Pergamon

Tetrahedron 54 (1998) 15305–15320

TETRAHEDRON

Lithium Enediolates and Dienediolates of Carboxylic Acids in Synthesis: Alkylation with Secondary Halides.

Eva M. Brun, Salvador Gil, Ramón Mestres and Margarita Parra*

Departament de Química Orgánica, Universitat de València, Burjassot, València, Spain

Received 7 August 1998; revised 25 September 1998; accepted 14 October 1998

Abstract

High yields in the alkylation of dianions of α,β-unsaturated carboxylic acids with secondary halides can be obtained despite elimination reactions occurring. α-Regioselectivity for the alkylation of but-2-enoic acids (**1-4**) is seldom obtained. Although double bond stereoselectivity is higher than 99% for γ-alkylated products, stereoselectivity is rather poor for most of the α-alkylated products.

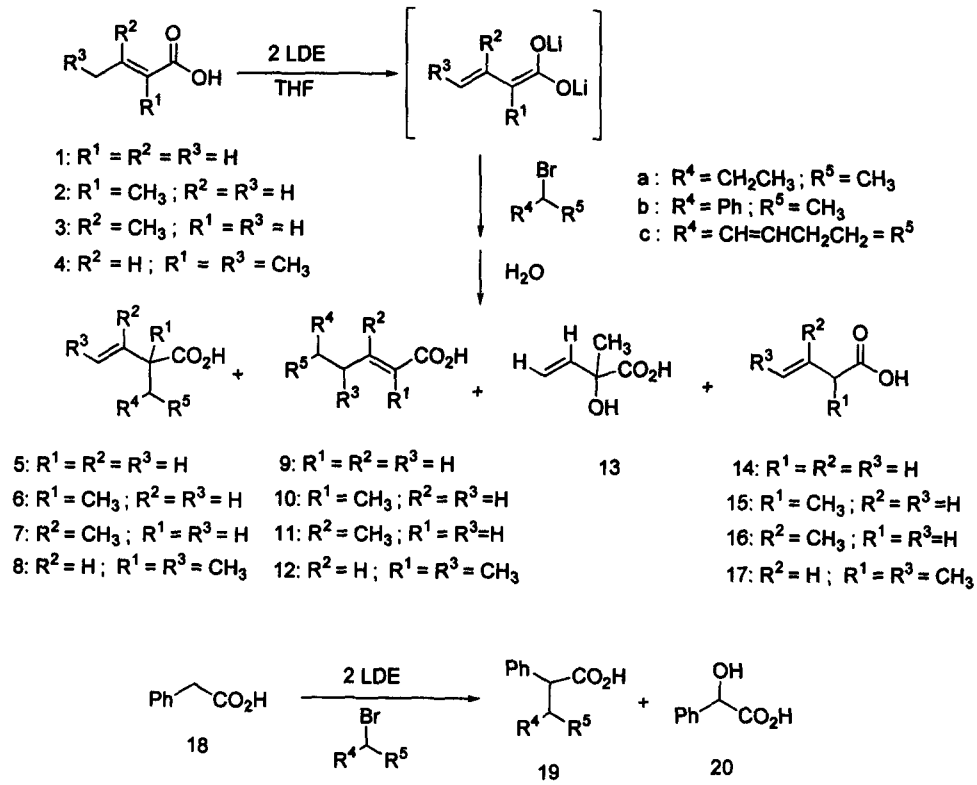
Keywords: Alkylation; Carboxylic acids; Lithium Enolates.

Double deprotonation of carboxylic acids by lithium dialkylamides is the most common method of generation of their lithium dienolates [1,2]. Regio and stereoselectivity studies of their reaction with several electrophiles have been reported [1-5]. Alkylation of the π-extended enolates of unsaturated carboxylic acids with primary halides is known to proceed through the α-carbon rather than the γ-carbon [6]. This selectivity can be reversed by counterion interchange with copper(I) salts, though only when allylic halides are used as electrophiles [7]. Surprisingly, alkylation of these dienolates with secondary halides has remained unexplored (Scheme 1), probably due to the elimination reactions which often compete under the basic reaction medium when nucleophilic attack is very slow [6].

Since alkylation should allow the easy synthesis of highly branched β,γ-unsaturated

0040-4020/98/$ - see front matter
PII: S0040-4020(98)00957-0

carboxylic acids, key starting point for butenolide synthesis [8], we have attempted alkylation of the enediolates of carboxylic acids with secondary bromides. Herein we report our results.



Scheme 1

The present alkylations were carried out under a set of standard conditions [9], originally devised for preparative purposes: usually 2.25 mmol of both the dienediolate and the halide, and a slight excess (4.8 mmol) of lithium diethylamide (LDE) as base. After slow addition (about 5 minutes) of the halide in THF, to the dienediolate in the same solvent at -78°C, the solution was stirred at room temperature for a period of time, between 7 and 24 hours, which was optimised for each halide and acid. After work-up a clean mixture of acids was obtained in every case. Enediolate generation is easier for unsaturated than for saturated acids. In the latter cases generation of the enediolates must be carried out at low temperature, as warming up to room

temperature, causes reprotonation from the amine.

The results obtained in the alkylation of phenylacetic acid (**18**), as a reference of α-deprotonation acids, and several α,β-unsaturated acids (**1-4**) with 2-bromobutane **a**, 1-phenyl-1-bromoethane **b** and 3-bromocyclohexene **c** are summarised in Table 1.

Table 1

Alkylation of dienolates of carboxylic acids with secondary halides

Entry	Starting acid	Bromide	Yield[a] (%)	Ratio of products: Starting acid	α	γ	Deconjugated acid
1	**1**	**a**	52		100		
2	**2**	**a**	55	31	29		6
3	**3**	**a**	71		82	18	
4	**4**	**a**	68	25	54	8	13
5	**18**	**a**	76	11	75		
6	**1**	**b**	67		83	17	
7	**2**	**b**	83		45	55	
8	**3**	**b**	75		73	27	
9	**4**	**b**	65	37	32	31	
10	**18**	**b**	80	13	87		
11	**1**	**c**	72	5	78	17	
12	**2**	**c**	82		65	35	
13	**3**	**c**	85	13	63	24	
14	**4**	**c**	72	7	61	26	6
15	**18**	**c**	76	6	94		

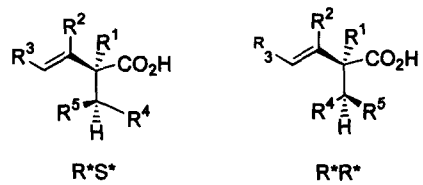
a.- Before isolation.

Whenever comparison is possible, lower α/γ alkylation ratio is obtained in most cases when compared to the corresponding primary bromides [6] and reactions are slower. Thus, for short reaction times the starting material is recovered either in the original form, α,β-unsaturated carboxylic acid (**1-4**), or as the deconjugated β,γ-unsaturated carboxylic acid (**14-17**) (from protonation at the α-position). As the alkylation becomes slower, lower yields are obtained, most probably due to an elimination reaction. In some cases, the elimination products have been detected in neutral fractions. Accordingly to what is usual [10-12], E-γ-adducts are selectively obtained from dianions of unsaturated carboxylic acids (**1,2** and **4**) with no further substituent at the β-carbon, in contrast to the Z-γ-adducts which are found on reaction of the lithium dianions of β-substituted acids (such as **3**) with electrophiles. In contrast with this high selectivity, product **11b** showed only a 2:1 Z/E ratio, probably due to the fact that obtention of a Z-γ-adduct implies, in this case, attack of a bulky electrophile onto a more crowded *s-cis* conformation of

the dianion. The double bond geometry has been determined by nOe experiments, when feasible, and by comparation of their ^{1}H nmr chemical shift and coupling constants with those of well stablished similar γ adducts [6].

Most surprisingly, reactions of poorly reactive bromides with tiglic and phenylacetic acid dianions afford α-hydroxyacids **13** and **20** in 34% and 14% yield respectively (entries 2 and 5). To rule out any contribution from the electrophile, a solution of the dianion of tiglic **2** or phenylacetic acid **18**, in THF, was left overnight under an argon atmosphere and similar yields of α-hydroxyacids were obtained.

Poor diastereoselectivity for most of the α-alkylated products has been observed. Thus, reaction with 2-bromobutane **a** lead to a similar diastereoisomeric ratio (R*S*, R*R* ≅ 4:1 except for **6a**, 1:1) (configurations determined by nOe experiments, when feasible). With 1-phenyl-1-bromoethane **b** and 3-bromocyclohexene **c**, a similar ratio result (R*S*, R*R* ≅ 2:1) in most cases. Higher diastereoselectivity was attained for products **7b** (8:1), **5c** (4:1) and, under optimised conditions, for **6b** (5:1).



Scheme 2

In the alkylation of lithium dienediolates of carboxylic acids with primary halides improved results, in relation to the use of LDE as base, had been obtained when the amide was generated from thienyl or butyllithium and 1,3,3-trimethyl-6-azabicyclo-3.2.1-octane [7] (TABO). Accordingly, we have assayed these reaction conditions for secondary bromides and some of the results are summarised in Table 2.

Table 2

Alkylation of dienolates of carboxylic acids, generated from different bases, with 2-bromobutane

Entry	Acid	Amide generated from: Amine	Organolithium	Yield (%)	Ratio of products α	γ	Other acids
1	1	DEA	2-thienyl	43	100		
2	1	TABO	butyl	51	57		43[a]
3	1	TABO	2-thienyl	34	56		44[a]
4	2	TABO	butyl	70	50	33	17[b]
5	2	TABO[c]	2-thienyl	82	42	42	16[b]

a.- α,α-Dialkylated product

b.- α-Hydroxyacid **13**

c.- Dienolate generated from thienyllithium (2eq.) and this amine (0.3eq.)

It may be noticed that, under unoptimised reaction conditions, a poor yield and a higher α/γ regioselectivity ratio is observed (entry 2 of Table1) but, as soon as a normal yield is attained, the α/γ ratio becomes similar to that of the other examples (entries 4 and 5 of Table 2). This can be explained assuming that α-alkylation is quicker than γ-alkylation and, as the reaction proceeds γ-alkylation predominates. This observation is in agreement with previous results on alkylation with primary halides [6]. The regioselectivity shift along the progress of the reaction may be due to the chemical species resulting from the alkylation, namely lithium bromide and/or the lithium salt of the acid. When the alkylation of tiglic acid **2** with 1-phenylbromoethane **b** was carried out in the presence of 2 equivalents of lithium bromide added to the solution before the base, a higher γ-alkylation ratio resulted (47% yield, α/γ 40:60) which contrasts with the trend observed in alkylation with benzylbromide [6].

On the other hand generation of the dienolate with a catalytic amount of amine led to comparable results to those obtained when a stoichiometric amount is used which follows the trend of our preliminary results [9].

In conclusion, α,β-unsaturated acids can be alkylated, in good yield, with secondary halides but regio- and diastereoselectivites are low except for a limited number of substrates. We have found that the regioselectivity of the alkylation strongly depends on the reactivity of the electrophile and, accordingly, the next step will be the study of other leaving groups in order to increase both regio- and diastereoselectivities.

Experimental Part

Melting points were determined on a Reichert apparatus and are uncorrected. IR spectral data were obtained for liquid film or KBr discs, with a Perkin-Elmer 281 spectrophotometer. NMR spectra were recorded for $CDCl_3$ solutions, with Varian Unity 300 or Unity 400 spectrometers. Elemental analyses were determined by "Servicio de Semimicroanálisis del Centro de Investigación y Desarrollo (CSIC) de Barcelona". Mass spectra were determined with a UG Autoespec spectrometer. Silica gel Merck 60 (230-400 mesh) was used for flash column chromatography, with hexane/ether mixtures as eluent.

All reactions were carried out under argon in oven dried glassware, in THF freshly distilled from blue benzophenone ketyl and with diethylamine distilled from CaH_2.

General procedure for alkylation of carboxylic acids.- Carboxylic acid (2.25 mmol) in THF (2 ml) was slowly added to stirred lithium diethylamide or the amide generated from 1,3,3-trimethyl-6-azabicyclo-3.2.1-octane (4.8 mmol) in THF (2 ml) at -78°C, by cooling with CO_2/acetone bath (prepared according to the method already described [9]). The solution was stirred for 30 minutes at 0°C for unsaturated acids (-78°C for phenylacetic acid), and cooled again at -78°C. Halide (2.25 mmol) in THF (2 ml) was added dropwise, and the solution stirred at room temperature for a period which is indicated in each case. Water was added and extracted with (3x15 ml) diethyl ether. The aqueous layer was acidified under ice-cooling by careful addition of conc. HCl, and then extracted with (3x15 ml) ethyl acetate. The organic layer was washed with water, aqueous NaCl, and water, and dried. Evaporation of the solvent gave crude acid reaction mixture. For analytical purposes selected individual components of the mixtures were isolated by column chromatography as free acids or, when convenient, after esterification with methanol and catalytic sulphuric acid.

Alkylation of 2-butenoic acid with 2-bromobutane.- (*E*)-2-butenoic acid **1** (194 mg, 2.25 mmol) and 2-bromobutane **a** (0.25 ml, 2.25 mmol) were added to the reaction mixture, and the solution was stirred at room temperature for 16 h. Work-up gave a yellow oil (167 mg, 52%) as a diastereoisomeric mixture (60% d.e.). Column chromatography led to isolation of a diastereoisomeric mixture of 2-(1-methylpropyl)-3-butenoic acid **5a** as a yellow thick oil. Found C, 67.60; H, 10.10. $C_8H_{14}O_2$ requires C, 67.57; H, 9.92 %; HRMS found M^+142.0998, $C_8H_{14}O_2$ requires 142.0994; ν_{max} 3300-2700, 1690, 1400, 1275, 1200 and 920 cm^{-1}; δ_H 5.81 (1H, ddd, J 18.0, 10.0 and 9.9 Hz, C<u>H</u>=CH_2), 5.19 (1H, d, J 10.2 Hz, CH=C<u>H</u>$_2$), 5.14 (1H, d, J 17.7 Hz, CH=C<u>H</u>$_2$), 2.28 (1H, dd, J 9.6 and 7.2 Hz, C<u>H</u>-CO_2H), 1.84 (1H, m, C<u>H</u>-CH-CO_2H), 1.41 (1H, m, C<u>H</u>$_2$$CH_3$), 1.19 (1H, m, C<u>H</u>$_2$$CH_3$), 0.91 (3H, t, J 7.2 Hz, CH_2C<u>H</u>$_3$), 0.89 (3H, d, J 6.9 Hz, C<u>H</u>$_3$CH) ppm; δ_C (major diastereoisomer) 180.4 (CO_2H), 133.8 (<u>C</u>H=CH_2), 118.7 (CH=<u>C</u>H$_2$), 55.8 (<u>C</u>H-CO_2H), 36.7 (<u>C</u>H-CH-CO_2H), 27.3 (<u>C</u>H$_2$$CH_3$), 15.8 (<u>C</u>H$_3$-CH), 11.3 (<u>C</u>H$_3$-$CH_2$); δ_C (minor diastereoisomer) 180.4 (CO_2H), 134.6 (<u>C</u>H=CH_2), 118.6 (CH=<u>C</u>H$_2$), 56.5 (<u>C</u>H-CO_2H), 36.8 (<u>C</u>H-CH-CO_2H), 25.9 (<u>C</u>H$_2$$CH_3$), 16.7 (<u>C</u>H$_3$-CH), 10.9 (<u>C</u>H$_3$-$CH_2$) ppm.

Alkylation of 2-methyl-2-butenoic acid with 2-bromobutane.- (*E*)-2-methyl-2-butenoic acid **2** (225 mg, 2.25 mmol) and 2-bromobutane **a** (0.25 ml, 2.25 mmol) were added to the reaction mixture, and the solution was stirred at room temperature for 16 h. Work-up gave a yellow oil (194 mg, 55%) as a mixture **6a** (0% d.e.) / **13** 29:34. Column chromatography led to isolation of a diastereoisomeric mixture of 2-methyl-2-(1-methylpropyl)-3-butenoic acid **6a** as a colourless oil. Found C, 69.28; H, 10.53. $C_9H_{16}O_2$ requires C, 69.19; H, 10.32 %; HRMS Found M^++1 157.1231, $C_9H_{17}O_2$ requires 157.1229. ν_{max} 3300-2700, 1685, 1450, 1380, 1265 and 910 cm^{-1};

δ_H (minor diastereoisomer) 5.97 (1H, dd, J 17.7 and 10.8 Hz, C<u>H</u>=CH_2), 5.17 (1H, dd, J 10.8 and 0.9 Hz, CH=C<u>H</u>$_2$), 5.10 (1H, dd, J 17.7 and 0.9 Hz, CH=C<u>H</u>$_2$), 1.84-1.79 (1H, m, CH), 1.40-1.36 (1H, m, CH_2), 1.25 (3H, s, CH_3-C), 1.10-1.00 (1H, m, CH_2), 0.88 (3H, t, C<u>H</u>$_3$-CH_2), 0.85 (3H, d, J 6.9 Hz, C<u>H</u>$_3$-CH) ppm. δ_H (major diastereoisomer) 5.90 (1H, dd, J 17.7 and 10.8 Hz, C<u>H</u>=CH_2), 5.15 (1H, dd, J 10.8 and 0.6 Hz, CH=C<u>H</u>$_2$), 5.09 (1H, dd, J 17.7 and 0.6 Hz, CH=C<u>H</u>$_2$), 1.84-1.79 (1H, m, CH), 1.44-1.43 (2H, m, CH_2), 1.16 (3H, s, CH_3-C), 0.88 (3H, t, C<u>H</u>$_3$-CH_2), 0.80 (3H, d, J 6.6 Hz, CH_3-CH) ppm; δ_C (minor diastereoisomer) 183.0 (CO_2H), 140.6 (<u>C</u>H=CH_2), 115.2 (CH=<u>C</u>H$_2$), 53.1 (<u>C</u>-CO_2H), 41.6 (CH), 24.0 (CH_2), 14.2 (<u>C</u>H$_3$-C), 13.8 (<u>C</u>H$_3$-CH), 12.6 (<u>C</u>H$_3$-CH_2). δ_C (major diastereoisomer) 182.5 (CO_2H), 141.0 (<u>C</u>H=CH_2), 114.9 (CH=<u>C</u>H$_2$), 53.0 (<u>C</u>-CO_2H), 41.4 (CH), 25.2 (CH_2), 13.9 (<u>C</u>H$_3$-C), 13.3 (<u>C</u>H$_3$-CH), 12.7 (<u>C</u>H$_3$-CH_2) ppm.

Further elution allowed isolation of 2-hydroxy-2-methyl-3-butenoic acid **13** as a yellow oil. ν_{max} 3300-2800, 1680, 1400, 1265, 1185, 1120, 920 and 730 cm^{-1}; δ_H 6.03 (1H, dd, J 17.3 and 10.5 Hz, C<u>H</u>=CH_2), 5.47 (1H, dd, J 17.0 and 0.9 Hz, CH=C<u>H</u>$_2$), 5.20 (1H, dd, J 10.5 and 0.9 Hz, CH=C<u>H</u>$_2$), 1.53 (3H, s, CH_3) ppm. δ_C 180.2 (CO_2H), 138.9 (<u>C</u>H=CH_2), 115.1 (CH=<u>C</u>H$_2$), 74.7 (<u>C</u>-CO_2H), 25.7 (CH_3).

Alkylation of 3-methyl-2-butenoic acid with 2-bromobutane.- 3-methyl-2-butenoic acid **3** (225 mg, 2.25 mmol) and 2-bromobutane **a** (0.25 ml, 2.25 mmol) were added to the reaction mixture, and the solution was stirred at room temperature for 8 h. Work-up gave a yellow oil (249 mg, 71%) as a regioisomeric mixture α (58% d.e.) / γ 82:18. Column chromatography led to isolation of a diastereoisomeric mixture of 3-methyl-2-(1-methylpropyl)-3-butenoic acid **7a** as a colourless oil. Found: C, 69.14; H, 10.56. $C_9H_{16}O_2$ requires C, 69.19; H, 10.32 %; ν_{max} 3300-2800, 1680, 1620, 1380 and 890 cm^{-1}; δ_H (R*,S* diastereoisomer) 4.96 (2H, s, C=C<u>H</u>$_2$), 2.79 (1H, d, J 10.8 Hz, C<u>H</u>-CO_2H), 1.94-1.84 (1H, m, C<u>H</u>-CH-CO_2H), 1.77 (3H, s, CH_3-C=), 1.55-1.48 (1H, m, CH_2), 1.18-1.08 (1H, m, CH_2), 0.92 (3H, t, J 7.5 Hz, C<u>H</u>$_3$-CH_2), 0.81 (3H, d, J 6.9 Hz, C<u>H</u>$_3$-CH) ppm; δ_H (R*,R* diastereoisomer) 4.96 (2H, s, C=C<u>H</u>$_2$), 2.82 (1H, d, J 11.1 Hz, C<u>H</u>-CO_2H), 1.94-1.84 (1H, m, C<u>H</u>-CH-CO_2H), 1.77 (3H, s, CH_3-C=), 1.55-1.48 (1H, m, CH_2), 1.18-1.08 (1H, m, CH_2), 0.92 (3H, t, J 7.5 Hz, C<u>H</u>$_3$-CH_2), 0.81 (3H, d, J 6.9 Hz, CH_3-CH) ppm; δ_C (R*,S* diastereoisomer) 180.0 (CO_2H), 141.4 (<u>C</u>=CH_2), 115.9 (C=<u>C</u>H$_2$), 60.1 (<u>C</u>H-CO_2H), 34.1 (<u>C</u>H-CH-CO_2H), 27.6 (CH_2), 19.7 (<u>C</u>H$_3$-C=), 15.7 (<u>C</u>H$_3$-CH), 11.1 (<u>C</u>H$_3$-CH_2). δ_C (R*,R* diastereoisomer) 180.0 (CO_2H), 141.4 (<u>C</u>=CH_2), 115.9 (C=<u>C</u>H$_2$), 59.9 (<u>C</u>H-CO_2H), 33.9 (<u>C</u>H-CH-CO_2H), 25.8 (CH_2), 19.8 (<u>C</u>H$_3$-C=), 16.9 (CH_3-CH), 10.8 (<u>C</u>H$_3$-CH_2) ppm.

Separation of γ alkylation product was not feasible, but spectral data for (*Z*)-3,5-dimethyl-2-heptenoic acid **11a** were obtained from the crude spectra. δ_H 5.90 (1H, s, C=CH), 2.15 (2H, d, J

12.8 Hz, CH_2-C=), 1.93 (3H, s, CH_3-C=), 1.35 (1H, m, CH), 1.25-1.15 (2H, m, CH_3-CH_2), 0.95 (3H, d, J 7.6 Hz, CH_3-CH), 0.86 (3H, t, J 7.2 Hz, CH_3-CH_2) ppm. δ_C 170.7 (CO_2H), 133.6 (C=CH), 98.6 (C=CH), 44.6 (CH_2-C=), 34.0 (CH), 24.7 (CH_2CH_3), 20.9 (CH_3-C=), 11.2 (CH_3-CH), 10.7 (CH_2CH_3) ppm.

Alkylation of (E)-2-methyl-2-pentenoic acid with 2-bromobutane.- (*E*)-2-methyl-2-pentenoic acid **4** (257 mg, 2.25 mmol) and 2-bromobutane **a** (0.25 ml, 2.25 mmol) were added to the reaction mixture, and the solution was stirred at room temperature for 21 h. Work-up gave a yellow oil (383 mg, 68%) as a regioisomeric mixture α (43% d.e.) / γ 54:8. Column chromatography led to isolation of a diastereoisomeric mixture of 2-(1-methylpropyl)-2-methyl-3-pentenoic acid **8a** as a colourless oil. Found C, 70.59; H, 10.59. $C_{10}H_{18}O_2$ requires C, 70.55; H, 10.66%. HRMS Found M^+170.1306, $C_{10}H_{18}O_2$ requires 170.1307. ν_{max} (NaCl) 3300-2400, 1680, 1445, 1350, 1260, 1145 and 950 cm^{-1}. δ_H (minor diastereoisomer) 5.56-5.53 (2H, m, CH=CH), 1.83-1.78 (1H, m, CH), 1.71 (3H, d, J 5.2 Hz, CH_3-C=), 1.13 (3H, s, CH_3-C), 1.08-1.02 (2H, m, CH_2), 0.90 (3H, t, J 7.2 Hz, CH_3CH_2), 0.80 (3H, d, J 6.8 Hz, CH_3-CH) ppm; δ_H (major diastereoisomer) 5.56-5.53 (2H, m, CH=CH), 1.83-1.78 (1H, m, CH), 1.71 (3H, d, J 4.8 Hz, CH_3-C=), 1.47-1.40 (1H, m, CH_2), 1.39-1.30 (1H, m, CH_2), 1.13 (3H, s, CH_3-C), 0.86 (3H, t, J 6.8 Hz, CH_3CH_2), 0.80 (3H, d, J 6.8 Hz, CH_3-CH) ppm δ_C (minor diastereoisomer) 183.0 (CO_2H), 134.0 (=CH-C), 125.4 (CH_3CH=), 52.3 (C-CO_2H), 41.6 (CH), 25.3 (CH_2), 18.2 (CH_3C=), 14.4 (CH_3-C), 13.3 (CH_3-CH), 12.7 (CH_3CH_2). δ_C (major diastereoisomer) 183.0 (CO_2H), 133.6 (=CH-C), 125.7 (CH_3CH=), 52.3 (C-CO_2H), 41.7 (CH), 24.0 (CH_2), 18.2 (CH_3C=), 14.7 (CH_3-C), 14.1 (CH_3-CH), 12.7 (CH_3CH_2) ppm.

Separation of γ alkylation product was not feasible, but spectral data for (*E*)-2,4,5-trimethyl-2-heptenoic acid **12a** can be deduced from the crude spectra. δ_H 6.71 (1H, d, J 10.8 Hz, CH=), 2.40 (1H, m, CH-C=), 1.84 (3H, s, CH_3-C=), 1.60 (1H, m, CH-CH-C=), 1.50-1.20 (2H, m, CH_2), 1.14 (3H, d, J 6.8 Hz, CH_3-CH-C=), 1.03 (3H, d, J 6.0 Hz, CH_3-CH-CH), 0.83 (3H, t, J 7.2 Hz, CH_3CH_2) ppm.

Alkylation of phenylacetic acid with 2-bromobutane.- Phenylacetic acid **18** (306mg, 2.25 mmol) and 2-bromobutane **a** (0.25 ml, 2.25 mmol) were added to the reaction mixture, and the solution was stirred at room temperature for 21 h. Work-up gave a yellow oil (331 mg, 76%) as a mixture **19a** (62% d.e.) / **20** 75:14. Recrystallization from hexane-diethyl ether gave 2-hydroxyphenylacetic acid **20** as a white solid; ν_{max} (KBr) 3400-2800 and 1700 cm^{-1}; δ_H 7.45-7.25 (5H, m, Ph), 5.20 (1H, s, CH) ppm. δ_C 180.0 (CO_2H), 129.4 (ArC1), 128.7 (2ArC2), 127.4 (2ArC3), 126.7 (ArC4), 72.7 (ArCCO_2H) ppm.

Column chromatography led to isolation of a diastereoisomeric mixture of 3-methyl-2-phenylpentenoic acid **19a** as white needles, m.p. 51-53°C. Found C, 75.05, H, 8.48. $C_{12}H_{16}O_2$ requires C, 74.97; H, 8.39 %; HRMS Found M^+ 192.1156, $C_{12}H_{16}O_2$ requires 192.1150; ν_{max} 3300-2700, 1690, 1410, 1285, 1210, 930 and 690 cm^{-1}; δ_H (2R*, 3R* diastereoisomer) 7.36-7.26 (5H, m, Ph), 3.27 (1H, d, J 10.8 Hz, C<u>H</u>-CO_2H), 2.19-2.10 (1H, m, C<u>H</u>-CH-CO_2H), 1.61 (1H, qdd, J 13.4, 7.4 and 3.3 Hz, CH_2), 1.23 (1H, m, CH_2), 0.96 (3H, t, J 7.5 Hz, $C\underline{H}_3$-CH_2), 0.68 (3H, d, J 6.6 Hz, $C\underline{H}_3$-CH). δ_H (2R*, 3S* diastereoisomer) 7.36-7.26 (5H, m, Ph), 3.27 (1H, d, J 10.8 Hz, C<u>H</u>-CO_2H), 2.20-2.10 (1H, m, C<u>H</u>-CH-CO_2H), 1.28-1.17 (1H, m, CH_2), 1.06 (3H, d, J 6.6 Hz, $C\underline{H}_3$-CH), 0.9-0.8 (1H, m, CH_2), 0.79 (3H, t, J 7.2 Hz, $C\underline{H}_3$-CH_2), δ_C (2S*, 3S* diastereoisomer) 180.4 (CO_2H), 137.6 (ArC1), 128.8 (2ArC3), 128.6 (2ArC2 and ArC4), 58.4 (<u>C</u>HCO_2H), 37.5 (<u>C</u>HCHCO_2H), 27.9 (CH_2), 16.0 (<u>C</u>H_3-CH), 11.1 (<u>C</u>H_3-CH_2); δ_C (2R*, 3S* diastereoisomer) 178.5 (CO_2H), 137.6 (ArC1), 128.8 (2ArC3), 128.6 (2ArC2 and ArC4), 58.4 (<u>C</u>HCO_2H), 37.4 (<u>C</u>HCHCO_2H), 25.9 (CH_2), 17.3 (<u>C</u>H_3-CH), 10.6 (<u>C</u>H_3-CH_2) ppm.

Alkylation 2-butenoic acid with 1-phenyl-1-bromoethane.- (*E*)-2-butenoic acid **1** (194 mg, 2.25 mmol) and 1-phenyl-1-bromoethane **b** (0.25 ml, 2.25 mmol) were added to the reaction mixture, and the solution was stirred at 0°C for 7 h. Work-up gave a yellow oil (300 mg, 67%) as a regioisomeric mixture α (30% d.e.) / γ 83:17. Column chromatography led to isolation of a diastereoisomeric mixture of 2-(1-phenylethyl)-3-butenoic acid **5b** as a yellow oil. HRMS Found M^+190.1002, $C_{12}H_{14}O_2$ requires 190.0994; ν_{max} 3400-2400, 1680, 1400, 1340, 915, 750 and 690 cm^{-1}; δ_H (major diastereoisomer) 7.28-7.12 (5H, m, Ph), 5.85 (1H, ddd, J 8.9, 10.7 and 17.1 Hz, C<u>H</u>=CH_2), 5.24 (1H, d, J 10.7 Hz, CH=C<u>H</u>$_2$), 5.20 (1H, d, J 17.2 Hz, CH=C<u>H</u>$_2$), 3.15 (2H, m, C<u>H</u>CO_2H and CH-Ph), 1.25 (3H, d, J 6.7 Hz, CH_3) ppm; δ_H (minor diastereoisomer) 7.28-7.12 (5H, m, Ph), 5.59 (1H, ddd, J 8.6, 10.2 and 17.1 Hz, C<u>H</u>=CH_2), 4.98 (1H, d, J 10.3 Hz, CH=C<u>H</u>$_2$), 4.94 (1H, d, J 16.8 Hz, CH=C<u>H</u>$_2$), 3.15 (2H, m, C<u>H</u>CO_2H and CH-Ph), 1.30 (3H, d, J 6.4 Hz, CH_3) ppm. δ_C (major diastereoisomer) 179.1 (CO_2H), 143.9 (ArC1), 134.3 (<u>C</u>H=CH_2), 128.4 (2ArC2 or 2ArC3), 127.4 (2ArC3 or 2ArC2), 126.6 (ArC4), 119.6 (CH=<u>C</u>H_2), 58.2 (<u>C</u>HCO_2H), 41.6 (<u>C</u>HPh), 18.9 (CH_3). δ_C (minor diastereoisomer) 180.0 (CO_2H), 143.1 (ArC1), 134.0 (<u>C</u>H=CH_2), 128.4 (2ArC2 or 2ArC3), 127.8 (2ArC3 or 2ArC2), 127.4 (ArC4), 118.7 (CH=<u>C</u>H_2), 57.4 (<u>C</u>HCO_2H), 42.3 (<u>C</u>HPh), 20.4 (CH_3) ppm.

(*E*)-5-phenyl-2-hexenoic acid **9b** was characterised from its crude spectral data: δ_H 7.30-7.11 (5H, m, Ph), 6.97 (1H, dt, J 15.6 and 7.6 Hz, C<u>H</u>=CHCO_2H), 5.78 (1H, d, J 15.6 Hz, CH=C<u>H</u>CO_2H), 2.90 (1H, m, CH), 2.53 (1H, m, CH_2), 2.48 (1H, m, CH_2), 1.28 (3H, d, J 6.8 Hz, CH_3);. δ_C 171.3 (CO_2H), 150.1 (<u>C</u>H=CHCO_2H), 145.8 (ArC1), 128.5 (2ArC2 or 2ArC3), 126.8 (2ArC3 or 2ArC2), 126.4 (ArC4), 118.5 (CH=<u>C</u>HCO_2H), 41.0 (CH_2), 39.0 (CH), 22.2 (CH_3).

Alkylation of 2-methyl-2-butenoic acid with 1-phenyl-1-bromoethane.- (*E*)-2-methyl-2-butenoic acid **2** (225 mg, 2.25 mmol) and 1-phenyl-1-bromoethane **b** (0.25 ml, 2.25 mmol) were added to the reaction mixture and the solution was stirred at a steady raise of temperature from -47°C to 8°C for 15 h. Work-up gave a yellow oil (380 mg, 83%) as a regioisomeric mixture α (68% d.e.) / γ 45:55. Column chromatography led to isolation a diastereoisomeric mixture of 2-methyl-2-(1-phenylethyl)-3-butenoic acid **6b** as a yellow oil. HRMS Found M^+ 204.1153, $C_{13}H_{16}O_2$ requires 204.1150; ν_{max} 3300-2700, 1690, 1370 and 920 cm^{-1}. δ_H (R*, R* diastereoisomer) 7.28-7.16 (5H, m, Ph), 6.24 (1H, dd, J 10.8 and 17.4 Hz, C<u>H</u>=CH_2), 5.26 (1H, d, J 10.8 Hz, CH=C<u>H</u>$_2$), 5.05 (1H, d, J 17.6 Hz, CH=C<u>H</u>$_2$), 3.34 (1H, q, J 7.2 Hz, CH), 1.28 (3H, d, J 7.2 Hz, C<u>H</u>$_3$-CH), 1.17 (3H, s, CH_3-C); δ_H (R*, S* diastereoisomer) 7.28-7.16 (5H, m, Ph), 6.02 (1H, dd, J 10.8 and 17.4 Hz, C<u>H</u>=CH_2), 5.11 (1H, d, J 10.8, CH=C<u>H</u>$_2$), 4.95 (1H, d, J 17.2 Hz, CH=C<u>H</u>$_2$), 3.34 (1H, q, J 7.2 Hz, CH), 1.32 (3H, d, J 7.2 Hz, C<u>H</u>$_3$-CH), 1.25 (3H, s, CH_3-C). δ_C (R*, R* diastereoisomer) 181.9 (CO_2H), 140.0 (C<u>H</u>=CH_2), 139.3 (ArC1), 129.3 (2ArC2), 128.0 (2ArC3), 127.0 (ArC4), 116.2 (CH=C<u>H</u>$_2$), 53.3 (<u>C</u>CO_2H), 46.5 (CH), 16.4 (CH_3-CH), 16.1 (CH_3-C); δ_C (R*, S* diastereoisomer) 181.9 (CO_2H), 141.8 (ArC1), 140.0 (C<u>H</u>=CH_2), 129.5 (2ArC2), 127.9 (2ArC3), 126.9 (ArC4), 115.3 (CH=C<u>H</u>$_2$), 53.3 (<u>C</u>CO_2H), 46.5 (CH), 16.2 (CH_3-CH), 16.0 (CH_3-C) ppm.

(*E*)-2-methyl-5-phenyl-2-hexenoic acid **10b** was isolated as methyl-ester: HRMS Found M^+ 218.1308, $C_{14}H_{18}O_2$ requires 218.1307; ν_{max} 3500, 3020, 2950, 1700, 1450, 1250, 920 and 690 cm^{-1}; δ_H 7.21-7.36 (5H, m, Ph), 6.77 (1H, t, J 7.5 Hz, CH=C), 3.72 (3H, s, CH_3O), 2.90 (1H, m, CH), 2.49 (2H, m, CH_2), 1.80 (3H, s, CH_3-C), 1.31 (3H, d, J 8.1 Hz, CH_3-CH). δ_C 168.3 (CO_2H), 146.1 (<u>C</u>=CH and ArC1), 140.4 (C=<u>C</u>H), 128.3 (2ArC3), 126.6 (2ArC2), 126.0 (2ArC4), 51.5 (CH_3O), 39.2 (CH), 37.2 (CH_2), 21.4 (CH_3-C), 12.3 (CH_3-CH) ppm.

Alkylation of 3-methyl-2-butenoic acid with 1-phenyl-1-bromoethane.- 3-methyl-2-butenoic acid **3** (225 mg, 2.25 mmol) and 1-phenyl-1-bromoethane **b** (0.25 ml, 2.25 mmol) were added to the reaction mixture and the solution was stirred at room temperature for 8 h. Work-up gave a colourless oil (342 mg, 75%) as a regioisomeric mixture α (78% d.e.) / γ (Z:E, 2:1) 73:27. Column chromatography led to isolation of only one diastereoisomer of 3-methyl-2-(1-phenylethyl)-3-butenoic acid **7b** as a white solid, m.p. 64-66°C; ν_{max} 3200-2700, 1680, 1380, and 890 cm^{-1}; HRMS Found M^+ 204.1144, $C_{13}H_{16}O_2$ requires 204.1150. δ_H 7.26-7.17 (5H, m, Ph), 5.07 (1H, s, C=C<u>H</u>$_2$), 5.03 (1H, s, C=C<u>H</u>$_2$), 3.24 (1H, d, J 11.7 Hz, C<u>H</u>-CO_2H), 3.22-3.12 (1H, m, CHPh), 1.82 (3H, s, C<u>H</u>$_3$-C=), 1.14 (3H, d, J 6.9 Hz, C<u>H</u>$_3$-CH) ppm. δ_C 177.7 (CO_2H), 144.8 (<u>C</u>=CH_2), 141.0 (ArC1), 128.6 (2ArC2 or 2ArC3), 127.6 (2ArC3 or 2ArC2), 126.7 (ArC4), 116.8 (C=<u>C</u>H$_2$), 61.0 (<u>C</u>H-CO_2H), 39.7 (CHPh), 20.0 (<u>C</u>H$_3$-C=), 19.8 (<u>C</u>H$_3$-CH) ppm.

(*Z*)-3-methyl-5-phenyl-2-hexenoic acid **11b** was isolated from column chromatography as a colourless oil: HRMS Found M^+ 204.1154, $C_{13}H_{16}O_2$ requires 204.1150; ν_{max} 3288-2800, 1620, 1250 and 690 cm^{-1}; δ_H 7.32-7.17 (5H, m, Ph), 5.72 (1H, s, C<u>H</u>=C), 3.15 (1H, dd, J 7.5 and 11.7 Hz, CH_2), 3.06 (1H, m, CH), 2.78 (1H, dd, J 7.2 and 12.0 Hz, CH_2), 1.77 (3H, s, CH_3-C=), 1.30 (3H, d, J 6.6 Hz, CH_3-CH) ppm. δ_C 171.5 (CO_2H), 162.3 (<u>C</u>=CH), 146.5 (ArC1), 128.3 (2ArC2), 127.0 (2ArC3), 126.2 (ArC4), 116.8 (C=<u>C</u>H), 41.7 (CH_2), 39.2 (CH), 26.0 (<u>C</u>H_3-C=), 21.7 (<u>C</u>H_3-CH) ppm.

Alkylation of (E)-2-methyl-2-pentenoic acid with 1-phenyl-1-bromoethane.- (*E*)-2-methyl-2-pentenoic acid **4** (257 mg, 2.25 mmol) in THF (2 ml) and 1-phenyl-1-bromoethane **b** (0.25 ml, 2.25 mmol) were added to the reaction mixture, and the solution was stirred at room temperature for 5 h. Work-up gave a yellow oil (318 mg, 65%) as a regioisomeric mixture α (31% d.e.) / γ 32:31. Column chromatography led to isolation of (*E*)-*2*-methyl-2-(1-phenylethyl)-3-pentenoic acid **8b** as a colourless oil. HRMS Found M^+ 180.1147, $C_{11}H_{16}O_2$ requires 180.1150; ν_{max} 3200-2800, 1680, 1250 and 960 cm^{-1}. δ_H (minor diastereoisomer) 7.30-7.14 (5H, m, Ph), 5.83 (1H, d, J 15.8 Hz, C<u>H</u>=CHCH$_3$), 5.48-5.37 (1H, m, CH$_3$C<u>H</u>=), 3.35-3.25 (1H, m, CH), 1.79 (3H, d, J 6.4 Hz, C<u>H</u>$_3$CH=), 1.26 (3H, d, J 7.5 Hz, C<u>H</u>$_3$-CH), 1.14 (3H, s, CH$_3$-C) ppm; δ_H (major diastereoisomer) 7.30-7.14 (5H, m, Ph), 5.63 (1H, d, J 15.8 Hz, C<u>H</u>=CHCH$_3$), 5.35-5.26 (1H, m, CH$_3$C<u>H</u>=), 3.35-3.25 (1H, m, CH), 1.64 (3H, d, J 6.4 Hz, C<u>H</u>$_3$CH=), 1.30 (3H, d, J 7.5 Hz, C<u>H</u>$_3$-CH), 1.19 (3H, s, CH$_3$-C). δ_C (major diastereoisomer) 182.3 (CO_2H), 141.8 (<u>C</u>H=CHCH$_3$), 132.9 (ArC1), 129.3 (2ArC2 or 2ArC3), 127.5 (2ArC3 or 2ArC2), 126.5 (ArC4), 125.5 (CH$_3$<u>C</u>H=), 52.3 (<u>C</u>CO_2H), 46.4 (CH), 18.1 (<u>C</u>H_3C=), 16.3 (<u>C</u>H_3CH), 15.7 (<u>C</u>H_3-C), δ_C (minor diastereoisomer) 182.3 (CO_2H), 141.8 (<u>C</u>H=CHCH$_3$), 132.9 (ArC1), 129.2 (2ArC2 or 2ArC3), 127.7 (2ArC3 or 2ArC2), 126.5 (ArC4), 125.5 (CH$_3$<u>C</u>H=), 52.3 (<u>C</u>CO_2H), 46.4 (CH), 18.1 (<u>C</u>H$_3$CH=), 16.9 (<u>C</u>H$_3$CH), 15.9 (<u>C</u>H$_3$-C) ppm.

(*E*)-2,4-dimethyl-5-phenyl-2-hexenoic acid **12b** was characterised from the crude spectral data: δ_H (major diastereoisomer) 7.30-7.14 (5H, m, Ph), 6.78 (1H, d, J 10.8 Hz, C<u>H</u>=C), 2.75-2.53 (2H, m, 2CH), 1.83 (3H, s, CH$_3$-C), 1.20 (3H, d, J 6.6 Hz, C<u>H</u>$_3$CHPh), 0.82 (3H, d, J 6.6 Hz, C<u>H</u>$_3$CHC=) ppm; δ_H (minor diastereoisomer) 7.30-7.14 (5H, m, Ph), 6.65 (1H, d, J 9.6 Hz, C<u>H</u>=C), 2.75-2.53 (2H, m, 2CH), 1.67 (3H, s, CH$_3$-C), 1.20 (3H, d, J 6.6 Hz, C<u>H</u>$_3$CHPh), 1.03 (3H, d, J 6.3 Hz, C<u>H</u>$_3$CHC=) ppm. δ_C (major diastereoisomer) 174.0 (CO_2H), 149.1 (<u>C</u>H=C), 145.4 (ArC1), 128.3 (2ArC2), 127.4 (2ArC3), 126.5 (ArC4), 125.9 (<u>C</u>-CO_2H), 45.8 (<u>C</u>H-Ph), 40.3 (<u>C</u>H-CH=), 20.0 (CH$_3$-CH-Ph), 18.4 (<u>C</u>H$_3$-CH-CH=), 12.3 (<u>C</u>H$_3$-CH=) ppm. δ_C (minor diastereoisomer) 178.0 (CO_2H), 148.9 (<u>C</u>H=C), 144.9 (ArC1), 128.1 (2ArC2), 127.6 (2ArC3), 126.2 (ArC4), 125.8 (<u>C</u>-CO_2H), 45.0 (<u>C</u>H-Ph), 39.9 (<u>C</u>H-CH=), 17.4 (<u>C</u>H$_3$-CH-CH=), 15.9

(CH_3-CH-Ph), 12.0 ($\underline{C}H_3$-CH=) ppm.

Alkylation of phenylacetic acid with 1-phenyl-1-bromoethane.- Phenylacetic acid **18** (306mg, 2.25 mmol) and 1-phenyl-1-bromoethane **b** (0.25 ml, 2.25 mmol) were added to the reaction mixture, and the solution was stirred at room temperature for 5 h. Work-up gave a white solid (436 mg, 80%) as a diastereoisomeric mixture (31% d.e.). Recrystallization from hexane-diethyl ether afforded the major diastereoisomer of 2,3-diphenylbutanoic acid **19b** as white prisms, m.p. 192-194°C; Found C, 79.97; H, 6.78. $C_{16}H_{16}O_2$ requires C, 79.96, H, 6.72 %; ν_{max} 3300-2400, 1670, 1400, 1275, 1075, 900 and 680 cm^{-1}; δ_H (R*, R* diastereoisomer) 7.44-6.94 (10H, m, 2Ph) 3.67 (1H, d, J 13.2 Hz, $C\underline{H}CO_2H$), 3.42 (1H, m, $C\underline{H}CH_3$), 1.40 (3H, d, J 6.9 Hz, CH_3); δ_C (R*, R* diastereoisomer) 179.6 (CO_2H), 143.3 (ArC1), 136.9 (ArC1), 128.7, 127.3, 126.6 (Ar), 59.2 ($\underline{C}HCO_2H$), 43.4 ($\underline{C}HCH_3$), 21.1 (CH_3) ppm.

The minor diastereoisomer was characterised by comparison with crude spectral data. δ_H (R*, S* diastereoisomer) 7.42-7.16 (10H, m, 2Ph), 3.69 (1H, d, J 11.6 Hz, $C\underline{H}CO_2H$), 3.42 (1H, m, $C\underline{H}CH_3$), 1.00 (3H, d, J 7.2 Hz, CH_3) ppm. δ_C (R*, S* diastereoisomer) 176.6 (CO_2H), 144.5 (ArC1), 137.1 (ArC1), 128.7, 127.3, 126.6 (Ar), 58.9 ($\underline{C}HCO_2H$), 43.0 ($\underline{C}HCH_3$), 19.9 (CH_3) ppm.

Alkylation of 2-butenoic acid with 3-bromocyclohexene.- (*E*)-2-butenoic acid **1** (194 mg, 2.25 mmol) and 3-bromocyclohexene **c** (0.26 ml, 2.25 mmol) were added to the reaction mixture, and it was stirred at room temperature for 7 h. Work-up gave a yellow oil (267 mg, 72%) as a regioisomeric mixture α (60% d.e.) / γ 78:17. Column chromatography led to isolation of a diastereoisomeric mixture of 2-(2-cyclohexenyl)-3-butenoic acid **5c** as a yellow oil. HRMS Found M^+ 166.0992, $C_{10}H_{14}O_2$ requires 166.0994; ν_{max} 3300-2700, 1700, 1400, 1280, 1210 and 920 cm^{-1}; δ_H (major diastereoisomer) 5.88-5.72 (2H, m, $C\underline{H}$=CH_2 and CHCH=C$\underline{H}$), 5.54 (1H, dd, J 10.2 and 1.8 Hz, CHC$\underline{H}$=CH), 5.21-5.15 (2H, m, CH=C$\underline{H}_2$), 2.87 (1H, dd, J 9.0 and 9.3 Hz, $C\underline{H}CO_2H$), 2.60-2.45 (1H, m, $C\underline{H}CHCO_2H$), 1.98 (2H, m, CH_2-C=), 1.79-1.65 (2H, m, =CC$\underline{H}_2CH_2$ ax and =CC$\underline{H}_2CH_2$ eq), 1.60-1.42 (1H, m, =CC$\underline{H}_2CH_2$ eq), 1.40-1.22 (1H, m, =CC$H_2C\underline{H}_2$ ax) ppm; δ_H (minor diastereoisomer) 5.88-5.72 (2H, m, $C\underline{H}$=CH_2 and CHCH=C$\underline{H}$), 5.63 (1H, dd, J 10.2 and 2.1 Hz, CHC$\underline{H}$=CH), 5.21-5.15 (2H, m, CH=C$\underline{H}_2$), 2.87 (1H, dd, J 9.0 and 9.3 Hz, $C\underline{H}CO_2H$), 2.60-2.45 (1H, m, $C\underline{H}CHCO_2H$), 1.98 (2H, m, CH_2-C=), 1.79-1.65 (2H, m, =CC$\underline{H}_2CH_2$ ax and =CC$\underline{H}_2CH_2$ eq), 1.60-1.42 (1H, m, =CC$\underline{H}_2CH_2$ eq), 1.40-1.22 (1H, m, =CC$H_2C\underline{H}_2$ ax) ppm; δ_C (major diastereoisomer) 179.7 (CO_2H), 134.3 ($\underline{C}H$=CH_2), 129.2 ($\underline{C}H$=CH or CH=$\underline{C}H$), 128.2 (CH=$\underline{C}H$ or $\underline{C}H$=CH), 118.8 (CH=$\underline{C}H_2$), 56.1 ($\underline{C}HCO_2H$), 37.2 ($\underline{C}HCHCO_2H$), 25.9 ($\underline{C}H_2CH$=), 25.0 ($\underline{C}H_2CH$), 20.9 ($\underline{C}H_2CH_2CH$); δ_C (minor diastereoisomer) 179.7 (CO_2H), 134.1 ($\underline{C}H$=CH_2), 134.1 ($\underline{C}H$=CH or CH=$\underline{C}H$), 129.1 (CH=$\underline{C}H$ or $\underline{C}H$=CH),

119.1 (CH=$\underline{C}H_2$), 56.1 ($\underline{C}HCO_2H$), 37.3 ($\underline{C}HCHCO_2H$), 27.3 ($\underline{C}H_2CH$=), 25.0 ($\underline{C}H_2CH$), 21.3 ($\underline{C}H_2CH_2CH$) ppm.

(*E*)-4-(2-cyclohexenyl)-2-butenoic acid **9c** was characterised from the crude spectral data: δ_H 7.05 (1H, dt, J 15.6 and 7.5 Hz, C$\underline{H}$=CHCO$_2$H), 5.84 (1H, d, J 14.1 Hz, =C$\underline{H}$CO$_2$H), 5.70 (1H, m, CH$_2$C$\underline{H}$=CH), 5.60 (1H, dd, CH$_2$CH=C$\underline{H}$), 2.56-2.47 (1H, m, CH), 2.50-2.18 (2H, m, C$\underline{H}_2$CH=), 1.96 (2H, m, CH$_2$C$\underline{H}_2$CH=), 1.80-1.67 (2H, m, C$\underline{H}_2$CH$_2$CHax and CH$_2$C$\underline{H}_2$CH eq), 1.56-1.44 (1H, m, C$\underline{H}_2$CH$_2$CHeq), 1.38-1.19 (1H, m, CH$_2$C$\underline{H}_2$CH ax) ppm; δ_C 174.4 (CO_2H), 148.1 ($\underline{C}H$=CHCO$_2$H), 130.4 (CH=$\underline{C}H$CO$_2$H), 128.1 (CH$_2\underline{C}H$=CH), 122.1 (CHCH=$\underline{C}H$), 38.9 ($\underline{C}H_2$CH=CHCO$_2$H), 34.5 (CH), 28.8 ($\underline{C}H_2$C=), 27.2 ($\underline{C}H_2$CHCH$_2$), 21.2 (CH$_2\underline{C}H_2$CH$_2$) ppm.

Alkylation of 2-methyl-2-butenoic acid with 3-bromocyclohexene.- (*E*)-2-methyl-2-butenoic acid **2** (225 mg, 2.25 mmol) and 3-bromocyclohexene **c** (0.26 ml, 2.25 mmol) were added to the reaction mixture and the solution was stirred at room temperature for 7h. Work-up gave a yellow oil (334 mg, 82%) as a regioisomeric mixture α (40% d.e.) / γ 65:35. Column chromatography led to isolation of a diastereoisomeric mixture of 2-cyclohexenyl-2-methyl-3-butenoic acid **6c** as a yellow oil; HRMS Found M^+ 180.1151, $C_{11}H_{16}O_2$ requires 180.1150; ν_{max} 3200-2700, 1680, 1400, 1260 and 910 cm^{-1}; δ_H (major diastereisomer) 6.00 (1H, dd, J 17.3 and 10.8 Hz, C$\underline{H}$=CH$_2$), 5.82-5.74 (1H, m, C$\underline{H}$=CH-CH), 5.46 (1H, dd, J 9.9 and 1.5 Hz, CH=C$\underline{H}$-CH), 5.25 (1H, d, J 11.0 Hz, C$\underline{H}_2$=CH), 5.15 (1H, d, J 17.1 Hz, C$\underline{H}_2$=CH), 2.78-2.60 (1H, m, CH), 1.96 (2H, m, CH=CH-C$\underline{H}_2$), 1.85-1.63 (2H, m, CH$_2$C$\underline{H}_2$CH$_2$ax and CH$_2$CH$_2$C$\underline{H}_2$eq), 1.60-1.42 (1H, m, CH$_2$C$\underline{H}_2$CH$_2$eq), 1.36-1.17 (1H, m, CH$_2$CH$_2$C$\underline{H}_2$ax), 1.20 (3H, s, CH$_3$-C) ppm; δ_H (minor diastereoisomer) 6.02 (1H, dd, J 17.5 and 10.8 Hz, CH$_2$=C$\underline{H}$), 5.82-5.74 (1H, m, C$\underline{H}$=CH-CH), 5.46 (1H, dd, J 9.9 and 1.5 Hz, CH=C$\underline{H}$-CH), 5.20 (1H, d, J 11.0 Hz, C$\underline{H}_2$=CH), 5.17 (1H, d, J 17.6 Hz, C$\underline{H}_2$=CH), 2.78-2.60 (1H, m, CH), 1.96 (2H, m, CH=CH-C$\underline{H}_2$), 1.85-1.63 (2H, m, CH$_2$C$\underline{H}_2$CH$_2$ax and CH$_2$CH$_2$C$\underline{H}_2$eq), 1.60-1.42 (1H, m, CH$_2$C$\underline{H}_2$CH$_2$eq), 1.36-1.17 (1H, m, CH$_2$CH$_2$C$\underline{H}_2$ax), 1.20 (3H, s, CH$_3$-C) ppm; δ_C (major diastereoisomer) 181.1 (CO_2H), 140.0 (CH$_2$=$\underline{C}$H), 129.6 (CH=$\underline{C}$H), 127.5 ($\underline{C}$H=CH), 115.2 ($\underline{C}H_2$=CH), 51.8 (C), 42.6 (CH), 25.1 ($\underline{C}H_2$-CH=), 23.9 (CH$_2\underline{C}H_2$CH$_2$), 22.3 (CH$_2\underline{C}H_2$CH$_2$), 15.1 (CH$_3$-C); δ_C (minor diastereoisomer) 181.1 (CO_2H), 140.2 (CH$_2$=$\underline{C}$H), 129.6 (CH=$\underline{C}$H), 126.8 ($\underline{C}$H=CH), 115.7 ($\underline{C}H_2$=CH), 51.8 (C), 42.4 (CH), 25.0 ($\underline{C}H_2$-CH=), 24.2 (CH$_2\underline{C}H_2$CH$_2$), 22.2 (CH$_2\underline{C}H_2$CH$_2$), 14.9 (CH$_3$-C) ppm.

(2*E*)-4-(2-Cyclohexenyl)-2-methyl-2-butenoic acid **10c** was characterised as methyl ester: δ_H 6.79 (1H, t, J 7.6 Hz, C=CH), 5.69 (1H, m, C$\underline{H}$=CH-CH), 5.53 (1H, dd, J 10.4 and 1.6 Hz, CH=C$\underline{H}$-CH), 3.73 (3H, s, CH$_3$O), 2.28-2.21 (1H, m, CH), 2.22-2.10 (2H, m, C=CH-C$\underline{H}_2$), 1.96 (2H, m, CH=CH-C$\underline{H}_2$), 1.83 (3H, s, CH$_3$-C=), 1.80-1.66 (2H, m, CH$_2$C$\underline{H}_2$CH$_2$ax and

$CH_2CH_2\underline{CH_2}$eq), 1.58-1.46 (1H, m, $CH_2\underline{CH_2}CH_2$eq), 1.28-1.20 (1H, m, $CH_2CH_2\underline{CH_2}$ax) ppm. δ_C 179.4 (CO_2H), 141.3 ($\underline{C}H$=C-CO_2H), 131.0 (CH=CH), 128.1 (CH=CH), 128.0 (=$\underline{C}$-CO_2H), 51.9 (CH_3-O), 35.5 ($\underline{C}H_2$-CH=), 35.3 (CH), 29.1 ($\underline{C}H_2$-CH=CH), 25.4 (CH_2-$\underline{C}H_2$-CH_2), 21.5 (CH_2-$\underline{C}H_2$-CH), 12.8 (CH_3) ppm.

Alkylation of 3-methyl-2-butenoic acid with 3-bromocyclohexene.- 3-methyl-2-butenoic acid **3** (225 mg, 2.25 mmol) and 3-bromocyclohexene **c** (0.26 ml, 2.25 mmol) were added to the reaction mixture, and the solution stirred at room temperature for 7 h. Work-up gave a yellow oil (346 mg, 85%) as a regioisomeric mixture α (44% d.e.) / γ 63:24. Column chromatography led to isolation of 2-(2-cyclohexenyl)-3-methyl-3-butenoic acid **7c** as a white solid. m.p. 54-56°C; HRMS Found M^+ 180.1152, $C_{11}H_{16}O_2$ requires 180.1150; ν_{max} 3200-2800, 1690 and 890 cm^{-1}. δ_H (R*, R* diastereoisomer) 5.75 (1H, m, $\underline{C}H$=CH-CH), 5.59 (1H, d, J 8.4 Hz, CH=$\underline{C}H$-CH), 4.98 (2H, s, $\underline{C}H_2$=C); 2.88 (1H, d, J 11.2 Hz, $\underline{C}H$-CO_2H), 2.60 (1H, m, $\underline{C}H$-CH-CO_2H), 1.99 (2H, m, CH=CH-$\underline{C}H_2$), 1.78 (3H, s, CH_3-C=), 1.67 (2H, m, $CH_2\underline{CH_2}CH_2$ax and $CH_2CH_2\underline{CH_2}$eq), 1.53 (1H, m, $CH_2\underline{CH_2}CH_2$eq), 1.24 (1H, m, $CH_2CH_2\underline{CH_2}$ax) ppm; δ_H (R*, S* diastereoisomer) 5.75 (1H, m, $\underline{C}H$=CH-CH), 5.52 (1H, d, J 9.6 Hz, CH=$\underline{C}H$-CH), 5.00 (2H, s, $\underline{C}H_2$=C); 2.85 (1H, d, J 12.4 Hz, $\underline{C}H$-CO_2H), 2.60 (1H, m, $\underline{C}H$-CH-CO_2H), 1.99 (2H, m, CH=CH-$\underline{C}H_2$), 1.82 (3H, s, CH_3-C=), 1.67 (2H, m, $CH_2\underline{CH_2}CH_2$ax and $CH_2CH_2\underline{CH_2}$eq), 1.53 (1H, m, $CH_2\underline{CH_2}CH_2$eq), 1.24 (1H, m, $CH_2CH_2\underline{CH_2}$ax) ppm; δ_C (R*, R* diastereoisomer) 179.4 (CO_2H), 140.7 (CH_2=$\underline{C}$), 129.1 (CH=$\underline{C}$H-CH), 128.6 ($\underline{C}$H=CH-CH), 116.0 ($\underline{C}H_2$=C), 59.0 ($\underline{C}$H-CO_2H), 34.4 ($\underline{C}$H-CH-CO_2H), 25.9 (CH=CH-$\underline{C}H_2$), 25.2 ($CH_2CH_2\underline{C}H_2$), 20.5 ($CH_2\underline{C}H_2CH_2$), 19.6 (CH_3-C=) ppm; δ_C (R*, S* diastereoisomer) 179.4 (CO_2H), 140.7 (CH_2=$\underline{C}$), 130.4 (CH=$\underline{C}$H-CH), 127.5 ($\underline{C}$H=CH-CH), 116.3 ($\underline{C}H_2$=C), 48.0 ($\underline{C}$H-CO_2H), 34.8 ($\underline{C}$H-CH-CO_2H), 27.6 (CH=CH-$\underline{C}H_2$), 25.9 ($CH_2CH_2\underline{C}H_2$), 21.1 ($CH_2\underline{C}H_2CH_2$), 20.2 (CH_3-C=) ppm.

(2*Z*)-4-(2-Cyclohexenyl)-3-methyl-2-butenoic acid **11c** was isolated from column chromatography as a white solid. m.p. 35-37 °C; HRMS Found M^+ 180.1155, $C_{11}H_{16}O_2$ requires 180.1150; ν_{max} 3200-2800, 1680, 1440, 930 and 870 cm^{-1}; δ_H 5.75 (1H, s, CH=C), 5.69 (1H, m, $\underline{C}H$=CH-CH), 5.52 (1H, dd, J 9.4 Hz, CH=$\underline{C}H$-CH), 2.77 (1H, dd, J 12.6 and 8.8 Hz, CH=C-$\underline{C}H_2$), 2.56 (1H, dd, J 12.8 and 6.8 Hz, CH=C-$\underline{C}H_2$), 2.37 (1H, m, CH), 1.96 (2H, m, CH=CH-$\underline{C}H_2$), 1.93 (3H, s, CH_3-C=), 1.75-1.67 (2H, m, $CH_2\underline{CH_2}CH_2$ax and $CH_2CH_2\underline{CH_2}$eq), 1.54-1.42 (1H, m, $CH_2\underline{CH_2}CH_2$eq), 1.32-1.24 (1H, m, $CH_2CH_2\underline{CH_2}$ax) ppm; δ_C 171.6 (CO_2H), 162.1 (CH=$\underline{C}$); 131.0 (CH=$\underline{C}$H), 127.6 ($\underline{C}$H=CH), 117.0 ($\underline{C}$H=C), 39.3 (CH=C-$\underline{C}H_2$), 34.2 (CH), 28.5 (CH=CH-$\underline{C}H_2$), 25.9 (CH_3-C), 25.2 (CH_2), 21.2 (CH_2).

Alkylation of (E)-2-methyl-2-pentenoic acid with 3-bromocyclohexene.- (*E*)-2-methyl-2-pentenoic acid **4** (257 mg, 2.25 mmol) and 3-bromocyclohexene **c** (0.26 ml, 2.25 mmol), were added to the reaction mixture, and the solution was stirred at room temperature for 7 h. Column chromatography led to isolation of a diastereoisomeric mixture of 2-(2-cyclohexenyl)-2-methyl-3-pentenoic acid **8c** (314 mg, 72%) as a colourless oil as a regioisomeric mixture α (30% d.e.) / γ 61:26. HRMS Found M^+ 195.1385, $C_{12}H_{19}O_2$ requires 195.1388; ν_{max} 3200-2800, 1680, 1260 and 960 cm^{-1}; δ_H (major diastereoisomer) 5.80-5.72 (1H, m, CH=C<u>H</u>-CH_2), 5.57 (2H, m, C<u>H</u>=C<u>H</u>-CH_3), 5.43 (1H, dd, J 9.4 and 1.2 Hz, C<u>H</u>=CH-CH_2), 2.70 (1H, m, C<u>H</u>-CH=CH), 1.96 (2H, m, CH=CH-C<u>H</u>$_2$), 1.81-1.63 (2H, m, $CH_2C\underline{H}_2CH_2$ax and $CH_2CH_2C\underline{H}_2$eq), 1.71 (3H, d, J 4.4 Hz, $C\underline{H}_3$CH=CH), 1.59-1.43 (1H, m, $CH_2C\underline{H}_2CH_2$eq), 1.32-1.19 (1H, m, $CH_2CH_2C\underline{H}_2$ax), 1.16 (3H, s, $C\underline{H}_3$-C-CO_2H) ppm. δ_H (minor diastereoisomer) 5.80-5.72 (1H, m, CH=C<u>H</u>-CH_2), 5.60 (2H, m, C<u>H</u>=C<u>H</u>-CH_3), 5.47 (1H, dd, J 11.8 and 1.8 Hz, C<u>H</u>=CH-CH_2), 2.62 (1H, m, C<u>H</u>-CH=CH), 1.96 (2H, m, CH=CH-C<u>H</u>$_2$), 1.81-1.63 (2H, m, $CH_2C\underline{H}_2CH_2$ax and $CH_2CH_2C\underline{H}_2$eq), 1.73 (3H, d, J 4.4 Hz, $C\underline{H}_3$CH=CH), 1.59-1.43 (1H, m, $CH_2C\underline{H}_2CH_2$eq), 1.32-1.19 (1H, m, $CH_2CH_2C\underline{H}_2$ax), 1.13 (3H, s, $C\underline{H}_3$-C-CO_2H); δ_C (major diastereoisomer) 182.1 (CO_2H), 133.0 (<u>C</u>H=$CHCH_3$), 129.3 (CH=<u>C</u>HCH_2), 128.0 (<u>C</u>H=$CHCH_2$), 125.8 (CH=<u>C</u>HCH_3), 51.2 (C-CO_2H), 42.7 (<u>C</u>H-CH=), 25.1 ($CH_2CH_2\underline{C}H_2$), 23.8 (=CH-<u>C</u>H_2), 22.4 ($CH_2\underline{C}H_2CH_2$), 18.1 (<u>C</u>H_3-CH=), 15.5 (<u>C</u>H_3-C-CO_2H) ppm. δ_C (minor diastereoisomer) 182.1 (CO_2H), 133.2 (<u>C</u>H=$CHCH_3$), 129.2 (CH=<u>C</u>HCH_2), 127.1 (<u>C</u>H=$CHCH_2$), 126.2 (CH=<u>C</u>HCH_3), 51.2 (C-CO_2H), 42.6 (<u>C</u>H-CH=), 25.1 ($CH_2CH_2\underline{C}H_2$), 24.3 (=CH-<u>C</u>H_2), 22.3 ($CH_2\underline{C}H_2CH_2$), 18.1 (<u>C</u>H_3-CH=), 15.4 (<u>C</u>H_3-C-CO_2H) ppm.

(2*E*)-4-(2-Cyclohexenyl)-2-methyl-2-pentenoic acid **12c** was characterised from the crude spectral data. δ_H 6.80 (1H, d, J 10.4 Hz, C<u>H</u>=C-CO_2H), 5.67 (1H, m, CH_2C<u>H</u>=CH), 5.55 (1H, m, CH_2CH=C<u>H</u>), 2.48-2.40 (1H, m, C<u>H</u>-CH_3), 1.96 (2H, m, CH=CH-C<u>H</u>$_2$), 1.83 (3H, s, $C\underline{H}_3$CH=), 1.72-1.65 (2H, m, $CH_2C\underline{H}_2CH_2$ax and $CH_2CH_2C\underline{H}_2$eq), 1.60-1.48 (1H, m, $CH_2C\underline{H}_2CH_2$eq), 1.30-1.20 (1H, m, $CH_2CH_2C\underline{H}_2$ax), 1.03 (3H, d, J 6.8 Hz, $C\underline{H}_3$-CH); δ_C 173.0 (CO_2H), 129.6 (=<u>C</u>-CO_2H), 149.9 (<u>C</u>H=C-CO_2H), 129.1 and 128.9 (CH=CH), 40.8 (<u>C</u>H_2-CH=), 38.4 (<u>C</u>H-CH_3), 27.0 (<u>C</u>H_2-CH), 22.6 ($CH_2\underline{C}H_2CH_2$), 25.5 (CH_2CH=), 25.4 (<u>C</u>H_3-CH=), 17.1 (<u>C</u>H_3-CH) ppm.

Alkylation of phenylacetic acid with 3-bromocyclohexene.- Phenylacetic acid **18** (306 mg, 2.25 mmol) and 3-bromocyclohexene **c** (0.26 ml, 2.25 mmol), were added to the reaction mixture, and the solution was stirred at room temperature for 7 h. Work-up gave a yellow solid (371 mg, 76%) as a diastereoisomeric mixture (46% d.e.). Recrystallization from hexane-diethyl ether afforded a diastereoisomeric mixture of 2-(2-cyclohexenyl)-2-phenylethanoic acid **19c** as white

prisms. M.p. 133-135°C; HRMS Found M^+ 216.1150, $C_{14}H_{16}O_2$ requires 216.1150; ν_{max} 3200-2800, 1700, 1410, 1290, 1200, 940, 720 and 695 cm^{-1}; δ_H (major diastereoisomer) 7.35-7.25 (5H, m, Ph), 5.81-5.78 (1H, m, C<u>H</u>=CH-CH), 5.71 (1H, dd, J 10.2 and 1.6 Hz, CH=C<u>H</u>-CH), 3.31 (1H, d, J 11.2 Hz. C<u>H</u>-CO_2H), 2.87-2.80 (1H, m, C<u>H</u>-CH-CO_2H), 1.97 (2H, m, =CH-C<u>H_2</u>CH_2), 1.60 (1H, m, =CH-CH_2C<u>H_2</u>), 1.45 (1H, m, =CH-C<u>H_2</u>CH_2), 1.40 (1H, m, CH_2CH_2C<u>H_2</u>eq), 1.05 (1H, m, CH_2CH_2C<u>H_2</u>ax) ppm; δ_H (minor diastereoisomer) 7.35-7.25 (5H, m, Ph), 5.66-5.63 (1H, m, C<u>H</u>=CH-CH), 5.15 (1H, dd, J 10.2 and 1.6 Hz, CH=C<u>H</u>-CH), 3.31 (1H, d, J 11.2 Hz. C<u>H</u>-CO_2H), 2.87-2.80 (1H, m, C<u>H</u>-CH-CO_2H), 1.97 (3H, m, 2 =CH-C<u>H_2</u>CH_2 and =CH-C<u>H_2</u>CH_2), 1.76 (1H, m, =CH-C<u>H_2</u>CH_2), 1.56 (1H, m, CH_2CH_2C<u>H_2</u>eq), 1.40 (2H, m, CH_2CH_2C<u>H_2</u>ax) ppm; δ_C (major diastereoisomer) 179.5 (CO_2H), 137.0 (ArC1),131.7 (<u>C</u>H=<u>C</u>H), 129.2, 128.6, 127.5 (5Ar), 57.4 (<u>C</u>H-CO_2H), 38.1 (<u>C</u>H-CH-CO_2H), 26.2 (=CH-<u>C</u>H_2CH_2), 25.2 (=CH-<u>C</u>H_2CH_2), 20.6 (CH_2CH_2<u>C</u>H_2) ppm; δ_C (minor diastereoisomer) 179.5 (CO_2H), 136.8 (ArC1), 131.7 (<u>C</u>H=<u>C</u>H), 129.2, 128.6, 127.5 (5Ar), 57.5 (<u>C</u>H-CO_2H), 38.0 (<u>C</u>H-CH-CO_2H), 28.0 (=CH-CH_2<u>C</u>H_2), 25.2 (=CH-<u>C</u>H_2CH_2), 20.5 (CH_2CH_2<u>C</u>H_2) ppm.

Acknowledgements

The present research has been financed by DCICYT (PB-95-1121-C02-01). One of us (E.M.B.) acknowledges a grant by DGICYT.

References

[1] Mekelburger HB. and Wilcox CS. Formation of enolates. In Trost BM. Fleming I. editors. Comprehensive Organic Synthesis. Oxford: Pergamon Press, 1991: 99-131.

[2] Thomson CM. Dianion Chemistry in Organic synthesis. Boca Raton (Florida): CRS Press, 1994: 88-129.

[3] Aurell MJ. Gil S. Mestres R. Parra M. Tortajada A. Tetrahedron 1994: 5: 5109-5118.

[4] Parra M. Mestres R. Aparicio D. Durana N. Rubiales G. J. Chem. Soc. Perkin Trans. I 1989: 327-332.

[5] Brun EM. Gil S. Mestres R. Parra M. Villar F. Tetrahedron Letters 1998: 39: 1055-58 and references cited therein.

[6] Aurell MJ. Gil S. Mestres R. Parra M. Parra L. Tetrahedron 1998: 54: 4357-66.

[7] Katzenellenbogen JA. Crumrine AL. J. Am. Chem. Soc. 1976: 98: 4925-35.

[8] Harcken C. Brückner R. Angew. Chem. Int. Ed. Engl. 1997: 36: 2750-2752

[9] Brun EM. Casades I. Gil S. Mestres R. Parra M. Tetrahedron Letters 1998: 39: 5443-5446.

[10] Casinos I. Mestres R. J.Chem.Soc.Perkin Trans I 1978: 1651-1655.

[11] Johnson PR. White JD. J. Org. Chem. 1984: 49: 4424-4429.

[12] Aurell MJ. Gaviña P. Mestres R. Tetrahedron 1994: 50: 2571-2582.