Supporting Information

Synthesis of γ–Keto Esters through a Neighboring Carbonyl Group-Assisted Hydration of 3-Alkynoates

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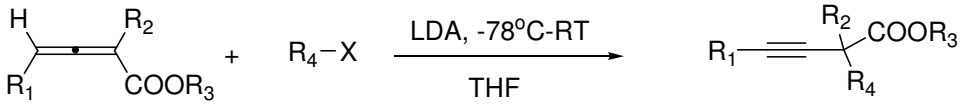
Contents

General

^{1}H, ^{13}C and ^{19}F NMR spectra were recorded at 500, 126 and 470 MHz respectively, using $CDCl_3$ as a solvent. The chemical shifts are reported in δ (ppm) values relative to $CHCl_3$ (δ 7.26 ppm for ^{1}H NMR and δ 77.0 ppm for ^{13}C NMR) and $CFCl_3$ (δ 0 ppm for ^{19}F NMR), multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), h (hextet), m (multiplet) and br (broad). Coupling constants, *J*, are reported in Hertz. Coupling constants are reported in hertz (Hz). All air and/or moisture sensitive reactions were carried out under argon atmosphere. Solvents (tetrahydrofuran, ether, dichloromethane and DMF) were chemically dried using a commercial solvent purification system. All other reagents and solvents were employed without further purification. The products were purified using a commercial flash chromatography system or a regular glass column. TLC was developed on silica gel 60 F254 aluminum sheets. Elemental analysis was performed at an outside libratory. When needed, reactions were monitored using ^{19}F NMR and the mixture percentage yield was obtained using α,α,α-trifluoromethylbenzene as internal reference.

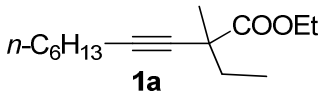
Preparation of 3-alkynoates 1[1,2]



1

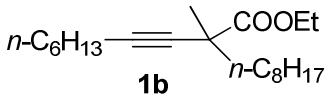
To a oven-dried, air free 10 mL flask of corresponding allene 0.5mmol was added by dry THF (2 mL), then the reaction mixture was cooled down to -78°C, LDA (2M in THF, 0.375ml, 0.75mmol) was added slowly over 5min. The reaction mixture was stirred at -78°C for 5mins, and then alkyl bromide (0.75 mmol) was injected drop wise slowly. The resulting solution was stirred for 10 mins, then warm up to room temperature and was stirred for overnight at room

temperature. Then reaction mixture was quenched with saturated NH_4Cl solution (2-3ml). After stirring for 5mins at the room temperature, the resulting aqueous mixture was extracted with ether (three times) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified by flash silica gel chromatography (25% CH_2Cl_2 in hexane - 50% CH_2Cl_2 in hexane) to give the α,α-disubstituted β-alkynyl ester products.



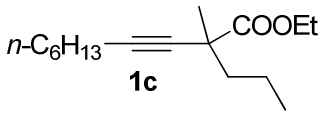
1a

Compound **1a** (Colorless oil , 74%): ^{1}H NMR (500 MHz, $CDCl_3$) 0.88 (t, *J* = 6.5 Hz, 3H), 0.95 (t, *J* = 7 Hz, 3H), 1.25-1.32 (m, 3H), 1.35-1.41 (m, 2H), 1.39 (s, 2H), 1.46-1.51 (m, 2H), 1.61-1.66 (m, 2H), 1.79-1.84 (m, H), 2.18 (t, *J* = 7 Hz, 2H), 4.16 (q, *J* = 7 Hz, 2H).



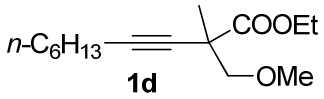
1b

Compound **1b** (Colorless oil , 67%) : ^{1}H NMR (500 MHz, $CDCl_3$) 0.85-0.89 (m, 6H), 1.24-1.33 (m, 17H), 1.39 (s, 3H), 1.35-1.45 (m, 2H), 1.45-1.51 (m, 2H), 1.55-1.61 (m,2H), 1.73-1.77 (m, 2H), 2.18 (t, *J* =7Hz, 2H), 4.16 (q, *J* = 7 Hz, 2H).



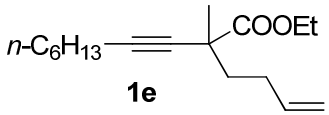
1c

Compound **1c** (Colorless oil , 54%) : ^{1}H NMR (500 MHz, $CDCl_3$) 0.87-0.92 (m, 6H), 1.25-1.31 (m, 7H), 1.31-1.38 (m, 4H), 1.40 (s, 3H), 1.44-1.50 (m, 2H), 1.54-1.60 (m, 1H), 1.73-1.79 (m, 1H), 2.18 (t, *J* = 6.5 Hz, 2H), 4.16 (q, *J* = 7.0 Hz, 2H).



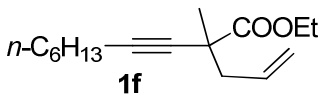
1d

Compound **1d** (Colorless oil , 90%) : ^{1}H NMR (500 MHz, $CDCl_3$) 0.85 (t, *J* = 7.0 Hz, 3H), 1.23-1.29 (m, 7H), 1.31-1.36 (m, 2H), 1.39 (s, 3H), 1.42-1.46 (m, 2H), 2.14 (t, *J* = 7.0 Hz, 2H), 3.33 (s, 3H), 3.45 (d, *J* = 8.5 Hz, 1H), 3.59 (d, *J* = 9.0 Hz, 1H), 4.16 (q, *J* = 7.0 Hz, 2H).



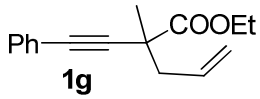
1e

Compound **1e** (Colorless oil , 81%) : ^{1}H NMR (500 MHz, $CDCl_3$) 0.88 (t, *J* = 6.5 Hz, 3H), 1.25-1.32 (m, 7H), 1.36-1.40 (m, 2H), 1.42 (s, 3H), 1.46-1.50 (m, 2H), 1.65-1.70 (m, 1H), 1.86-1.92 (m, 1H), 2.11-2.14 (m, 2H), 2.18 (d, *J* = 6.5 Hz, 2H), 4.16 (q, *J* = 6.5 Hz, 2H), 4.93-5.03 (m, 2H), 5.77-5.83 (m, 1H).



1f

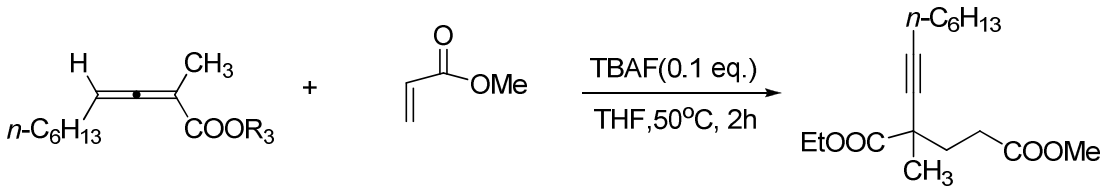
Compound **1f** (Colorless oil , 88%) : ^{1}H NMR (500 MHz, $CDCl_3$) 0.89 (t, *J* = 7.0 Hz, 3H), 1.26-1.31 (m, 7H), 1.4 (s, 3H), 1.38-1.52 (m, 4H), 2.19 (t, *J* = 6.5 Hz, 2H), 2.38-2.42 (m,1H), 2.52-2.56 (m, 1H), 4.17 (q, *J* =7Hz, 2H), 5.08-5.11 (m, 2H), 5.82-5.88 (m, 1H).



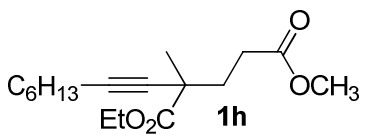
1g

Compound **1g** (Colorless oil , 79%): ^{1}H NMR (500 MHz, $CDCl_3$) 1.32 (t, *J* = 7.0 Hz, 3H), 1.55 (s, 3H), 2.53-2.57 (m, H), 2.67-2.71 (m, H), 4.24 (q, *J* = 7.0 Hz, 2H), 5.16-5.20 (m, 2H), 5.92-5.98 (m, 1H), 7.20-7.30 (m, 3H),7.44-7.45 (m, 2H).

General procedure for preparation of **1i and lh**:[2]

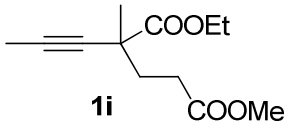


To a solution of ethyl α-methyl-γ-(*n*-hexyl)-allenoate (63 mg, 0.3 mmol) and methyl acrylate (31 mg, 0.36 mmol) in THF (2.0 mL) was add a solution of TBAF in THF (1.0 M solution in THF, 0.03 mL). The mixture was stirred for 2 hr at 50 ^{o}C, afterwards the solvent was removed under reduced pressure and the residue was subjected to a flash column chromatography (eluent: ethyl acetate/petroleum ether , 1:20) to give product **1h** (71 mg, 80%) as a colorless oil.



1h

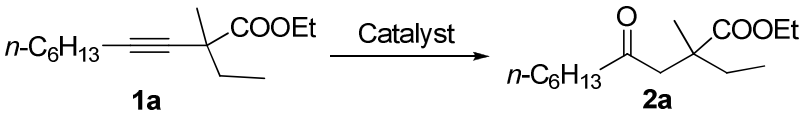
Compound **1h**: a colorless oil; IR (neat) ν 2933, 2859, 1739, 1437, 1238, 1024 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.87 (3H, t, *J* = 7.0 Hz), 1.26-1.50 (14H, m), 1.87-1.92 (1H, m), 1.93-2.18 (m, 3H), 2.39-2.45 (m, 1H), 2.49-2.55 (m, 1H), 3.66 (s, 3H), 4.16 (q, *J* = 7.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 14.0, 14.1, 18.7, 22.5, 26.0, 28.4, 28.7, 30.5, 31.3, 34.8, 42.2, 51.6, 61.4, 80.0, 84.1, 173.4, 173.6; MS (EI) *m/z* 286 (M^+, 100), 252, 214; Anal. Calcd. for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52. Found: C, 68.94; H, 9.61.



1i

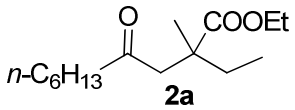
Compound **1i**: a colorless oil; IR (neat) ν 2983, 1738, 1443, 1241, 1115, 1022, 1126 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.24 (t, *J* = 7.0 Hz, 3H), 1.39 (s, 3H), 1.78 (s, 3H), 1.85-1.91 (m, 1H), 2.09-2.15 (m, 1H), 2.35-2.42 (m, 1H), 2.45-2.52 (m, 1H), 3.63 (s, 3H), 4.14 (q, *J* = 7.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 3.5, 14.0, 25.9, 30.4, 34.8, 42.2, 51.5, 61.4, 79.0, 79.4, 173.2, 173.5; MS (EI) *m/z* 226 (M^+, 100), 178, 151; Anal. Calcd. for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.90; H, 8.13.

General procedure for hydration of alkyne 1.



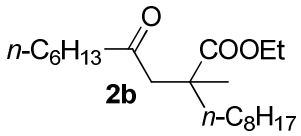
1a **2a**

$NaAuCl_4 \cdot 2H_2O$ (3mg, 5%) was added to a stirring solution of alkyne **1a** (71.4 mg, 0.3 mmol) in EtOH/H_2O (4:1, 1 mL). After stirring for 12-18h at r.t., the reaction mixture was concentrated under reduced pressure and the crude product was purified by flash silica gel chromatography (EtOAc/hexane 1: 20 - 1:4) to give the final product **2a** as a colorless oil (**60** mg, 78%).



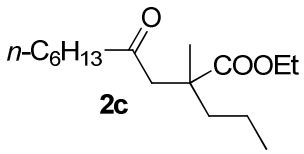
2a

IR (neat): 2957, 2930, 2859, 1734, 1457, 1177, 1134 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.83-0.89 (m , 6H), 1.20(s, 3H), 1.22-1.32 (m, 9H), 1.52-1.67 (m, 4H), 2.34-2.38 (m, 2H), 2.49 (d, *J* = 17.5 Hz, 1H), 2.89 (d, *J* = 17.5 Hz, 1H), 4.13 (q, *J* = 7.0 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 8.7, 14.2, 14.4, 21.3, 22.7, 24.0, 29.1, 31.8, 32.7, 43.6, 44.0, 50.8, 60.6, 176.8, 209.1; GC/MS (EI) *m/z:* 257, 211, 171, 143, 113, 85, 69, 42; HRMS (ESI) calcd. for $(C_{15}H_{28}O_3 + Na)^+$ 279.1936, found 279.1930.



2b

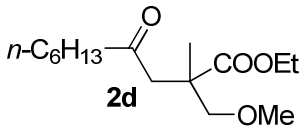
2b (Colorless oil , 93%): IR (neat): 2927, 2855, 2359, 1717, 1457, 1176 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.87 (t, *J* =7.0 Hz, 6H), 1.20-1.29 (m, 24H), 1.52-1.55 (m, 4H), 2.29-2.36 (m, 2H), 2.49 (d, *J* = 17.5 Hz, 1H), 2.88 (d, *J* = 17.5 Hz, 1H), 4.12 (q, *J* = 7.0 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 14.2, 14.3, 14.4, 21.8, 22.7, 22.9, 24.0, 24.3, 29.1, 29.4, 29.6, 30.2, 31.8, 32.1, 40.1, 43.6, 43.7, 51.1, 60.6, 176.9, 209.1; GC/MS (EI) *m/z:* 341, 295, 270, 227, 181, 163, 135, 112. HRMS (ESI) calcd. for $(C_{21}H_{40}O_3 + Na)^+$ 363.2875, found 363.2872.



2c

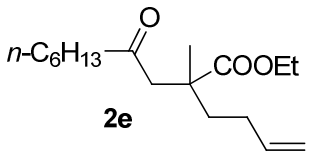
2c (Colorless oil , 74%): IR (neat): 2931, 2873, 1717, 1457, 1176 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.86-0.90 (m, 6H), 1.19-1.31 (m, 14H), 1.46-1.55 (m, 4H), 2.32-2.36 (m, 2H), 2.50 (d,

J = 17.5 Hz, 1H), 2.89 (d, *J* =17.5 Hz, 1H), 4.12 (q, *J* = 7.5 Hz, 2H); ^{13}C-NMR(125MHz, $CDCl_3$): δ 14.2, 14.4, 14.7, 17.6, 21.8, 22.7, 24.0, 29.1, 31.8, 42.4, 43.6, 43.8, 51.1, 60.6, 176.9, 209.1; GC/MS (EI) *m/z:* 271, 225, 197, 157, 112, 85, 42.



2d

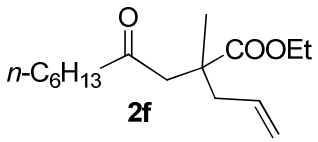
2d (Colorless oil , 89%): IR (neat): 2927, 2857, 2359, 1733, 1457, 1110 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85-0.88 (m, 3H), 1.21-1.29 (m, 12H), 1.52-1.55 (m, 2H), 2.36 (t, *J* =6.5 Hz, 2H), 2.63 (d, *J* =17.5 Hz, 1H), 2.90 (d, *J* = 17.5 Hz, 1H), 3.30 (s, 3H), 3.39 (d, *J* = 9.0 Hz, 1H), 3.53 (d, *J* = 9.0 Hz, 1H), 4.13 (q, *J* = 7.5Hz, 2H); ^{13}C-NMR(125MHz,$CDCl_3$):δ 14.2, 14.3, 21.3, 22.7, 24.0, 29.1, 29.9, 31.8, 43.5, 45.1, 47.0, 59.4, 60.8, 175.5, 209.3; GC/MS (EI) *m/z:* 273, 227, 187, 145, 99, 42.



2e

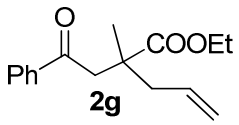
2e (Colorless oil , 91%): IR (neat): 2929, 2857, 1717, 1457, 1176, 910cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (t, *J* =7.0 Hz, 3H), 1.21-1.30 (m, 12H), 1.52-1.66 (m, 4H), 1.94-2.00 (m, 2H), 2.32-2.36 (m, 2H), 2.52 (d, *J* = 17.5 Hz, 1H), 2.89 (d, *J* = 17.5 Hz, 1H), 4.11 (q, *J* = 7.5 Hz, 2H), 5.72-5.77 (m, 1H), 4.93 (d, *J* =10.0 Hz, 1H), 4.99 (d, *J* =10.0Hz, 1H) ; ^{13}C-NMR(125MHz,$CDCl_3$): δ 14.2, 14.3, 21.8, 22.7, 24.0, 28.7, 29.1, 31.8, 39.1, 43.5, 51.0, 60.7,

114.9, 138.3, 176.6, 208.9; GC/MS (EI) *m/z:* 283, 237, 209, 182, 151, 95, 42. HRMS (ESI) calcd. for $(C_{17}H_{30}O_3 + Na)^+$ 305.2093, found 305.2084.



2f

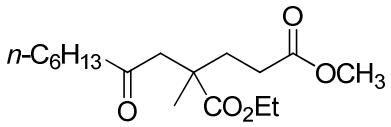
2f (Colorless oil , 91%): IR (neat): 2929, 2857, 2359, 1717, 1457, 1175, 917 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.86 (t, *J* =7.0 Hz, 3H), 1.20-1.29 (m, 12H), 1.50-1.53 (m, 2H), 2.31-2.34 (m, 4H), 2.53 (d, *J* = 17.5 Hz, 1H), 2.81 (d, *J* = 17.5 Hz, 1H), 4.09-4.13 (m, 2H), 5.00-5.06 (m, 2H), 5.66-5.71 (m, 1H); ^{13}C-NMR (125MHz, $CDCl_3$): δ 14.2, 14.3, 22.3, 22.7, 23.9, 29.0, 31.8, 43.3, 43.5, 43.6, 50.1, 60.7, 118.7, 133.6, 176.5, 208.9; GC/MS (EI) *m/z:* 269, 223, 195, 141, 113, 42. HRMS (ESI) calcd. for $(C_{16}H_{28}O_3 + Na)^+$ 292.1936, found 292.1934.



2g

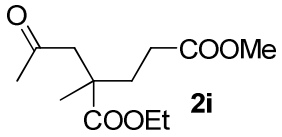
2g (Colorless oil , 58%): IR (neat): 2926, 1733, 1685, 1456, 1224, 753cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.20-1.26 (m, 3H), 1.32 (s, 3H), 2.45-2.47 (m, 2H), 3.16 (d, *J* =17.5 Hz, 1H), 3.41 (d, *J* =17.5 Hz, 1H), 4.15 (q, *J* = 7.5 Hz, 2H), 5.06-5.10 (m, 2H), 5.75-5.81 (m, H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.56 (t, *J* = 7.0 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 14.4,

22.4, 43.4, 43.7, 46.4, 60.7, 118.9, 128.1, 128.8, 133.3, 133.6, 137.4, 176.6, 197.8; GC/MS (EI) *m/z:* 261, 215, 187, 170, 141, 105, 77; Anal. Calcd. for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.97; H, 8.00.



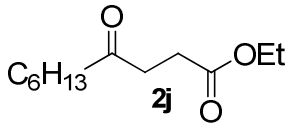
2h

2h (Colorless oil , 92%): IR (neat): 2928, 2856, 1734, 1457, 1175cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.22-1.31 (m, 12H), 1.53-1.56 (m, 2H), 1.82-1.87 (m, 1H), 1.92-1.98 (m, 1H), 2.27-2.37 (m, 4H), 2.55 (d, *J* = 17.5 Hz, 1H), 2.88 (d, *J* = 17.5Hz, H), 3.67 (s, 3H), 4.13 (q, *J* = 7.0 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 14.2, 14.3, 21.7, 22.7, 24.0, 29.0, 29.5, 31.8, 34.4, 43.0, 43.5, 51.0, 51.9, 60.9, 173.9, 176.0, 208.6; GC/MS (EI) *m/z:* 315, 269, 229, 201, 155, 85;



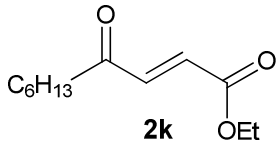
2i

2i (Colorless oil , 80%): IR (neat): 2981, 2361, 1734, 1363, 1176, 1117, 1026 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23-1.25 (m, 6H), 1.82-1.88 (m, 1H), 1.92-1.98 (m, 1H), 2.12 (s, 3H), 2.25-2.33 (m, 2H), 2.57 (d, *J* = 17.5 Hz, 1H), 2.92 (d, *J* = 17.5 Hz, 1H), 3.67 (s, 3H), 4.13 (q, *J* = 7.5 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 14.3, 21.7, 29.5, 30.7, 34.3, 43.1, 51.8, 51.9, 61.0, 173.8, 176.0, 206.1; GC/MS (EI) *m/z:* 245, 200, 141, 113, 85; Anal. Calcd. for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 59.41; H, 8.41.



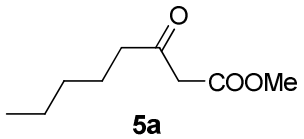
2j

2j (Colorless oil , 74%): IR (neat): 2929, 2858, 1735, 1373, 1187, 1033 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.5 Hz, 3H), 1.24-1.30 (m, 9H), 1.57-1.60 (m, 2H), 2.44 (t, *J* = 7.5 Hz, 2H), 2.57 (t, *J* = 6.5 Hz, 2H), 2.71 (t, *J* = 6.0 Hz, 2H), 4.12 (q, *J* = 7.0 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 14.2, 14.4, 22.7, 24.0, 28.2, 29.1, 31.8, 37.2, 43.1, 60.8, 173.1, 209.5; GC/MS (EI) *m/z:* 215, 169, 144, 127, 113, 98, 85, 69.



2k (Colorless oil , 74%): IR (neat): 2930, 2858, 1727, 1466, 1302, 1182, 1033 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.87 (t, *J* = 7.0 Hz, 3H), 1.25-1.33 (m, 9H), 1.61-1.64 (m, 2H), 2.62 (t, *J* = 7.0 Hz, 2H), 4.26 (q, *J* = 7.0 Hz, 2H), 6.66 (d, *J* = 16.5 Hz, 1H), 7.05 (d, *J* = 16.5 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 14.2, 14.3, 22.7, 23.9, 29.0, 31.8, 41.8, 61.6, 130.9, 140.0, 165.8, 200.2; GC/MS (EI) *m/z:* 213, 169, 139, 127, 114, 97, 85, 69, 56; Anal. Calcd. for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 68.38; H, 9.79.

Synthesis of compound 5.



Compound **3c** (Colorless oil , 76%): IR (neat): 2955, 2860, 2359, 1749, 1716, 1320, 1241, 1154, 1014 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.86 (t, *J* = 7.0 Hz, 3H), 1.23-1.30 (m, 4H), 1.56-1.59

(m, 2H), 2.50 (t, J = 7.5 Hz, 2H), 3.42 (s, 2H), 3.71 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 14.1, 22.6, 23.3, 31.3, 43.2, 49.2, 52.5, 167.9, 203.1; GC/MS (EI) *m/z:* 173, 130, 100, 40. GC/MS (EI) *m/z:* 269, 223, 195, 141, 113, 42. HRMS (ESI) calcd. for $(C_9H_{16}O_3 + Na)^+$ 195.0997, found 195.0998.

References:

(1) Wang, W.; Xu, B.; Hammond, G. B. *Org. Lett.* **2008**, *10*, 3713-3716.

(2) Liu, L.-P.; Xu, B.; Hammond, G. B. *Org. Lett.* **2008**, *10*, 3887-3890.