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Experimental and theoretical investigations for the tandem alkylation–isomerization reactions between unsaturated carboxylic acids and allyl halides

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Abstract—Alkylation of dienediolates from unsaturated carboxylic acids with allylic halides when followed by solventless thermal treatment at 150 to 200°C afford rearranged products on a trend highly dependent on the α carbon substitution. Thus, 2,2-bisallylated acids with H atoms at C-2 lead to its 1,3-shift, whereas 2-methyl-2,2-bisallylated acids lead to the corresponding Cope rearrangement product. In the latter case, this tandem allylation-Cope reaction lead, in a highly regio and diastereoselective way, to products not accessible from direct alkylation. B3LYP/6-31G* energies for the compounds involved at these isomerizations are in reasonable agreement with the experiments, allowing to explain the formation of the more stable product under thermodynamic equilibrations.

1. Introduction

Regio and stereoselectivity studies on the reaction of lithium dienediolates with several electrophiles have been reported in the last years[1–3] showing that, on reaction with primary halides, the regioselectivity of the corresponding alkylation products strongly depends on the reactivity of the electrophile. Saturated alkyl halides show a high α-selectivity regardless of steric effects, whereas highly reactive allyl and benzyl halides lead to poor α-selectivities when steric effects become significant.[4] It is worth to note that lithium halide and carboxylate, generated in the ongoing reaction, have opposite effects on the regioselectivity, α-selectivity is favoured by the first whereas the second leads to lower α/γ ratios. Combination of both effects renders the alkylation process less selective along the progress to its end.

Comparable small effects on the regioselectivity were observed when reaction conditions are modified, such as concentration of reagents, higher amounts of halide, deficit of amine, temperature or inversion in the order of addition of reagents. On the contrary, important changes were observed when the nature of the leaving group was changed and α-regioselectivity is obtained with sulfonyloxyalkene as alkylating agent.[5,6] However, regioselective γ-alkylation of dienediolates of unsaturated carboxylic acids has not yet satisfactorily achieved despite some limited success by counter ion interchange,[7,8] or addition of crown ethers.[9] As an alternative to diastereoselective γ-alkylation, we have described the esterification of 3-methyl-2-butenoic acid with allylic alcohols and consecutive Ireland–Claisen and Cope rearrangements.[10]

The latter results showed the way to a simple approach to γ-regioselective alkylation by a tandem process of dienediolate alkylation-Cope rearrangement. The resulting products, equivalent to those γ-products expected from a conjugate substitution (S_N') of the corresponding allylic halide and dienediolate, are not accessible by direct alkylation because a complete regioselectivity towards the direct substitution of the halide (S_N2) have always been observed.[4] We want to report here the scope and limitations of this method by using representatives unsaturated acids and allyl halides.

2. Results and discussion

We have prepared alkylation products of lithium π-extended enolates of unsaturated carboxylic acids (**1**–**3**) with allylic primary halides (**a**–**c**) (Scheme 1). Alkylation have been carried out under standard conditions[11] (see Section 3). Results, yield and α/γ ratios, are summarized in Table 1. Some structure-regioselectivity correlations can be found: Allyl are less selective than saturated halides because reaction time is very short and alkylation is practically complete by the end of the addition of the electrophile at

Keywords: allyl halides; unsaturated carboxylic acids; Cope rearrangement; H migration; regioselectivity; DFT calculation.
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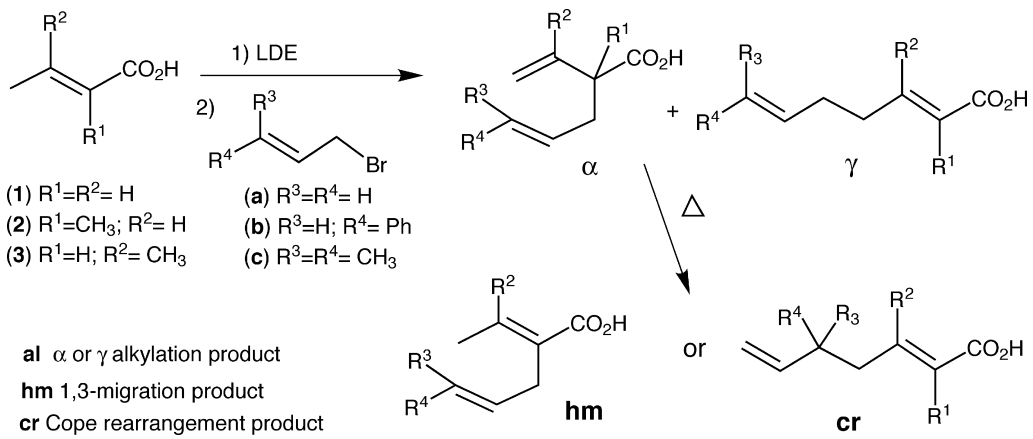


Scheme 1.

−78°C. α-Selectivity strongly depends on the steric hindrance, but cinnamyl bromide (**b**) lead exclusively to α-alkylation products regardless the substitution of the acid. A π-stacking effect, in the transition state, between both π-systems could approach the C–Br bond to the dienediolate C-2 and thus, overcoming steric effects.

Cope rearrangement (CR) was optimized by previous purification of each α-regioisomer. But we have checked that a tandem procedure (alkylation and heating of the evaporated crude acidic fraction) is feasible with a minor decrease of yield. The best conditions were to heat at 200°C the acid in a sealed pressure tube for 5 days without solvent. In some cases, no more than 150°C can be used as higher temperature leads to decomposition of product (see Table 1). Yields are quantitative in every case, with no loss of starting mass. Isomerization is very successful for α-allyl derivatives and only the addition product from acid **1** and halide **a** gives a final isomerization product with 39% of α-adduct unconverted (entry 1, Table 1). This ratio does not change with time and the mixture lead to decomposition at higher temperatures. Similar behavior is obtained for the α-adducts of tiglic acid **2** with halides **b** and **c** where a final mixture α:CR (ca. 30:70) is obtained despite time and temperature modifications (entries 5 and 8; Table 1). As mentioned above, this CR products would match with those from an hypothetical γ-addition-S_N' of acid **2** to halides **b** and **c**.

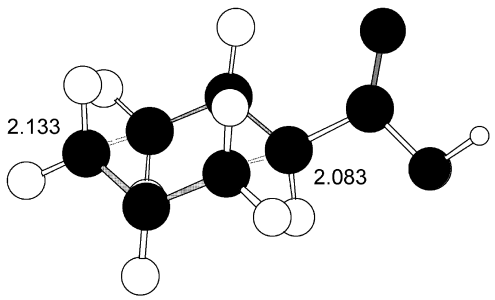
Surprisingly, in some cases, a quantitative conversion of α-adducts to the tautomeric products 13HM is observed by 1,3-hydrogen migration. No CR products were observed in any case, despite several modifications of reaction conditions. 13HM products are synthetically interesting as they are not accessible by direct alkylation and this curious result deserved a theoretical study.

Density functional theory (DFT) calculations at the B3LYP/6-31G* level have been performed in order to rationalize the experimental results. The mechanism of the CR for the 1,5-hexadiene has been widely studied.[12–22] The barrier for the CR reaction computed at the B3LYP/6-31G* level, 34.2 kcal/mol, was estimated closer to the experimental value, 33.5 kcal/mol.[12] The reaction takes place trough a chair transition state where the bonds are breaking and forming in a concerted fashion. The barrier for the CR for the acid derivative **1a** presents a lower value, 28.4 kcal/mol. The presence of the carboxyl substituent on the 1,5-hexadiene system decreases the barrier of the CR in ca. 5 kcal/mol. These large barriers justify the high temperature required for these CRs. The geometry of the corresponding chair transition structure, **TS-CR**, is given in Figure 1. The lengths of the breaking and forming bonds along the concerted process are 2.083 and 2.133 Å. These values are slightly larger than those computed for the CR of the 1,5-hexadiene 1.969 Å.[12] On the other hand, we have also calculated the barrier for the concerted 13HM process. For but-3-enoic acid, as a reduced model of the β,γ-unsaturated acids **1a**–**3b**, the barrier for the 13HM is 82.8 kcal/mol. This very large value prevents the 13HM through a

Table 1. Alkylation of dienolate of tiglic acid (**1**). Introduction of additives

Entry	Acid	R–X	Addition yield (%)	Proportion α:γ	Isomerization yield (%)	Proportion		
						α	**cr**	**hm**
1	**1**	a	77	68:32	100	39	61	0
2	**2**	a	90	71:29	100	0	100	0
3	**3**	a	68	82:18	100	0	100	0
4	**1**	b	58	100:0	100	0	0	100[a]
5	**2**	b	84	100:0	100	23	77	0
6	**3**	b	58	100:0	100	0	0	100[a]
7	**1**	c	63	64:36	100	0	0	100[a]
8	**2**	c	72	36:64	100	34	66	0[b]
9	**3**	c	70	89:11	100	0	0	100

[a] At 150°C.
[b] Starting form isolated α-adduct only.



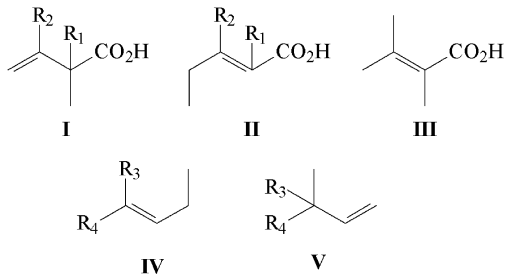
TS-CR

Figure 1. B3LYP/6-31G* geometry of the TS corresponding to Cope rearrangement of **1a**, **TS-CR**. The bond lengths directly involved in the reaction are given in angstroms.

concerted path. Therefore, 13HM must take place though a stepwise mechanism involving radical or ionic species.

An analysis of the thermodynamic data for the CR and 13HM isomerizations of the acid derivative **1a** shows that these reactions present a very low value of ΔS_{503}, 0.7 and 0.8 cal/mol K, respectively. In consequence, the $T\Delta S$ contribution to ΔG is less than 0.5 kcal/mol. As a consequence, the computed values of ΔE for both reactions, −7.2 kcal/mol for the CR and −6.0 kcal/mol for the 13HM, are found to be closer to the computed values of ΔG_{503}, −7.0 and −5.0 kcal/mol, respectively. Therefore, the values of ΔE for the CR and 13HM reactions of the acids **1a**–**3b** will be used for the energetic discussion. The calculated B3LYP/6-31G* total and relative energies of compounds involved in CR and 13HM reactions of the tiglic acid derivatives **1a**–**3c** are given in Table 2. A first analysis of the energetic results indicates that while the 13HM processes are exothermic in the range of −2.8 to −6.8 kcal/mol, the ΔE for the CR processes are between 2.2 and −9.6 kcal/mol.

In order to perform a systematic analysis of both experimental and theoretical results the structures of the compounds involved in the isomerizations of the acid derivatives **1a**–**3c** have been shared in the frameworks **I**–**V** given in Scheme 2. In this Scheme the frameworks **II/V** correspond with the CR products, while **III/IV** ones correspond with the 13HM products. For **1a** the **IV** and **V** frameworks are structural equivalents with the same energy. Therefore, the absence of the product of the 13HM together with the closer energies computed for CR and 13HM products for **1a** indicate that the barrier for the 13HM of **1a** must be larger than that for the CR one.



Scheme 2.

For the phenyl derivative series, **1b**–**3b** the isomers containing the framework **IV**, isomers of the 13HM, are thermodynamically more favorable than the those containing the framework **V**, isomers of the CR, because of the lost of conjugation at the latter. For **1b** and **3b** there are a complete conversion on the 13HM products (100%) (entries 4 and 6, Table 1) in clear agreement with the energetic results (**1b**–**hm** and **3b**–**hm** in Table 2). The more stable isomer under equilibrium conditions corresponds to the structure **III/IV** where the two C–C double bonds remain conjugated to both carboxyl and phenyl π systems. For the CR of the derivatives **1b** and **3b** the processes are endothermic in 0.8 and 1.2 kcal/mol, respectively. For the 2-methyl derivative **2b**, for with the 13HM is not feasible, the 23:77 composition of the mixture of reaction account for a ΔG_{437}=−1.13 kcal/mol. This value is in reasonable agreement with that computed for ΔE for the CR, −1.7 kcal/mol. The low conversion for **2b** can be rationalized as a consequence of the lost of the phenyl conjugation on the framework **V** along the CR.

Finally, an analysis of the experimental result given in Table 1 for the dimethyl substituted alkenes **1c**–**3c** indicates a similar behavior than that found for the phenyl substituted **1b**–**3b** one. For the derivatives **1c** and **3c** the 13HM take place in a 100%, in clear agreement with the ΔE given in Table 2. The structures containing the framework **IV** present a larger stabilization than those containing the framework **V**, because the larger alkyl substitution on the former. For the β,γ-unsaturated acid **2c**, for which the 13HM is not feasible, the 36:66 composition of the mixture of the CR account for a ΔG_{443}=−0.50 kcal/mol. This low value indicates a closer stabilization for the conjugated carboxyl system present at the framework **III**, and the trialkyl substituted C–C double bond present at the framework **IV**. Along the CR of **2c** the energetic

Table 2. Total (in au) and relative energies (ΔE, in kcal/mol, in parenthesis) for reactants and CR and 13HM products for the thermal isomerization of the acid derivatives **1a**–**3c**

a-al	−423.175058	**a-al**	−462.487829	**a-al**	−462.492282
1a-cr	−423.187060 (−7.5)	**2a-cr**	−462.503168 (−9.6)	**3a-cr**	−462.503866 (−7.3)
1a-hm	−423.184669 (−6.0)			**3a-hm**	−462.499158 (−4.3)
1b-al	−654.235589	**2b-al**	−693.547524	**3b-al**	−693.552768
1b-cr	−654.234389 (0.8)	**2b-cr**	−693.550169 (−1.7)	**3b-cr**	−693.550793 (1.2)
1b-hm	−654.246417 (−6.8)			**3b-hm**	−693.559906 (−4.5)
1c-al	−501.812494	**2c-al**	−541.123653	**3c-al**	−541.130733
1c-cr	−501.812242 (0.2)	**2c-cr**	−541.128177 (−2.8)	**3c-cr**	−541.127149 (2.2)
1c-hm	−501.820791 (−5.2)			**3c-hm**	−541.135225 (−2.8)

Relative to **1a-al**–**3c-al**. The **-al**, **-cr** and **-hm** acronyms are related to the alkylation, the Cope rearrangement and the -hydrogen migration products, respectively.

stabilization obtained with the carboxyl conjugation is lost in part with the destabilization of the non-conjugated C–C double bond, and a mixture of both isomers is obtained in agreement with the reversible character of the CR process.

In conclusion, thermal treatment of the alkylation products of dienediolates from unsaturated carboxylic acids with allylic halides affords rearranged products depending on the α carbon substitution. Thus, 2,2-bisallylated acids with H atoms at C-2 lead to its 1,3-shift, whereas when 2-methyl substituted, the corresponding Cope rearrangement products are obtained. In the latter case, this tandem allylation-Cope reaction lead, in a highly regio and diastereoselective way, to products not accessible from direct alkylation.

DFT calculations for ΔE for the CR and 13HM of the α-alkylated β,γ unsaturated acids **1a**–**3c** are in reasonable agreement with the expected ΔG for the isomerization processes. An analysis for the thermodynamic stabilization of the alkenyl frameworks **I**–**V** present on the CR and 13HM products of isomerization reactions allows to explain the behaviors of these acid derivatives. Under equilibrium conditions these reactions appear to be controlled by the maximum stabilization of the diene systems present on these acid derivatives.

3. Experimental

Mps were determined with 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 a Varian Unity 300 or Unity 400 spectrometers. High resolution mass spectra were determined with a UG Autoespec spectrometer. Silica gel Merck 60 (230–400 mesh) was used for flash column chromatography, with hexane/diethylether mixtures for elution.

All reactions were carried out under argon atmosphere, using standard conditions for exclusion of moisture, in oven dried glassware, in THF freshly distilled from blue benzophenone ketyl and with diethyl amine and diisopropylamine distilled from CaH_2. The reaction temperature (−78°C) was achieved by cooling with a CO_2/acetone bath. Organic extracts were dried over anhydrous $MgSO_4$, and solutions were evaporated under reduced pressure with a rotatory evaporator and a bath at 40°C.

Melting point value and spectroscopic data are in agreement with these already described. Other starting compounds were purchased and used without purification.

3.1. General procedure for alkylation of carboxylic acids

Carboxylic acid (2.25 mmol) in THF (2 mL) was slowly added to stirred lithium diethylamide (0.5 mL, 4.8 mmol) in THF (2 mL) at −78°C, according to the method already described.[5] The solution was stirred for 30 min at 0°C and cooled again to −78°C. Halide (2.25 mmol) in THF (2 mL) was added dropwise (5 min), and the solution stirred 1 h at room temperature. The reaction was quenched with water (20 mL) and the mixture extracted with diethyl ether (3×15 mL). The aqueous layer was acidified under ice-cooling bath by careful addition of conc. hydrochloric acid, and then extracted with ethyl acetate (3×15 mL). The organic layer was washed with brine and dried ($MgSO_4$). Evaporation of solvent gave the crude acid reaction mixture. For analytical purposes individual components of mixtures were isolated by column chromatography.

3.1.1. Alkylation of (*E*)-2-butenoic acid with allyl bromide. From (*E*)-2-butenoic acid **1** (194 mg, 2.25 mmol) and allyl bromide **a** (0.2 mL, 2.25 mmol). Work-up gave white oil (219 mg, 77%) as a α:γ mixture (68:32), which on separation by column chromatography gave 2-vinyl-pent-4-enoic acid **1a**-α[4,7] as a white oil: HRMS found M^+ 126.0678, $C_7H_{10}O_2$ requires 126.0680; ν_{max} 3100–2740 (OH), 1695 (C=O), 1415, 1275 and 910 cm^{-1}; δ_H 11.66 (1H, br s, COOH), 5.89–5.68 (2H, m, 2C*H*=CH_2), 5.22–5.00 (4H, m, 2CH=CH_2), 3.12 (1H, dd, J=14.7, 4.5 Hz, C*H*–CO_2H), 2.39–2.30 (1H, m, CH_2), 2.23–2.19 (1H, m, CH_2) ppm; δ_C 179.9 (COOH), 135.1 (CH_2=C*H*CH_2), 134.8 (CH_2=*C*H), 117.5 (*C*H_2=CHCHCOOH), 115.9 (*C*H_2=CHCH_2), 50.1 (*C*HCOOH), 36.3 (*C*H_2CHCOOH) ppm.

Further elution allowed isolation of (*E*)-hepta-2,6-dienoic acid **1a**-γ[4,7] as a white oil: HRMS found M^+ 126.0686, $C_7H_{10}O_2$ requires 126.0680; ν_{max} 3100–2740 (OH), 1635 (C=O), 1220 and 975 cm^{-1}; δ_H 11.66 (1H, br s, COOH), 7.07 (1H, dt, J=15.9, 6.9 Hz, C*H*=CHCO_2H), 6.78 (2H, m, C*H*=CH_2 and CH=C*H*CO_2H), 5.22–5.00 (2H, m, CH=CH_2); 2.58–2.48 and 2.39–2.30 (4H, m, 2CH_2) ppm; δ_C 172.3 (COOH), 151.6 (*C*H=CHCOOH), 137.1 (CH_2=*C*H), 121.3 (*C*HCOOH), 118.2 (*C*H_2=), 32.1 (CH_2=CH*C*H_2), 31.8 (HOOCCH=CH*C*H_2) ppm.

3.1.2. Alkylation of (*E*)-2-methyl-2-butenoic acid with allyl bromide. From (*E*)-2-methyl-2-butenoic acid **2** (225 mg, 2.25 mmol) and allyl bromide **a** (0.2 mL, 2.25 mmol). Work-up gave a white oil (284 mg, 90%) as a α:γ mixture (71:29), which on separation by column chromatography gave 2-methyl-2-vinyl-pent-4-enoic acid **2a**-α[4,7] as a white oil: HRMS found M^+ 140.0835, $C_8H_{12}O_2$ requires 140.0837; ν_{max} 3100–2800 (OH), 1690 (C=O), 1640 (C=C), 1415, 1280, 995 and 915 cm^{-1}; δ_H 6.02 (1H, dd, J=17.1, 10.8 Hz, C*H*=CH_2), 5.84–5.68 (1H, m, CH_2–C*H*=CH_2), 5.18–4.98 (4H, m, 2CH=CH_2), 2.50 (1H, dd, J=13.8, 7.2 Hz, CH_2), 2.34 (1H, dd, J=13.8, 7.2 Hz, CH_2), 1.27 (3H, s, CH_3) ppm; δ_C 182.1 (*C*OOH), 140.5 (*C*H=), 133.3 (CH_2–*C*H=), 118.5 (*C*H_2=CH–CH_2), 114.5 (*C*H_2=), 43.1 (*C*–CO_2H), 28.2 (*C*H_2), 20.1 (*C*H_3) ppm.

Further elution allowed isolation of (*E*)-2-methyl-hepta-2,6-dienoic acid **2a**-γ[4,7] as a white oil: HRMS found M^+ 140.0839, $C_8H_{12}O_2$ requires 140.0837; ν_{max} 3100–2800 (OH), 1690 (C=O), 1640 (C=C), 1415, 1280, 995 and 915 cm^{-1}; δ_H 6.90 (1H, t, J=7.2 Hz, CH_2–C*H*=C), 5.84–5.68 (1H, m, C*H*=CH_2), 5.18–4.98 (2H, m, CH=CH_2), 2.28 (2H, t, J=6.9 Hz, CH_2–CH=C), 2.20 (2H, t, J=6.9 Hz, CH_2–CH=CH_2), 1.82 (3H, s, CH_3) ppm.

3.1.3. Alkylation of 3-methyl-2-butenoic acid with allyl bromide. From 3-methyl-2-butenoic acid **3** (225 mg,

2.25 mmol) and allyl bromide **a** (0.2 mL, 2.25 mmol). Work-up gave white oil (215 mg, 68%) as a α:γ mixture (82:18), which on separation by column chromatography gave 2-isopropenyl-pent-4-enoic acid **3a**-α as a white oil: HRMS found M^+ 140.0834, $C_8H_{12}O_2$ requires 140.0837; ν_{max} 3100–2853 (OH), 1701 (C=O), 1638 (C=C), 1458 and 912 cm^{-1}; δ_H 5.80 (1H, m, C*H*=CH_2), 5.05 (2H, m, CH_2=C), 4.95 (2H, d, *J*=6.4 Hz, CH_2=CH), 3.12 (1H, t, *J*=8 Hz, HOOC–C*H*), 2.58 (1H, dt, *J*=14.8, 6.8 Hz, CH_2–CH–COOH), 1.79 (3H, s, CH_3) ppm; δ_C 179.0 (*C*OOH), 141.4 (*C*CH_3), 135.1 (CH_2=*C*H), 116.8 (*C*H_2=CH), 114.6 (*C*H_2=C), 52.6 (HOOC–*C*H), 34.1 (HOOC–CH–*C*H_2), 20.3 (*C*H_3) ppm.

Further elution allowed isolation of (*E*)-3-methyl-hepta-2, 6-dienoic acid **3a**-γ as a white oil: HRMS found M^+ 140.0837, $C_8H_{12}O_2$ requires 140.0837; ν_{max} 3100–2848 (OH), 1727 (C=O), 1636 (C=C), 1454, 1151, 909 and 727 cm^{-1}; δ_H 5.80 (1H, m, C*H*=CH_2), 5.71 (1H, s, C*H*–COOH), 5.02 (2H, m, CH_2=C), 2.74 (2H, t, *J*=7.6 Hz, CH_2–CCH_3), 2.27 (3H, s, CH_3), 2.25 (3H, s, CH_3) ppm; δ_C 172.0 (*C*OOH), 162.5 (*C*CH_3), 137.7 (*C*H=CH_2), 115.5 (*C*H–COOH), 115.0 (CH_2=C), 41.0 (CH_2CH_3), 32.8 (CH_2CH=CH_2), 19.5 (CH_3) ppm.

3.1.4. Alkylation of (*E*)-2-butenoic acid with 1-[(*E*)-3-bromo-1-propenyl]benzene. From (*E*)-2-butenoic acid **1** (194 mg, 2.25 mmol) and 1-[(*E*)-3-bromo-1-propenyl]benzene **b** (443 mg, 2.25 mmol). Work-up gave white oil (263 mg, 58%) as a $\alpha \geq 99\%$, which on separation by column chromatography gave (*E*)-5-phenyl-2-vinyl-pent-4-enoic acid **1b**-α as a white oil: HRMS found M^+ 202.0993, $C_{13}H_{14}O_2$ requires 202.0993; ν_{max} 3100–2890 (OH), 1705 (C=O), 1640 (C=C), 1413, 1283, 965 and 925 cm^{-1}; δ_H 7.32 (5H, m, Ar–H), 6.47 (1H, d, *J*=15.6 Hz, Ph–C*H*), 6.15 (1H, dt, *J*=15.6, 7.2 Hz, PhCH=C*H*), 5.88 (1H, ddd, *J*=17.1, 10.2, 8.4 Hz, CH_2=C*H*), 5.25 (1H, d, *J*=8.1 Hz, CH_2=CH), 5.21 (1H, s, CH_2=CH), 3.22 (1H, q, *J*=7.5 Hz, HOOCC*H*), 2.70 (1H, dtd, *J*=15, 7.8, 0.9 Hz, HOOCCHCH_2), 2.53 (1H, dtd, *J*=14.1, 6.9, 1.2 Hz, HOOCCHCH_2) ppm; δ_C 179.7 (*C*OOH), 137.5 (*C* Ar), 134.9 (CH_2=*C*H), 132.8 (Ph–*C*H), 128.8, 127.5 and 126.4 (5CHAr), 126.4 (CH=*C*HCH$_2$), 118.5 (CH_2=CH), 50.2 (HOOC–*C*H) and 35.6 (*C*H_2) ppm.

3.1.5. Alkylation of (*E*)-2-methyl-2-butenoic acid with 1-[(*E*)-3-bromo-1-propenyl]benzene. From (*E*)-2-methyl-2-butenoic acid **2** (225 mg, 2.25 mmol) and 1-[(*E*)-3-bromo-1-propenyl]benzene **b** (443 mg, 2.25 mmol). Work-up gave white oil (408 mg, 84%) as a $\alpha \geq 99\%$, which on separation by column chromatography gave (*E*)-5-phenyl-2-methyl-2-vinyl-pent-4-enoic acid **2b**-α as a white oil: HRMS found M^+ 216.1150, $C_{14}H_{16}O_2$ requires 216.1143; ν_{max} 3090–2500 (OH), 1690 (C=O), 1630 (C=C) cm^{-1}; δ_H 7.37–7.22 (5H, m, Ar–H), 6.46 (1H, d, *J*=15.9 Hz, Ph–C*H*=C), 6.15 (1H, dt, *J*=15.6, 7.5 Hz, C*H*=CH_2), 6.09 (1H, dd, *J*=17.1, 11.1 Hz, C*H*=CH_2), 5.25 (1H, d, *J*=11.0 Hz, CH=CH_2), 5.21 (1H, d, *J*=17.1 Hz, CH=CH_2), 2.68 (1H, dd, *J*=13.5, 7.5 Hz, CH_2), 2.54 (1H, dd, *J*=14.0, 7.3 Hz, CH_2) and 1.35 (3H, s, CH_3) ppm; δ_C 182.0 (*C*OOH), 140.5 (CH_2=CH), 137.3 (CAr), 133.7, 127.3 and 126.2 (5CHAr), 128.5 (Ph*C*H=), 125.1 (CH_2*C*H=), 114.8 (*C*H_2=), 48.8 (HOOC–*C*H), 42.3 (*C*H_2C) and 20.3 (*C*H_3) ppm.

3.1.6. Alkylation of 3-methyl-2-butenoic acid with 1-[(*E*)-3-bromo-1-propenyl]benzene. From 3-methyl-2-butenoic acid **3** (225 mg, 2.25 mmol) and 1-[(*E*)-3-bromo-1-propenyl]-benzene **b** (443 mg, 2.25 mmol). Work-up gave white oil (282 mg, 58%) as a $\alpha \geq 99\%$, which on separation by column chromatography gave (*E*)-2-isopropenyl-5-phenyl-pent-4-enoic acid **3b**-α as a white oil: HRMS found M^+ 216.1142, $C_{14}H_{16}O_2$ requires 216.1150; ν_{max} 3606–3303, 3136–2878 (OH), 1767 (C=O), 1650 (C=C), 1166, 1023 and 702 cm^{-1}; δ_H 7.31 (5H, m, Ar–H), 6.46 (1H, d, *J*=16.0 Hz, Ph–C*H*), 6.17 (1H, dt, *J*=14.4, 7.2 Hz, PhCH=C*H*), 5.03 (2H, s, CH_2=C), 3.26 (1H, t, *J*=7.6 Hz, HOOC–C*H*), 2.56 (1H, dt, *J*=14.4, 7.2 Hz, =CH–CH_2) and 1.87 (3H, s, CH_3) ppm; δ_C 179.0 (*C*OOH), 141.8 (CH_2=*C*), 137.6 (CAr), 132.3, 128.8 and 126.5 (5CHAr), 127.5 (Ph*C*H=), 127.2 (Ph–CH=*C*H), 115.0 (*C*H_2=), 53.3 (HOOC–*C*H), 33.8 (HOOC*C*H_2) and 20.7 (*C*H_3) ppm.

3.1.7. Alkylation of (*E*)-2-butenoic acid with 1-bromo-3-methyl-2-butene. From (*E*)-2-butenoic acid **1** (194 mg, 2.25 mmol) and 1-bromo-3-methyl-2-butene **c** (0.26 mL, 2.25 mmol). Work-up gave white oil (219 mg, 63%) as a α:γ mixture (64:36), which on separation by column chromatography gave 5-methyl-2-vinyl-hex-4-enoic acid **1c**-α as a white oil: HRMS found M^+ 154.0997, $C_9H_{14}O_2$ requires 154.0993; ν_{max} 3100–2647 (OH), 1707 (C=O), 1638 (C=C), 1438, 1283 and 922 cm^{-1}; δ_H 5.84 (1H, ddd, *J*=17.4, 10.2, 8.4 Hz, CH_2=C*H*), 5.18 (1H, d, *J*=18 Hz, CH_2=), 5.17 (1H, d, *J*=10 Hz, CH_2=CH), 5.08 (1H, t, *J*=9 Hz, C=C*H*), 3.03 (1H, q, *J*=7.5 Hz, HOOCC*H*), 2.48 (1H, dt, *J*=14.4, 7.2 Hz, =CHCH_2), 2.28 (1H, dt, *J*=14.4, 7.2 Hz, =CH–CH_2), 1.69 (3H, s, CH_3) and 1.61 (3H, t, CH_3) ppm; δ_C 180.6 (*C*OOH), 135.6 (*C*=), 134.7 (CH_2=*C*), 120.5 (*C*H_2=), 118.1 (C=*C*H), 50.6 (HOOC–*C*H), 31.1 (*C*H_3), 26.2 (*C*H_3) and 18.3 (*C*H_2) ppm.

Further elution allowed isolation of (*E*)-7-methyl-octo-2,6-dienoic acid **1c**-γ as a white oil: HRMS found M^+ 154.0998, $C_9H_{14}O_2$ requires 154.0993; ν_{max} 3100–2673 (OH), 1651 (C=O), 1438, 1284 and 923 cm^{-1}; δ_H 7.06 (1H, dt, *J*=13.6, 6.8 Hz, HOOCCH=C*H*), 5.84 (1H, m, HOOCC*H*), 5.10 (1H, m, CH=C*H*), 2.25 (2H, q, *J*=6.8 Hz, CH_2), 2.16 (2H, q, *J*=6.8 Hz, CH_2), 1.61 (3H, s, CH_3) and 1.60 (3H, s, CH_3) ppm; δ_C 172.6 (*C*OOH), 152.4 (HOOCCH=*C*H), 135.4 (CH=*C*), 122.9 (*C*H=C), 121.0 (HOOC*C*H=), 30.9 (HOOC–CH=CH*C*H$_2$), 26.6 (*C*H_3), 25.9 (C=CH*C*H_2) and 18.1 (*C*H_3) ppm.

3.1.8. Alkylation of (*E*)-2-methyl-2-butenoic acid with 1-bromo-3-methyl-2-butene. From (*E*)-2-methyl-2-butenoic acid **2** (225 mg, 2.25 mmol) and 1-bromo-3-methyl-2-butene **c** (0.26 mL, 2.25 mmol). Work-up gave white oil (272 mg, 72%) as a α:γ mixture (36:64), which on separation by column chromatography gave 2,5-dimethyl-2-vinyl-hex-4-enoic acid **2c**-α as a white oil: HRMS found M^+ 168.1155, $C_{10}H_{16}O_2$ requires 168.1150; ν_{max} 3087–2650 (OH), 1696 (C=O), 1642 (C=C) and 923 cm^{-1}; δ_H 6.04 (1H, dd, *J*=17.2, 10.2 Hz. C*H*=CH_2), 5.12 (1H, m, C=C*H*), 5.10 (2H, m, CH=CH_2), 2.46 (1H, dd, *J*=14.0, 7.6 Hz, C*H*–C–COOH), 2.30 (1H, dd, *J*=14.0, 7.6 Hz, C*H*–C–COOH), 1.70 (3H, s, CH_3–C=), 1.69 (3H, s, CH_3–C=) and 1.27 (3H, s, CH_3–C–COOH) ppm; δ_C

182.5 (*C*OOH), 145.3 (CH_2=*C*H), 141.2 ((CH_3)$_2$*C*=), 119.2 (*C*H=C(CH_3)$_2$), 114.4 (*C*H_2=CH), 49.1 (*C*–COOH), 29.4 (*C*H_2), 26.2 (*C*H_3–C–COOH), 25.9 (*C*H_3–C=) and 18.2 (*C*H_3–C=) ppm.

Further elution allowed isolation of (*E*)-2,7-dimethyl-octo-2,6-dienoic acid **2c**-γ as a white oil: HRMS found M^+ 168.1152, $C_{10}H_{16}O_2$ requires 168.1150; ν_{max} 3090–2700 (OH), 1700 (C=O), 1650 (C=C) and 965 cm^{-1}; δ_H 6.91 (1H, dt, *J*=7.6, 1.6 Hz, C*H*=C–COOH), 5.06 (1H, t, *J*=8.8 Hz, C*H*=C(CH_3)$_2$), 2.23 (2H, dd, *J*=14.4, 7.2 Hz, C*H*$_2$), 2.13 (2H, dd, *J*=14.4, 7.2 Hz, C*H*$_2$), 1.83 (3H, s, C*H*$_3$–C–COOH), 1.70 (3H, s, C*H*$_3$C=) and 1.69 (3H, s, C*H*$_3$C=) ppm; δ_C 174.0 (*C*OOH), 140.3 (*C*–COOH), 135.1 (*C*H=C–COOH), 133.0 (=*C*(CH_3)$_2$), 123.3 (*C*H=C(CH_3)$_2$), 37.4 (*C*H_2–C=), 25.9 (*C*H_3–C=), 20.2 (*C*H_2–C=) and 17.9 (2*C*H_3) ppm.

3.1.9. Alkylation of 3-methyl-2-butenoic acid with 1-bromo-3-methyl-2-butene. From 3-methyl-2-butenoic acid **3** (225 mg, 2.25 mmol) and 1-bromo-3-methyl-2-butene **c** (0.26 mL, 2.25 mmol). Work-up gave white oil (265 mg, 70%) as a α:γ mixture (89:11), which on separation by column chromatography gave 2-isopropenyl-5-methyl-hex-4-enoic acid **3c**-α as a white oil: HRMS found M^+ 168.1149, $C_{10}H_{16}O_2$ requires 168.1150; ν_{max} 3080–2731 (OH), 1708 (C=O), 1648 (C=C),1411 and 899 cm^{-1}; δ_H 5.05 (1H, t, *J*=10.0 Hz, C=C*H*), 4.94 (2H, s, C*H*$_2$=), 3.05 (1H, t, *J*=7.6 Hz, HOOC–C*H*), 2.52 (1H, dt, *J*=14.8, 7.6 Hz.=CH–C*H*$_2$), 2.28 (1H, dt, *J*=14.4, 6.8 Hz, =CH–C*H*$_2$), 1.79 (3H, s, C*H*$_3$),1.68 (3H, s, C*H*$_3$) and 1.61 (3H, s, C*H*$_3$) ppm; δ_C 179.8 (*C*OOH), 142.2 (CH_2=*C*), 134.0 ((CH_3)$_2$*C*=), 123.0 ((CH_3)$_2$*C*=*C*H_2), 114.4 (*C*H_2=), 53.4 (HOOC–*C*H), 29.0 ((CH_3)$_2$C=CH–*C*H_2), 26.0 ((CH_3)$_2$C=), 20.7 ((CH_3)$_2$C=) and 17.9 (*C*H_3) ppm.

Further elution allowed isolation of (*E*)-3,7-dimethyl-octo-2,6-dienoic acid **2c**-γ as a white oil: HRMS found M^+ 168.1147, $C_{10}H_{16}O_2$ requires 168.1150; ν_{max} 3091–2727 (OH), 1702 (C=O), 1644 (C=C),1440 and 898 cm^{-1}; δ_H 5.68 (1H, m, C*H*–COOH), 4.94 (1H, m, C*H*=C(CH_3)$_2$), 2.63 (2H, t, *J*=8.0 Hz, C*H*$_2$), 2.52 (2H, m, C*H*$_2$), 2.16 (3H, s, C*H*$_3$–C=) and 1.60 (6H, s, 2C*H*$_3$) ppm; δ_C 172.4 (*C*OOH), 163.4 (HOOC–C=C), 132.9 ((CH_3)$_2$*C*=), 123.7 (*C*H=C(CH_3)$_2$), 115.5 (HOOC–*C*), 41.4 (*C*H_2–C–CH_3), 27.0 (*C*H_2–C=), 25.8 (*C*H_3) and 17.7 (*C*H_3) ppm.

3.1.10. General procedure for thermal treatment of alkylation products. Pure α-alkylation product (or crude allyl α:γ mixtures) were introduced in a pressure tube. The sealed tube was heated in a oven at 200°C for 5 h. The tube was opened at room temperature and the product directly identified.

(*E*)-2-((*E*)Ethylidene)-5-phenyl-pent-4-enoic acid **1b**–**hm** as a colourless oil: HRMS found M^+ 202.090, $C_{13}H_{14}O_2$ requires 202.0994; ν_{max} 3090–2848 (OH), 1697 (C=O), 1600 (C=C), 1418, 1285 and 966 cm^{-1}; δ_H 7.29 (5H, m, Ar–H), 7.14 (1H, q, *J*=7.2 Hz, C*H*=CH_3), 6.39 (1H, d, *J*=16.0 Hz, C*H*Ph), 6.20 (1H, dt, *J*=16.0, 6.4 Hz, C*H*=CHPh), 3.23 (2H, d, *J*=6.4 Hz, C*H*$_2$) and 1.90 (3H, d, *J*=7.2 Hz, C*H*$_3$) ppm; δ_C 173.0 (*C*OOH), 141.9 (*C*HCH$_3$), 137.6 (*C*Ar), 128.7, 127.3 and 126.3 (5*C*HAr), 130.5 (*C*HPh), 126.6 (*C*H=CHPh), 29.6 (*C*H_2) and 14.9 (*C*H_3) ppm.

(*E*)-2-Methyl-5-phenyl-hepta-2,6-dienoic acid **2b**–**cr** as a colourless oil: HRMS found M^+ 216.1140, $C_{14}H_{16}O_2$ requires 216.1143; ν_{max} 3098–2882 (OH), 1788 (C=O), 1693 (C=C), 1494, 1277 and 919 cm^{-1}; δ_H 7.4–7.1 (5H, m, Ar–H), 6.91 (1H, t, *J*=7.3 Hz, C*H*=CCOOH), 6.04 (1H, ddd, *J*=17.0, 10.0, 7.3 Hz, CH_2=C*H*–CPh), 5.11 (1H, d, *J*=17.0 Hz, *H*$_{trans}$CH=CH), 5.14 (1H, d, *J*=10.0 Hz, *H*$_{cis}$CH=CH), 3.48 (1H, q, *J*=7.3 Hz, C*H*Ph), 2.66 (2H, q, *J*=7.3 Hz, C*H*Ph) and 1.81 (3H, s, C*H*$_3$) ppm; δ_C 173.7 (*C*OOH), 143.5 (CAr), 143.2 (*C*H=CCOOH), 141.1 (CH_2=*C*H), 133.8 (*C*–COOH), 129.0 (2*C*HAr), 126.9 (*C*HAr), 115.5 (CH_2=), 49.1 (*C*H–Ph), 35.2 (*C*H_2) and 12.6 (*C*H_3) ppm.

(*E*)-2-(1-Isopropilidene)-5-phenyl-pent-4-enoic acid **3b**–**hm** as a colourless oil: HRMS found M^+ 216.1147, $C_{14}H_{16}O_2$ requires 216.1143; ν_{max} 3575–3257, 3106–2758 (OH), 1724 (C=O), 1664 (OH), 1451, 1194, 752 and 700 cm^{-1}; δ_H 7.2–7.5 (5H, m, Ar–H), 6.39 (1H, d, *J*=16.0 Hz, Ph–C*H*), 6.19 (1H, dt, *J*=16.0, 7.0 Hz, PhCH=C*H*), 2.91 (2H, t, *J*=7.0 Hz, C*H*$_2$), 1.76 (3H, s, C*H*$_3$) and 1.68 (3H, s, C*H*$_3$) ppm; δ_C 171.5 (*C*OOH), 138.8 (*C*Ar), 129.9 (*C*HAr), 128.9 (*C*HAr), 127.7 (*C*HAr), 133.5 (Ph*C*H=), 128.4 (Ph–CH=*C*H), 142.0 (*C*(CH_3)$_2$(, 122.0 (*C*COOH), 33.9 (*C*H_2), 26.3 and 20.8 (2*C*H_3) ppm.

(*E*)-2-Ethylidene-5-methyl-hex-4-enoic acid **1c**–**hm** as a colourless oil: HRMS found M^+ 154.0993 $C_9H_{14}O_2$ requires 154.0998; ν_{max} 3045–2758 (OH), 1706 (C=O), 1638 (C=C), 1281 and 1218 cm^{-1}; δ_H 6.98 (1H, q, *J*=7.2 Hz, CH_3–C*H*=), 5.20 (1H, m, C=C*H*), 3.00 (2H, d, *J*=7.2 Hz, C*H*$_2$), 1.84 (3H, d, *J*=7.2 Hz, C*H*$_3$CH=), 1.70 (3H, s, C*H*$_3$C=) and 1.68 (3H, t, CH_3) ppm; δ_C 173.2 (*C*OOH), 140.4 (CH_3*C*H=), 132.6 (*C*=*C*H), 132.2 (*C*COOH), 121.5 (C=CH), 25.4 (*C*H_2), 27.8 (*C*H_3C=), 18.1 (*C*H_3C=) and 14.7 (*C*H_3CH=) ppm.

(*E*)-2,2,5-Trimethyl-hept-2,6-dienoic acid **2c**–**cr** as a colourless oil: HRMS found M^+ 168.1145, $C_{10}H_{16}O_2$ requires 168.1150; ν_{max} 3030–2864 (OH), 1783 (C=O), 1698 (C=C), 1456 and 1120 cm^{-1}; δ_H 6.91 (1H, t, *J*=7.6 Hz, HOOCC=C*H*), 5.83 (1H, dd, *J*=17.6, 10.4 Hz, CH_2=CH), 5.16 (1H, d, *J*=10.4 Hz, HC*H*$_{cis}$=CH), 5.10 (1H, d, *J*=17.6 Hz, HC*H*$_{trans}$=CH), 1.87 (2H, d, *J*=7.6 Hz, C*H*$_2$–CH=), 1.39 (6H, s, 2C*H*$_3$) and 1.36 (3H, s, C*H*$_3$–CCOOH) ppm.

2-Isopropilydene-5-methyl-5-phenyl-pent-4-enoic acid **3c**–**hm** as a colourless oil: HRMS found M^+ 168.1154, $C_{10}H_{16}O_2$ requires 168.1150; ν_{max} 3030–2879 (OH), 1702 (C=O), 1667 (C=C), 1454, 1290, 1111 and 956 cm^{-1}; δ_H 5.29 (1H, m, C*H*=), 2.50 (2H, s, C*H*$_2$), 2.23 (3H, s, C*H*$_{3cis}$=CH), 1.85 (3H, s, C*H*$_{3trans}$=CH) and 1.35 (6H, s, 2CH_3C=) ppm; δ_C 171.2 (*C*OOH), 152.0 (*C*=*C*COOH), 123.7 (CH=*C*(CH_3)$_2$), 123.0 (*C*H=),122.3 (HOOC–*C*=), 33.6 (*C*H_2), 27.5 (2*C*H_3C=), 23.5 (*C*H_{3trans}=CCOOH), 23.4 (*C*H_{3cis}=CCOOH) ppm.

3.2. Computational methods

DFT calculations have been carried out using the B3LYP[23,24]

exchange-correlation functionals, together with the standard 6-31G* basis set.[25] The optimizations were carried out using the Berny analytical gradient optimization method.[26,27] The stationary points were characterized by frequency calculations in order to verify that the transition structures (TSs) have one and only one imaginary frequency. The values of the relative energies, ΔE, have been calculated based on the total electronic energies of stationary points. Relative enthalpies, ΔH, entropies, ΔS and free energies, ΔG, for the **1a** and the CR and 13HM products were calculated with the standard statistical thermodynamics at 500.15 K and 1 atm.[25] The thermal contributions to the vibrational energy and entropy have been scaled by 0.96.[28] All calculations were carried out with the Gaussian 98 suite of programs.[29]

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References

1. Mekelburger, H. B.; Wilcos, C. S. Formation of Enolates. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; pp 99–131.
2. Thomson, C. M. *Dianion Chemistry in Organic Synthesis*; CRC: Boca Ratón: Florida, 1994; pp 88–129.
3. Gil, S.; Parra, M. *Curr. Org. Chem.* **2002**, *6*, 283–302.
4. Aurell, M. J.; Gil, S.; Mestres, R.; Parra, M.; Parra, L. *Tetrahedron* **1998**, *54*, 4357–4366.
5. Brun, E. M.; Gil, S.; Mestres, R.; Parra, M. *Tetrahedron* **1998**, *54*, 15305–15320.
6. Brun, E. M.; Gil, S.; Mestres, R.; Parra, M. *Synthesis* **2000**, 1160–1165.
7. Katzenellenbogen, J. A.; Crumrine, A. L. *J. Am. Chem. Soc.* **1976**, *98*, 4925–4935.
8. Savu, P. M.; Katzenellenbogen, J. A. *J. Org. Chem.* **1981**, *46*, 239–250.
9. Brun, E. M.; Gil, S.; Parra, M. *Synlett* **2001**, 156–159.
10. Gil, S.; Lázaro, M. A.; Breitmaier, E.; Parra, M.; Mestres, R. *Synlett* **1998**, 70–72.
11. Brun, E. M.; Casades, I.; Gil, S.; Mestres, R.; Parra, M. *Tetrahedron Lett.* **1998**, *39*, 5443–5446.
12. Wiest, O.; Black, K. A.; Houk, K. N. *J. Am. Chem. Soc.* **1994**, *116*, 10336–10337.
13. Jiao, H. J.; Schleyer, P. V. *Angew. Chem. Int. Ed.* **1995**, *34*, 334–337.
14. Wiest, O.; Houk, K. N. *Top. Curr. Chem.* **1996**, *183*, 1–24.
15. Komaromi, I.; Tronchet, J. M. J. *J. Phys. Chem. A* **1997**, *101*, 3554–3560.
16. Houk, K. N.; Beno, B. R.; Nendel, M.; Black, K.; Yoo, H. Y.; Wilsey, S.; Lee, J. K. *J. Mol. Struct. (Theochem)* **1997**, *398-399*, 169–179.
17. Ikeda, H.; Naruse, Y.; Inagaki, S. *Chem. Lett.* **1999**, *4*, 363–364.
18. Hrovat, D. A.; Beno, B. R.; Lange, H.; Yoo, H. Y.; Houk, K. N.; Borden, W. T. *J. Am. Chem. Soc.* **1999**, *121*, 10529–10537.
19. Hrovat, D. A.; Chen, J. G.; Houk, K. N.; Borden, W. T. *J. Am. Chem. Soc.* **2000**, *122*, 7456–7460.
20. Staroverov, V. N.; Davidson, E. R. *J. Am. Chem. Soc.* **2000**, *122*, 7377–7385.
21. Aviyente, V.; Houk, K. N. *J. Phys. Chem. A* **2001**, *105*, 383–391.
22. Duncan, J. A.; Spong, M. C. *J. Org. Chem.* **2000**, *65*, 5720–5727.
23. Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652.
24. Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789.
25. Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986.
26. Schlegel, H. B. *J. Comput. Chem.* **1982**, *3*, 214–218.
27. Schlegel, H. B. Geometry Optimization on Potential Energy Surface. In *Modern Electronic Structure Theory*; Yarkony, D. R., Ed.; World Scientific Publishing: Singapore, 1994.
28. Scott, A. P.; Radom, L. *J. Phys. Chem.* **1996**, *100*, 16502–16513.
29. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. J. A.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M. W.; Gill, P. M.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian* 98, Revision A.6; Gaussian, Inc.: Pittsburgh PA, 1998.