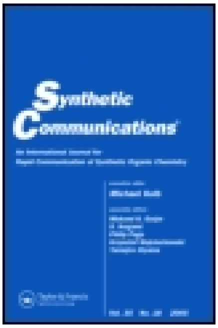

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A New Route to Substituted Glutaric Acid Derivatives from Allylic Malonates

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A NEW ROUTE TO SUBSTITUTED GLUTARIC ACID DERIVATIVES FROM ALLYLIC MALONATES.

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Abstract: A new, high yielding route to substituted glutaric acid derivatives *via* an ester enolate Claisen rearrangement of allylic malonates is described.

The synthetic utility of the Baylis-Hillman reaction[1] has been demonstrated in a number of preparations of necic acid synthons[2], but further elaboration of the 2-hydroxy-α-substituted acrylate unit *via* a Claisen rearrangement has received little attention. The Claisen rearrangement and its variations are a potentially powerful tool in the modification of 2-hydroxy-α-substituted acrylates towards natural product synthesis. This was first demonstrated by Gopalan *et al.*[3,4], who reported the acid catalysed [3, 3]-sigmatropic rearrangement of α-(*p*-cresoxy-methyl) acrylic acid to yield a coumarin derivative. Drewes *et al.*[5] subsequently reported a synthesis of 4-methyl-3-methylene-3,4-dihydrocoumarin from ethyl 3-

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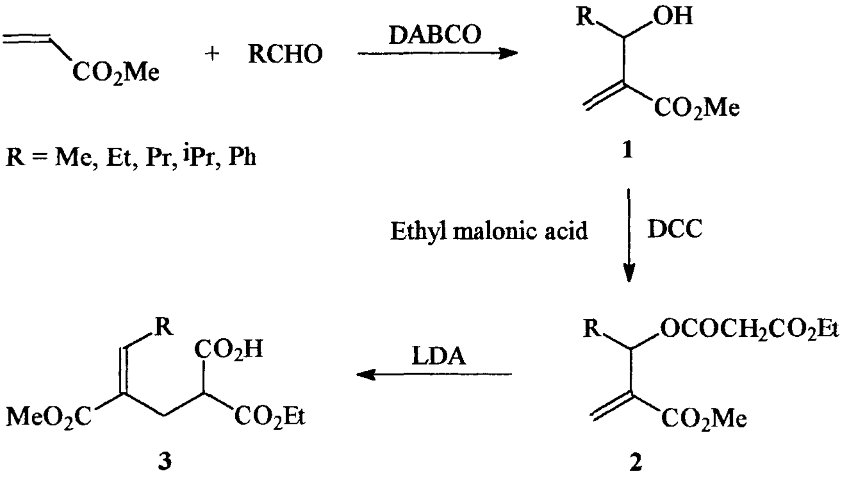
hydroxy-2-methylene-butanoate. Drewes and co-workers[5] furthered these studies to include the use of the Johnson orthoester Claisen rearrangement of allylic alcohol derivatives to prepare necic acid derivatives.

An interest in naturally occurring glutaric acid derivatives led to an investigation into the preparation of α-alkylmethylene- and α-arylmethylene-glutarates *via* the ester enolate Claisen rearrangement of allylic malonates.

The allylic alcohols **1a** -**1e** were prepared *via* the Baylis-Hillman reaction in high yield and the malonate ester group was introduced by the DCC esterification of **1** with ethyl malonic acid.[6] Subsequent Claisen rearrangement of the allylic malonates (**2a** - **2e**) yielded the substituted glutarates (**3a** - **3e**) in high yield with good (E)-selectivity, as shown in the Scheme and Table.



Scheme

Table: Yields of allylic alcohols (**1**), allylic malonates (**2**) and glutarates (**3**).

	R	% Yield of **1**	% Yield of **2**	% Yield of **3**	E : Z ratio of **3**[a]
a	Me	81	90	89	93 : 7
b	Et	83	88	92	95 : 5
c	Pr	80	84	83	91 : 9
d	^{i}Pr	76	94	78	93 : 7
e	Ph	85	84	79	90 : 10

[a] Determined by ^{1}H-nmr.

Experimental:

^{1}H-NMR and ^{13}C-NMR spectra were obtained using a Varian Gemini 200 spectrometer, mass spectra were obtained using a HP5988A Hewlett-Packard gas chromatographic-mass spectrometer and elemental analysis was carried out on a Perkin-Elmer 2400 CHN elemental analyser.

General procedure for the preparation of allylic malonates (**2a** - **2e**).

Allylic alcohol (**1**) (0.023 mol) was added to a solution of DCC (0.030 mol) in dry CH_2Cl_2 (50ml), followed by ethyl malonic acid (0.030 mol) at 0^oC (ice-bath). The mixture was allowed to warm to rt and stirred for 6h. The white precipitate of dicyclohexyl urea was filtered off and the solvent removed. The residue was dissolved in diethyl ether (50ml), filtered, and washed with 3M HCl (2x 50ml), 10% aq. $NaHCO_3$ (2x 50ml) and finally water (50ml). The organic layer was dried over anhydrous $MgSO_4$, the solvent removed and distilled to afford **2**.

2a Yield 90%, b.p. 150°/5mmHg. Anal. Calcd. for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60; Found: C, 54.19; H, 6.47. ^{1}H (200MHz) 1.30 (3H, t, $\mathrm{OCH_2C}H_3$), 1.43 (3H, d, $\mathrm{CHC}H_3$), 3.40 (2H, s, $\mathrm{O_2CC}H_2\mathrm{CO_2}$), 3.78 (3H, s, $\mathrm{OC}H_3$), 4.21 (2H, q, $\mathrm{OC}H_2\mathrm{CH_3}$), 5.75 (1H q, $\mathrm{C}H\mathrm{-O}$), 5.88 and 6.31 (2H, 2x s, $\mathrm{C}H_2\mathrm{=C}$); ^{13}C (50MHz) 14.09 (q, $\mathrm{OCH_2}C\mathrm{H_3}$), 20.10 (q, $\mathrm{CH}C\mathrm{H_3}$), 41.75 (t, $\mathrm{O_2C}C\mathrm{H_2CO_2}$), 52.00 (q, $\mathrm{O}C\mathrm{H_3}$), 61.53 (t, $\mathrm{O}C\mathrm{H_2CH_3}$), 69.42 (d, $C\mathrm{HCH_3}$), 125.08 (t, $C\mathrm{H_2=C}$), 140.49 (s, $C\mathrm{=CH_2}$), 165.35 and 165.53 (2x s, $\mathrm{O_2}C\mathrm{CH_2}C\mathrm{O_2}$), 166.42 (s, $C\mathrm{O_2CH_3}$); *m/z* 212 (M^+-32, 5%), 129 (94), 115 (83), 112 (100), 97 (79), 81 (49), 43 (38).

2b Yield 88%, b.p. 165°C/5mmHg. Anal. Calcd. for $C_{12}H_{18}O_6$: C, 55.81; H, 7.03; Found: C, 55.57; H, 7.00. ^{1}H (200MHz) 0.92 (3H, t, $\mathrm{CHCH_2C}H_3$), 1.28 (3H, t, $\mathrm{OCH_2C}H_3$), 1.75 (2H, m, $\mathrm{CHC}H_2\mathrm{CH_3}$), 3.42 (2H, s, $\mathrm{O_2CC}H_2\mathrm{CO_2}$), 3.77 (3H, s, $\mathrm{OC}H_3$), 4.20 (2H, q, $\mathrm{OC}H_2\mathrm{CH_3}$), 5.62 (1H, m, $\mathrm{C}H\mathrm{-O}$), 5.84 and 6.31 (2H, 2x s, $\mathrm{C}H_2\mathrm{=C}$); ^{13}C (50MHz) 9.47 (q, $\mathrm{CHCH_2}C\mathrm{H_3}$), 14.11 (q, $\mathrm{OCH_2}C\mathrm{H_3}$), 27.22 (t, $\mathrm{CH}C\mathrm{H_2CH_3}$), 41.75 (t, $\mathrm{O_2C}C\mathrm{H_2CO_2}$), 51.99 (q, $\mathrm{O}C\mathrm{H_3}$), 61.53 (t, $\mathrm{O}C\mathrm{H_2CH_3}$), 74.01 (d, $C\mathrm{HCH_2CH_3}$), 125.53 (t, $C\mathrm{H_2=C}$), 139.35 (s, $C\mathrm{=CH_2}$), 165.55 and 165.58 (2x s, $\mathrm{O_2}C\mathrm{CH_2}C\mathrm{O_2}$), 166.47 (s, $C\mathrm{O_2CH_3}$); *m/z* 226 (M^+-32, 2%), 143 (38), 126 (75), 115 (100), 111 (64), 67 (46), 43 (25).

2c Yield 84%, b.p. 195°C/5mmHg. Anal. Calcd. for $C_{13}H_{20}O_6$: C, 57.34; H, 7.40; Found: C, 57.05; H, 7.40. ^{1}H (200MHz) 0.92 (3H, t, $\mathrm{CH_2CH_2C}H_3$), 1.28 (3H, t, $\mathrm{OCH_2C}H_3$), 1.35 (2H, m, $\mathrm{CH_2C}H_2\mathrm{CH_3}$), 1.72 (2H, m, $\mathrm{C}H_2\mathrm{CH_2CH_3}$), 3.41 (2H, s, $\mathrm{O_2CC}H_2\mathrm{CO_2}$), 3.77 (3H, s, $\mathrm{OC}H_3$), 4.19 (2H, q, $\mathrm{OC}H_2\mathrm{CH_3}$), 5.67 (1H, m, $\mathrm{C}H\mathrm{-O}$), 5.84 and 6.30 (2H, 2x s, $\mathrm{C}H_2\mathrm{=C}$); ^{13}C (50MHz) 13.69 (q, $\mathrm{CHCH_2CH_2}C\mathrm{H_3}$), 14.10 (q, $\mathrm{OCH_2}C\mathrm{H_3}$), 18.57 (t, $\mathrm{CH_2}C\mathrm{H_2CH_3}$), 36.42 (t, $C\mathrm{H_2CH_2CH_3}$), 41.75 (t, $\mathrm{O_2C}C\mathrm{H_2CO_2}$), 51.98 (q, $\mathrm{O}C\mathrm{H_3}$), 61.54 (t, $\mathrm{O}C\mathrm{H_2CH_3}$), 72.79 (d, $C\mathrm{H\text{-}O}$), 125.32 (t, $C\mathrm{H_2=C}$), 139.76 (s, $C\mathrm{=CH_2}$), 165.54 and 165.58 (2x s, $\mathrm{O_2}C\mathrm{CH_2}C\mathrm{O_2}$), 166.45 (s, $C\mathrm{O_2CH_3}$); *m/z* 240 (M^+-32, 2%), 157 (31), 141 (28), 140 (35), 125 (100), 115 (90), 109 (26), 81 (52), 43 (34).

2d Yield 94%, b.p. 200°C/5mmHg. Anal. Calcd. for $C_{13}H_{20}O_6$: C, 57.34; H, 7.40; Found: C, 57.57; H, 7.53. ^{1}H (200MHz) 0.94 (6H, 2x d, $CH(CH_3)_2$), 1.29 (3H, t, OCH_2CH_3), 2.09 (1H, m,$CH(CH_3)_2$), 3.41 (2H, s, $O_2CCH_2CO_2$), 3.78 (3H, s, OCH_3), 4.21 (2H, q, OCH_2CH_3), 5.53 (1H, d, *CH*-O), 5.79 and 6.34 (2H, 2x s, CH_2=C); ^{13}C (50MHz) 14.11 (q, OCH_2CH_3), 16.66 and 18.99 (2x q, $CH(CH_3)_2$), 31.31 (d, $CH(CH_3)_2$), 41.73 (t, $O_2CCH_2CO_2$), 51.99 (q, OCH_3), 61.55 (t, OCH_2CH_3), 77.14 (d, *C*H-O), 126.24 (t, CH_2=C), 138.67 (s, *C*=CH_2), 165.54 and 165.69 (2x s, $O_2CCH_2CO_2$), 166.42 (s, CO_2CH_3); *m/z* 240 (M^+-32, 5%), 230 (49), 198 (59), 140 (52), 115 (100).

2e Yield 84%, b.p. 235-240°C/5mmHg. Anal. Calcd. for $C_{16}H_{18}O_6$: C, 62.74; H, 5.92; Found: C, 62.49; H, 6.12. ^{1}H (200MHz) 1.22 (3H, t, OCH_2CH_3), 3.41 (2H, s, $O_2CCH_2CO_2$), 3.68 (3H, s, OCH_3), 4.16 (2H, q, OCH_2CH_3), 5.93 and 6.41 (2H, 2x s, CH_2=C), 6.72 (1H, s, *CH*-O), 7.35 (5H, m, Ar-*H*); ^{13}C (50MHz) 14.00 (q, OCH_2CH_3), 41.69 (t, $O_2CCH_2CO_2$), 51.99 (q, CO_2CH_3), 61.56 (t, OCH_2CH_3), 74.19 (d, *C*H-O), 126.14 (t, CH_2=C), 127.70, 128.48 and 128.57 (3x d, Ar-*C*), 137.18 (s, Ar-*C*), 139.04 (s, CH_2=*C*), 164.98 and 165.20, (2x s, $O_2CCH_2CO_2$), 166.20 (s, CO_2CH_3); *m/z* 306 (M^+, <1%), 191 (78), 159 (47), 115 (100), 105 (77), 59 (10).

General procedure for the preparation of glutarates (**3a** - **3e**).

Diisopropylamine (0.003mol) in dry THF (25ml) was cooled to 0°C (ice bath) with stirring under N_2. nBuLi (0.002mol) in hexane was added dropwise and the resulting LDA stirred for a further 30min at 0°C. The mixture was then cooled to -78°C (acetone/dry ice) and allylic malonate (**2**) (0.002mol) in dry THF (5ml) was added dropwise. The mixture was kept at -78°C for a further 3h and then allowed to warm to rt. The mixture was kept at rt for 1h and then quenched with 3M HCl (50ml). The organic layer was separated and extracted with 10% aq. $NaHCO_3$ (3x 50ml). The combined aqueous extracts were acidified with 50% HCl and extracted with diethyl ether (3x 50ml). The organic extracts were combined, dried over anhydrous $MgSO_4$ and the solvent removed. The crude product was chromatographed on silica, using 30% diethyl ether/hexane as eluent, to afford **3**. The glutarates decarboxylate readily on heating (*ca* 120 °C), so boiling points or GC/MS data could not be obtained.

3a Yield 89%, (E)/(Z) = 93 : 7. Anal. Calcd. for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60; Found: C, 53.91; H, 6.51. ^{1}H (200MHz) 1.27 (3H, t, CH_2CH_3), 1.85 (3H, d, $CHCH_3$), 2.93 (2H, d, $CHCH_2$), 3.75 (3H, s, OCH_3), 3.75 (1H, t, $CHCO_2H$), 4.19 (2H, q, CH_2CH_3), 7.03 (1H, q, $CHCH_3$((Z)-isomer, 6.25)), 9.98 (1H, s, CO_2H); ^{13}C (50MHz) 14.01 (q, CH_2CH_3), 14.55 (q, $CHCH_3$), 25.79 (t, $CHCH_2$), 50.48 (d, $CHCH_2$), 51.91 (q, OCH_3), 61.81 (t, CH_2CH_3), 128.35 (s, C=CH), 141.67 (d, $CHCH_3$), 167.47 (s, CO_2CH_3), 168.86 (s, $CO_2CH_2CH_3$), 174.53 (s, CO_2H).

3b Yield 92%, (E)/(Z) = 95 : 5. Anal. Calcd. for $C_{12}H_{18}O_6$: C, 55.81; H, 7.03; Found: C, 55.68; H, 6.94. ^{1}H (200MHz) 1.03 (3H, t, $CHCH_2CH_3$), 1.27 (3H, t, OCH_2CH_3), 2.26 (2H, t, $CHCH_2CH_3$), 2.91 (2H, d, CH_2CHCO_2H), 3.75 (3H, s, OCH_3), 3.75 (1H, t, $CHCO_2H$), 4.17 (2H, q, OCH_2CH_3), 6.89 (1H, t, CH=C, ((Z)-isomer, 6.10)), 9.68 (1H, s, CO_2H); ^{13}C (50MHz) 13.17 (q, $CHCH_2CH_3$), 14.00 (q, OCH_2CH_3), 22.07 (t, $CHCH_2CH_3$), 26.10 (t, CH_2CHCO_2H), 50.63 (d, $CHCO_2H$), 51.89 (q, OCH_3), 61.77 (t, OCH_2CH_3), 126.69 (s, C=CH), 148.31 (d, $CHCH_2CH_3$), 167.60 (s, CO_2CH_3), 168.82 (s, $CO_2CH_2CH_3$), 174.50 (s, CO_2H).

3c Yield 85%, (E)/(Z) = 91 : 9. Anal. Calcd. for $C_{13}H_{20}O_6$: C, 57.34; H, 7.40; Found: C, 57.21; H, 7.51. ^{1}H (200MHz); 0.88 (3H, t, $CH_2CH_2CH_3$), 1.18 (3H, t, OCH_2CH_3), 1.40 (2H, m, $CH_2CH_2CH_3$), 2.17 (2H, q, $CH_2CH_2CH_3$), 2.87 (2H, d, CH_2CHCO_2H), 3.70 (3H, s, OCH_3), 3.71 (1H, s, $CHCO_2H$), 4.13 (2H, q, OCH_2CH_3), 6.86 (1H, t, CH=C, ((Z)-isomer, 6.07)), 11.06 (1H, s, CO_2H); ^{13}C (50MHz) 13.86 (q, $CH_2CH_2CH_3$), 14.01 (q, OCH_2CH_3), 22.01 (t, $CH_2CH_2CH_3$), 26.17 (t, CH_2CHCO_3H), 30.68 (t, $CH_2CH_2CH_3$), 50.68 (d, $CHCO_2H$), 51.93 (q, OCH_3), 61.79 (t, OCH_2CH_3), 127.36 (s, C=CH), 146.91 (d, C=CH), 167.66 (s, CO_2CH_3), 168.83 (s, $CO_2CH_2CH_3$), 174.67 (s, CO_2H).

3d Yield 78%, (E)/(Z) = 93 : 7. Anal. Calcd. for $C_{13}H_{20}O_6$: C, 57.34; H, 7.40; Found: C, 57.42; H, 7.38. ^{1}H (200MHz) 0.95 (6H, 2x d, $CH(CH_3)_2$), 1.25 (3H, t, OCH_2CH_3), 1.60 (1H, m, $CH(CH_3)_2$), 2.91 (2H, d, CH_2CHCO_2H), 3.73 (3H, s, OCH_3), 3.74 (1H, t, $CHCO_2H$), 4.15 (2H, q, OCH_2CH_3), 6.67 (1H, d, CH=C, ((Z)-isomer, 5.50)), 8.80 (1H, s, CO_2H); ^{13}C (50MHz) 14.04 (q, OCH_2CH_3), 22.11 and 22.15 (2x q, $CH(CH_3)_2$), 26.27 (t, CH_2CHCO_2H), 27.95 (d, $CH(CH_3)_2$), 50.74 (d, $CHCO_2H$), 51.87 (q, OCH_3), 61.77 (t, OCH_2CH_3), 124.83 (s, C=CH), 153.08 (d, C=CH), 167.76 (s, CO_2CH_3), 168.90 (s, $CO_2CH_2CH_3$), 174.43 (s, CO_2H).

3e Yield 79%, (E)/(Z) = 90 : 10. Anal. Calcd. for $C_{16}H_{18}O_6$: C, 62.74; H, 5.92; Found: C, 62.60; H, 5.95. ^{1}H (200MHz) 1.15 (3H, t, OCH_2CH_3), 3.21 (2H, m, CH_2CHCO_2H), 3.81 (3H, s, OCH_3), 3.81 (1H, t, $CHCO_2H$), 4.19 (2H, q, OCH_2CH_3), 7.36 (5H, s, Ar-H), 7.81 (1H, s, CH=C), 10.52 (1H, s, CO_2H); ^{13}C (50MHz) 13.85 (q, OCH_2CH_3), 26.28 (t, CH_2CHCO_2H), 50.37 (d, $CHCO_2H$), 52.21 (q, OCH_3), 61.72 (t, OCH_2CH_3), 128.43 (s, C=CH), 128.62, 128.77 and 129.07 (3x d, Ar-C), 134.83 (s, Ar-C), 142.43 (d, C=CH), 168.06 (s, CO_2CH_3), 168.65 (s, $CO_2CH_2CH_3$), 174.92 (s, CO_2H).

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