mg/mL and then diluted to different concentrations with deionized water. Each well contained 40 μL of sample with 80 μL of PBS, and 40 μL of mushroom tyrosinase (200 units/mL). Blank absorbance readings were recorded at 490 nm before incubation for 20 min at 37 °C. Then 40 μL of L-tyrosine (2.5 mM) was added to each well, followed by incubation at room temperature for 10 min. The absorbance was again measured at 490 nm. Kojic acid was used as the positive control. The results were compared with a control consisting of 10% DMSO in place of the sample. The percentage of tyrosinase inhibition was calculated as follows: $[(\Delta A\text{control} - \Delta A\text{sample})/\Delta A\text{control}] \times 100\%$.

Spectroscopic and spectrometric data for carvacrol 4-oxobutanoic and carvacrol alkyl 4-oxobutanoates

^{1}H NMR (400 MHz, $CDCl_3$)
^{13}C NMR (100 MHz, $CDCl_3$)



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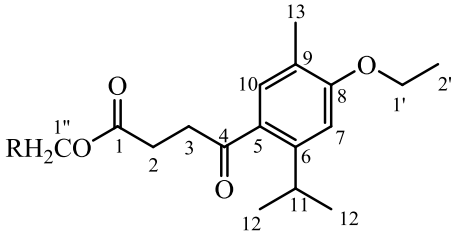


7-13

4-(4-Ethoxy-2-isopropyl-5-methylphenyl)-4-oxobutanoic acid (5)
Off white solid (10.6 g, 68%)
MP: 119-120°C
IR (ATR): 2500-3300 (OH), 1695 (C=O carboxylic acid), 1676 (C=O ketone), 1607 (C=C aromatic), 1252 (O-C[Ar]), 1151 (O-C[R]) cm^{-1}.
^{1}H NMR: δ 7.44 (1H, s, H-10), 6.83 (1H, s, H-7), 4.10 (2H, quartet, *J* = 7.2 Hz, H-1'), 3.65 (1H, septet, *J* = 6.8 Hz, H-11), 3.18 (2H, t, *J* = 6.4 Hz, H-3), 2.78 (2H, t, *J* = 6.4 Hz, H-2), 2.20 (3H, s, H-13), 1.45 (3H, t, *J* = 7.2 Hz, H-2'), 1.22 (6H, d, *J* = 6.8 Hz, H-12).
^{13}C NMR: δ 201.3 (C-4), 179.4 (C-1), 159.8 (C-8), 149.5 (C-6), 131.2 (C-10), 129.1 (C-5), 123.7 (C-9), 108.6 (C-7), 63.6 (C-1'), 36.3 (C-3), 29.1 (C-11), 28.7 (C-2), 24.2 (C-12), 15.9 (C-13), 14.9 (C-2').
HRMS (ESI): *m/z* 279.1596 $[M+H]^+$; calcd. for $C_{16}H_{23}O_4$; 279.1590.

Methyl 4-(4-ethoxy-2-isopropyl-5-methylphenyl)-4-oxobutanoate (7: R= H)
White solid (67%)
MP: 50-51°C
IR (ATR): 1734 (C=O ester), 1670 (C=O ketone), 1609 (C=C aromatic), 1249 (O-C[Ar]), 1150 (O-C[R]) cm^{-1}.
^{1}H NMR: δ 7.44 (1H, s, H-10), 6.81 (1H, s, H-7), 4.10 (2H, quartet, *J* = 7.2 Hz, H-1'), 3.69 (3H singlet, H-1''), 3.62 (1H, septet, *J* = 6.8 Hz, H-11), 3.18 (2H, t, *J* = 6.4 Hz, H-3), 2.71 (2H, t, *J* = 6.4 Hz, H-2), 2.19 (3H, s, H-13), 1.43 (3H, t, *J* = 7.2 Hz, H-2'), 1.20 (6H, d, *J* = 6.8 Hz, H-12).
^{13}C NMR: δ 201.5 (C-4), 173.6 (C-1), 159.7 (C-8), 149.3 (C-6), 131.2 (C-10), 129.3 (C-5), 123.6 (C-9), 108.6 (C-7), 63.6 (C-1'), 51.9 (C-1''), 36.6 (C-3), 29.1 (C-11), 28.6 (C-2), 24.3 (C-12), 15.9 (C-13), 14.9 (C-2').
HRMS (ESI): *m/z* 293.1750 $[M+H]^+$; calcd. for $C_{17}H_{25}O_4$; 293.1747.

Ethyl 4-(4-ethoxy-2-isopropyl-5-methylphenyl)-4-oxobutanoate (8: R = CH_3)
White solid (75%)
MP. 54-55°C
IR (ATR): 1730 (C=O ester), 1673 (C=O ketone), 1610 (C=C aromatic), 1251 (O-C[Ar]), 1150 (O-C[R]) cm^{-1}.
^{1}H NMR: δ 7.44 (1H, s, H-10), 6.81 (1H, s, H-7), 4.15 (2H, quartet, , *J* = 6.8 Hz, H-1''), 4.07 (2H quartet, *J* = 7.2 Hz, H-1'), 3.62 (1H, septet, *J* = 6.8 Hz, H-11), 3.17 (2H, t, *J* = 6.4 Hz, H-3), 2.70 (2H, t, *J* = 6.4 Hz, H-2), 2.19 (3H, s, H-13), 1.43 (3H, t, *J* = 7.2 Hz, H-2'), 1.25 (3H, t, *J* = 6.8 Hz, H-2''), 1.20 (6H, d, *J* = 6.8 Hz, H-12).

^{13}C NMR: δ 201.6 (C-4), 173.2 (C-1), 159.7 (C-8), 149.2 (C-6), 131.2 (C-10), 129.4 (C-5), 123.6 (C-9), 108.5 (C-7), 63.6 (C-1'), 60.7 (C-1"), 36.6 (C-3), 29.1 (C-11), 28.8 (C-2), 24.3 (C-12), 15.9 (C-13), 14.9 (C-2'), 14.3 (C-2").
HRMS (ESI): *m/z* 307.1920 $[M+H]^+$; calcd. for $C_{18}H_{27}O_4$; 307.1903.

Propyl 4-(4-ethoxy-2-isopropyl-5-methylphenyl)-4-oxobutanoate (9: R = CH_2CH_3)
Colorless oil (65%)
IR (ATR): 1732 (C=O ester), 1678 (C=O ketone), 1609 (C=C aromatic), 1254 (O-C[Ar]), 1150 (O-C[R]) cm^{-1}.
^{1}H NMR: δ 7.44 (1H, s, H-10), 6.80 (1H, s, H-7), 4.08 (2H, quartet, *J* = 7.2 Hz, H-1'), 4.04 (2H, t, *J* = 6.8 Hz, H-1"), 3.61 (1H, septet, *J* = 6.8 Hz, H-11), 3.16 (2H, t, *J* = 6.4 Hz, H-3), 2.70 (2H, t, *J* = 6.4 Hz, H-2), 2.19 (3H, s, H-13), 1.64 (2H, sextet, *J* = 6.8 Hz, H-2"), 1.42 (3H, t, *J* = 7.2 Hz, H-2'), 1.20 (6H, d, *J* = 6.8 Hz, H-12), 0.92 (3H, t, *J* = 6.8 Hz, H-3").
^{13}C NMR: δ 201.5 (C-4), 173.2 (C-1), 159.6 (C-8), 149.2 (C-6), 131.2 (C-10), 129.4 (C-5), 123.6 (C-9), 108.5 (C-7), 66.3 (C-1"), 63.6 (C-1'), 36.6 (C-3), 29.1 (C-11), 28.8 (C-2), 24.2 (C-12), 22.1 (C-2"), 15.9 (C-13), 14.9 (C-2'), 10.5 (C-3").
HRMS (ESI): *m/z* 321.2060 $[M+H]^+$; calcd. for $C_{19}H_{29}O_4$; 321.2060.

Allyl 4-(4-ethoxy-2-isopropyl-5-methylphenyl)-4-oxobutanoate (10: R = $CH=CH_2$)
Pale yellow oil (60%)
IR (ATR): 1735 (C=O ester), 1676 (C=O ketone), 1608 (C=C aromatic), 1253 (O-C[Ar]), 1149 (O-C[R]) cm^{-1}.
^{1}H NMR: δ 7.44 (1H, s, H-10), 6.81 (1H, s, H-7), 5.90 (1H, m, H-2"), 5.32 (1H, dd, *J* = 17.7, 1.6, H-3"-*trans*), 5.22 (1H, dd, *J* = 10.0, 1.6, H-3"-*cis*), 4.59 (2H, d, *J* = 5.6 Hz, H-1"), 4.09 (2H, quartet, *J* = 7.2 Hz, H-1'), 3.61 (1H, septet, *J* = 6.8 Hz, H-11), 3.19 (2H, t, *J* = 6.4 Hz, H-3), 2.75 (2H, t, *J* = 6.4 Hz, H-2), 2.19 (3H, s, H-13), 1.43 (3H, t, *J* = 7.2 Hz, H-2'), 1.20 (6H, d, *J* = 6.8 Hz, H-12).
^{13}C NMR: δ 201.4 (C-4), 172.8 (C-1), 159.7 (C-8), 149.3 (C-6), 132.3 (C-2"), 131.2 (C-10), 129.3 (C-5), 123.6 (C-9), 118.3 (C-3"), 108.6 (C-7), 65.4 (C-1"), 63.6 (C-1'), 36.5 (C-3), 29.1 (C-11), 28.7 (C-2), 24.3 (C-12), 15.9 (C-13), 14.9 (C-2').
HRMS (ESI): *m/z* 319.1915 $[M+H]^+$; calcd. for $C_{19}H_{27}O_4$; 319.1903.

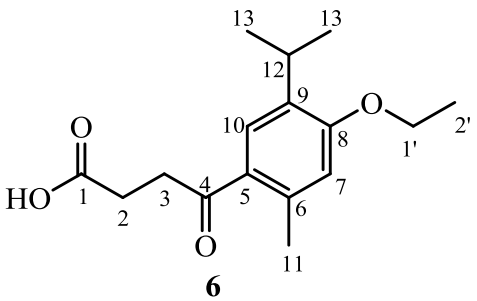
Butyl 4-(4-ethoxy-2-isopropyl-5-methylphenyl)-4-oxobutanoate (11: R = $CH_2CH_2CH_3$)
Pale yellow oil (60%)
IR (ATR): 1732 (C=O ester), 1677 (C=O ketone), 1609 (C=C aromatic), 1253 (O-C[Ar]), 1150 (O-C[R]) cm^{-1}.
^{1}H NMR: δ 7.44 (1H, s, H-10), 6.80 (1H, s, H-7), 4.10 (2H, t, H-1"), 4.07 (2H, quartet, *J* = 7.2 Hz, H-1'), 3.60 (1H, septet, *J* = 6.8 Hz, H-11), 3.17 (2H, t, *J* = 6.4 Hz, H-3), 2.70 (2H, t, *J* = 6.4 Hz, H-2), 2.19 (3H, s, H-13), 1.60 (2H, quintet, H-2"), 1.43 (3H, t, *J* = 7.2 Hz, H-2'), 1.36 (2H, sextet, H-3"), 1.20 (6H, d, *J* = 6.8 Hz, H-12), 0.91 (3H, t, H-4").
^{13}C NMR: δ 201.6 (C-4), 173.2 (C-1), 159.7 (C-8), 149.2 (C-6), 131.2 (C-10), 129.4 (C-5), 123.6 (C-9), 108.5 (C-7), 64.6 (C-1"), 63.6 (C-1'), 36.6 (C-3), 30.7 (C-2"), 29.1 (C-11), 28.8 (C-2), 24.3 (C-12), 19.2 (C-3"), 15.9 (C-13), 14.9 (C-2'), 13.8 (C-4").
HRMS (ESI): *m/z* 335.2223 $[M+H]^+$; calcd. for $C_{20}H_{31}O_4$; 335.2216.

Crotyl 4-(4-ethoxy-2-isopropyl-5-methylphenyl)-4-oxobutanoate (12: R = $CH=CHCH_3$)
Pale yellow oil (70%)

IR (ATR): 1732 (C=O ester), 1673 (C=O ketone), 1607 (C=C aromatic), 1252 (O-C[Ar]), 11510 (O-C[R]) cm^{-1}.
^{1}H NMR: δ 7.44 (1H, s, H-10), 6.80 (1H, s, H-7), 5.76 (1H, m, H-2"), 5.60 (1H, m, H-3"), 4.52 (2H, d, *J* = 6.8, H-1"), 4.09 (2H, quartet, *J* = 7.2 Hz, H-1'), 3.61 (1H, septet, *J* = 6.8 Hz, H-11), 3.17 (2H, t, *J* = 6.4 Hz, H-3), 2.73 (2H, t, *J* = 6.4 Hz, H-2), 2.19 (3H, s, H-13), 1.70 (3H, d, *J* = 6.4 Hz, H-4"), 1.42 (3H, t, *J* = 7.2 Hz, H-2'), 1.20 (6H, d, *J* = 6.8 Hz, H-12).
^{13}C NMR: δ 201.5 (C-4), 172.9 (C-1), 159.7 (C-8), 149.2 (C-6), 131.4 (C-2"), 131.2 (C-10), 129.4 (C-5), 125.2 (C-3") 123.6 (C-9), 108.5 (C-7), 65.5 (C-1"), 63.6 (C-1'), 36.6 (C-3), 29.1 (C-11), 28.8 (C-2), 24.3 (C-12), 17.9 (C-4"), 15.9 (C-13), 14.9 (C-2').
HRMS (ESI): *m/z* 333.2068 $[M+H]^{+}$; calcd. for $C_{20}H_{29}O_4$; 333.2060.

Benzyl 4-(4-ethoxy-2-isopropyl-5-methylphenyl)-4-oxobutanoate (13: R = C_6H_5)
Colorless oil (63%)
IR (ATR): 1734 (C=O ester), 1675 (C=O ketone), 1608 (C=C aromatic), 1253 (O-C[Ar]), 1148 (O-C[R]) cm^{-1}.
^{1}H NMR: δ 7.47 (1H, s, H-10), 7.36 (5H, m, H-3"- H-5"), 6.86 (1H, s, H-7), 5.17 (2H, s, H-1"), 4.12 (2H, quartet, *J* = 7.2 Hz, H-1'), 3.62 (1H, septet, *J* = 6.8 Hz, H-11), 3.22 (2H, t, *J* = 6.4 Hz, H-3), 2.80 (2H, t, *J* = 6.4 Hz, H-2), 2.23 (3H, s, H-13), 1.46 (3H, t, *J* = 7.2 Hz, H-2'), 1.25 (6H, d, *J* = 6.8 Hz, H-12).
^{13}C NMR: δ 201.4 (C-4), 173.0 (C-1), 159.7 (C-8), 149.3 (C-6), 136.1(C-2"), 131.2 (C-10), 129.4 (C-5), 128.6 (C-5"), 128.3 (C-3"/ C-4"), 123.7 (C-9), 108.6 (C-7), 66.5 (C-1"), 63.6 (C-1'), 36.6 (C-3), 29.1 (C-11), 28.8 (C-2), 24.3 (C-12), 15.9 (C-13), 14.9 (C-2').
HRMS (ESI): *m/z* 369.2072 $[M+H]^{+}$; calcd. for $C_{23}H_{29}O_4$; 369.2060.

Spectroscopic and spectrometric data for thymol 4-oxobutanoic and thymol alkyl 4-oxobutanoates
^{1}H NMR (400 MHz, $CDCl_3$)
^{13}C NMR (100 MHz, $CDCl_3$)



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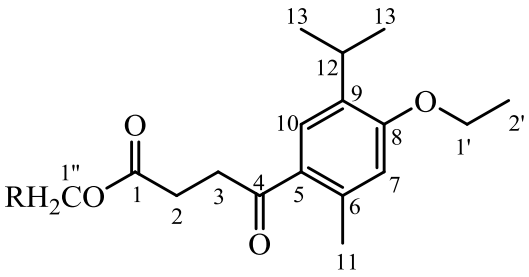

14-20

4-(4-Ethoxy-5-isopropyl-2-methylphenyl)-4-oxobutanoic acid (6)
Off white solid (10.9 g, 81%)
MP: 100-101°C
IR (ATR): 2500-3300 (OH), 1694 (C=O carboxylic acid), 1670 (C=O ketone), 1605 (C=C aromatic), 1251 (O-C[Ar]), 1153 (O-C[R]) cm^{-1}.
^{1}H NMR: δ 7.63 (1H, s, H-10), 6.64 (1H, s, H-7), 4.09 (2H, quartet, *J* = 7.2 Hz, H-1'), 3.26 (1H, septet, *J* = 6.8 Hz, H-12), 3.24 (2H, t, *J* = 6.4 Hz, H-3), 2.78 (2H, t, *J* = 6.4 Hz, H-2), 2.52 (3H, s, H-11), 1.43 (3H, t, *J* = 7.2 Hz, H-2'), 1.23 (6H, d, *J* = 6.8 Hz, H-13).

^{13}C NMR: δ 199.6 (C-4), 179.6 (C-1), 158.9 (C-8), 139.6 (C-6), 134.1 (C-9), 128.7 (C-5), 128.0 (C-10), 114.6 (C-7), 63.7 (C-1'), 35.2 (C-3), 28.7 (C-2), 27.0 (C-12), 22.6 (C-13), 22.4 (C-11), 14.9 (C-2').
HRMS (ESI): *m/z* 279.1617 $[M+H]^+$; calcd. for $C_{16}H_{23}O_4$, 279.1590.

Methyl 4-(4-Ethoxy-5-isopropyl-2-methylphenyl)-4-oxobutanoate (14: R = H)
Pale yellow amorphous solid (46%)
IR (ATR): 1726 (C=O ester), 1674 (C=O ketone), 1603 (C=C aromatic), 1249 (O-C[Ar]), 1151 (O-C[R]) cm^{-1}.
^{1}H NMR: δ 7.63 (s, 1H, H-10), 6.63 (s, 1H, H-7), 4.09 (quartet, 2H, *J* = 7.2 Hz, H-1'), 3.69 (3H, s, H-1''), 3.27 (1H, septet, *J* = 6.8 Hz, H-12), 3.24 (2H, t, *J* = 6.4 Hz, H-3), 2.72 (2H, t, *J* = 6.4 Hz, H-2), 2.51 (3H, s, H-11), 1.43 (3H, t, *J* = 7.2 Hz, H-2'), 1.23 (6H, d, *J* = 6.8 Hz, H-13).
^{13}C NMR: δ 199.8 (C-4), 173.8 (C-1), 158.8 (C-8), 139.4 (C-6), 134.1 (C-9), 128.8 (C-5), 127.9 (C-10), 114.6 (C-7), 63.7 (C-1'), 51.9 (C-1''), 35.4 (C-3), 28.5 (C-2), 26.9 (C-12), 22.6 (C-13), 22.5 (C-11), 14.9 (C-2').
HRMS (ESI): *m/z* 293.1771 $[M+H]^+$; calcd. for $C_{17}H_{25}O_4$; 293.1747.

Ethyl 4-(4-Ethoxy-5-isopropyl-2-methylphenyl)-4-oxobutanoate (15: R = CH_3)
Pale yellow oil (64%)
IR (ATR): 1732 (C=O ester), 1674 (C=O ketone), 1606 (C=C aromatic), 1250 (O-C[Ar]), 1150 (O-C[R]) cm^{-1}.
^{1}H NMR: δ 7.63 (1H, s, H-10), 6.63 (1H, s, H-7), 4.16 (2H, quartet, *J* = 7.2 Hz, H-1''), 4.06 (2H, quartet, *J* = 7.2 Hz, H-1'), 3.27 (1H, septet, *J* = 6.8 Hz, H-12), 3.23 (2H, t, *J* = 6.4 Hz, H-3), 2.72 (2H, t, *J* = 6.4 Hz, H-2), 2.51 (3H, s, H-11), 1.43 (3H, t, *J* = 7.2 Hz, H-2'), 1.25 (3H, t, *J* = 7.2 Hz, H-2''), 1.23 (6H, d, *J* = 6.8 Hz, H-13).
^{13}C NMR: δ 199.9 (C-4), 173.3 (C-1), 158.8 (C-8), 139.3 (C-6), 134.0 (C-9), 129.0 (C-5), 127.9 (C-10), 114.5 (C-7), 63.7 (C-1'), 60.6 (C-1''), 35.4 (C-3), 28.8 (C-2), 26.9 (C-12), 22.6 (C-13), 22.3 (C-11), 14.9 (C-2'), 14.3 (C-2'').
HRMS (ESI): *m/z* 307.1927 $[M+H]^+$; calcd. for $C_{18}H_{27}O_4$; 307.1903.

Propyl 4-(4-Ethoxy-5-isopropyl-2-methylphenyl)-4-oxobutanoate (16: R = CH_2CH_3)
Yellow oil (64%)
IR (ATR): 1733 (C=O ester), 1674 (C=O ketone), 1606 (C=C aromatic), 1250 (O-C[Ar]), 1149 (O-C[R]) cm^{-1}.
^{1}H NMR: δ 7.63 (1H, s, H-10), 6.63 (1H, s, H-7), 4.08 (2H, quartet, *J* = 7.2 Hz, H-1'), 4.06 (2H, t, *J* = 6.8 Hz, H-1''), 3.27 (1H, septet, *J* = 6.8 Hz, H-12), 3.23 (2H, t, *J* = 6.4 Hz, H-3), 2.71 (2H, t, *J* = 6.4 Hz, H-2), 2.51 (3H, s, H-11), 1.66 (2H, sextet, *J* = 6.8 Hz, H-2''), 1.43 (3H, t, *J* = 7.2 Hz, H-2'), 1.22 (6H, d, *J* = 6.8 Hz, H-13), 0.93 (3H, t, *J* = 6.8 Hz, H-3'').
^{13}C NMR: δ 199.9 (C-4), 173.4 (C-1), 158.8 (C-8), 139.3 (C-6), 134.0 (C-9), 129.0 (C-5), 127.9 (C-10), 114.5 (C-7), 66.3 (C-1''), 63.7 (C-1'), 35.5 (C-3), 28.8 (C-2), 26.9 (C-12), 22.6 (C-13), 22.3 (C-11), 22.1 (C-2''), 14.9 (C-2'), 10.5 (C-3'').
HRMS (ESI): *m/z* 321.2088 $[M+H]^+$; calcd. for $C_{19}H_{29}O_4$; 321.2060.

Allyl 4-(4-Ethoxy-5-isopropyl-2-methylphenyl)-4-oxobutanoate (17: R = $CH=CH_2$)
Yellow oil (64%)
IR (ATR): 1735 (C=O ester), 1673 (C=O ketone), 1606 (C=C aromatic), 1250 (O-C[Ar]), 1149 (O-C[R]) cm^{-1}.

^{1}H NMR: δ 7.63 (1H, s, H-10), 6.64 (1H, s, H-7), 5.92 (1H, m, H-2"), 5.32 (1H, dd, *J* = 17.2, 1.6, H-3"-*trans*), 5.22 (1H, dd, *J* = 10.0, 1.2, H-3"-*cis*), 4.60 (2H, d, *J* = 5.6 Hz, H-1"), 4.08 (2H, quartet, *J* = 7.2 Hz, H-1'), 3.27 (1H, septet, *J* = 6.8 Hz, H-12), 3.25 (2H, t, *J* = 6.4 Hz, H-3), 2.75 (2H, t, *J* = 6.4 Hz, H-2), 2.51 (3H, s, H-11), 1.43 (3H, t, *J* = 7.2 Hz, H-2'), 1.22 (6H, d, *J* = 6.8 Hz, H-13).
^{13}C NMR: δ 199.7 (C-4), 173.0 (C-1), 158.8 (C-8), 139.3 (C-6), 134.1 (C-9), 132.3 (C-2"), 128.9 (C-5), 127.9 (C-10), 118.2 (C-3"), 114.5 (C-7), 65.4 (C-1"), 63.7 (C-1'), 35.4 (C-3), 28.7 (C-2), 26.9 (C-12), 22.6 (C-13), 22.4 (C-11), 14.9 (C-2').
HRMS (ESI): *m/z* 319.1922 $[M+H]^{+}$; calcd. for $C_{19}H_{27}O_4$; 319.1903.

Butyl 4-(4-Ethoxy-5-isopropyl-2-methylphenyl)-4-oxobutanoate (18: R = $CH_2CH_2CH_3$)
Yellow oil (63%)
IR (ATR): 1733 (C=O ester), 1675 (C=O ketone), 1607 (C=C aromatic), 1250 (O-C[Ar]), 1149 (O-C[R]) cm^{-1}.
^{1}H NMR: δ 7.63 (1H, s, H-10), 6.63 (1H, s, H-7), 4.10 (2H, t, *J* = 6.8 Hz, H-1"), 4.08 (2H, quartet, *J* = 7.2 Hz, H-1'), 3.28 (1H, septet, *J* = 6.8 Hz, H-12), 3.23 (2H, t, *J* = 6.4 Hz, H-3), 2.71 (2H, t, *J* = 6.4 Hz, H-2), 2.51 (3H, s, H-11), 1.60 (2H, quintet, *J* = 6.8 Hz, H-2"), 1.43 (3H, t, *J* = 7.2 Hz, H-2'), 1.36 (2H, sextet, *J* = 6.8 Hz, H-3"), 1.22 (6H, d, *J* = 6.8 Hz, H-13), 0.91 (3H, t, *J* = 6.8 Hz, H-4").
^{13}C NMR: δ 199.9 (C-4), 173.4 (C-1), 158.8 (C-8), 139.3 (C-6), 134.0 (C-9), 129.0 (C-5), 127.9 (C-10), 114.5 (C-7), 64.6 (C-1"), 63.7 (C-1'), 35.5 (C-3), 30.7 (C-2"), 28.8 (C-2), 26.9 (C-12), 22.6 (C-13), 22.3 (C-11), 19.2 (C-3"), 14.9 (C-2'), 13.8 (C-4").
HRMS (ESI): *m/z* 335.2223 $[M+H]^{+}$; calcd. for $C_{20}H_{31}O_4$; 335.2232.

Crotyl 4-(4-Ethoxy-5-isopropyl-2-methylphenyl)-4-oxobutanoate (19: R = $CH=CHCH_3$)
Pale yellow oil (43%)
IR (ATR): 1733 (C=O ester), 1674 (C=O ketone), 1606 (C=C aromatic), 1250 (O-C[Ar]), 1149 (O-C[R]) cm^{-1}.
^{1}H NMR: δ 7.63 (1H, s, H-10), 6.63 (1H, s, H-7), 5.78 (1H, m, H-2"), 5.61 (1H, m, H-3"), 4.53 (2H, d, *J* = 6.4 Hz, H-1"), 4.08 (2H, quartet, *J* = 7.2 Hz, H-1'), 3.27 (1H, septet, *J* = 6.8 Hz, H-12), 3.23 (2H, t, *J* = 6.4 Hz, H-3), 2.72 (2H, t, *J* = 6.4 Hz, H-2), 2.50 (3H, s, H-11), 1.71 (3H, d, *J* = 6.4 Hz, H-4"), 1.43 (3H, t, *J* = 7.2 Hz, H-2'), 1.22 (6H, d, *J* = 6.8 Hz, H-13).
^{13}C NMR: δ 199.8 (C-4), 173.1 (C-1), 158.8 (C-8), 139.3 (C-6), 134.0 (C-9), 131.4 (C-2"), 128.9 (C-5), 127.9 (C-10), 125.2 (C-3"), 114.6 (C-7), 65.5 (C-1"), 63.7 (C-1'), 35.4 (C-3), 28.8 (C-2), 26.9 (C-12), 22.6 (C-13), 22.3 (C-11), 17.9 (C-4"), 14.9 (C-2').
HRMS (ESI): *m/z* 333.2091 $[M+H]^{+}$; calcd. for $C_{20}H_{29}O_4$; 333.2060.

Benzyl 4-(4-Ethoxy-5-isopropyl-2-methylphenyl)-4-oxobutanoate (20: R = C_6H_5)
Colorless oil (89%)
IR (ATR): 1734 (C=O ester), 1673 (C=O ketone), 1606 (C=C aromatic), 1251 (O-C[Ar]), 1149 (O-C[R]) cm^{-1}.
^{1}H NMR: δ 7.63 (1H, s, H-10), 7.30 (5H, m, H-3"- H-5"), 6.64 (1H, s, H-7), 5.15 (2H, s, H-1"), 4.09 (2H, quartet, *J* = 7.2 Hz, H-1'), 3.27 (1H, septet, *J* = 6.8 Hz, H-12), 3.24 (2H, t, *J* = 6.4 Hz, H-3), 2.78 (2H, t, *J* = 6.4 Hz, H-2), 2.51 (3H, s, H-11), 1.45 (3H, t, *J* = 7.2 Hz, H-2'), 1.23 (6H, d, *J* = 6.8 Hz, H-13).
^{13}C NMR: δ 199.7 (C-4), 173.2 (C-1), 158.8 (C-8), 139.4 (C-6), 136.1 (C-2"), 134.1 (C-9), 128.9 (C-5), 128.6 (C-5"), 128.3 (C-3"/ C-4"), 127.9 (C-10), 114.6 (C-7), 66.5 (C-1"), 63.7 (C-1'), 35.4 (C-3), 28.8 (C-2), 27.0 (C-12), 22.6 (C-13), 22.4 (C-11), 14.9 (C-2').
HRMS (ESI): *m/z* 369.2064 $[M+H]^{+}$; calcd. for $C_{23}H_{29}O_4$; 369.2060.