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Unsaturated Acid Derivatives in Diels-Alder Cycloadditions: Effect of the Extended or Cross Conjugation.

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Abstract. Behaviour of pentadienoic acid derivatives in Diels-Alder cycloadditions has been examined in the light of experimental results and theoretical calculations. The effect of cross conjugation to an electron-releasing group has also been investigated for these systems and for simple acrylic acid derivatives.

INTRODUCTION

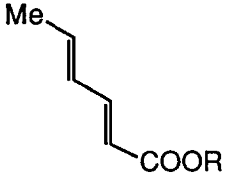
α,β-Unsaturated esters (i.e. acrylic acid derivatives) have been widely used as dienophiles in Diels-Alder cycloadditions. Nevertheless, only scarce and dispersed examples exist on the reactivity of dienophiles with extended conjugation to a second C-C double bond or with cross conjugation to an additional functional group, compared with the parent acrylic ester.

In this paper we present an interpretation of the behaviour of the title compounds, based on experimental findings and on theoretical calculations. The study resulted in a noteworthy complexity since regiochemistry, i.e. selective reaction at one of the two C-C double bonds, must be considered when 2,4-dienoates behave as dienophiles. Moreover, these products behaved as dienes when reacted with more electron-deficient dienophiles,[1] or with non electron-rich dienes.[2] The effect caused by cross conjugation with an electron-donor substituent, i.e. a captodative system, has also been investigated.

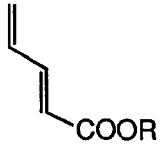
RESULTS AND DISCUSSION

Chart I shows the conjugated esters whose Diels-Alder cycloadditions were investigated. AM1 Theoretical calculations were carried out on the carboxylic acid molecules which result by changing the alkyl substituents by hydrogen atoms. The same numeration is used for the experimental dienophiles **(n)** and for the related molecule **(na)** theoretically studied in each case.

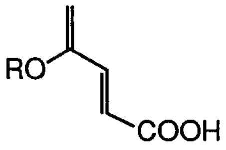
Chart I



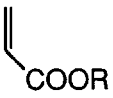
R = Me (1)
H (1a)



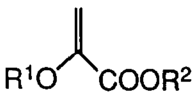
R = Me (2)
H (2a)



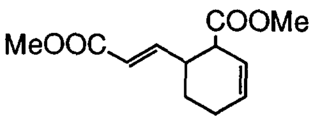
R = Ac (3)
H (3a)



R = Me (4)
H (4a)

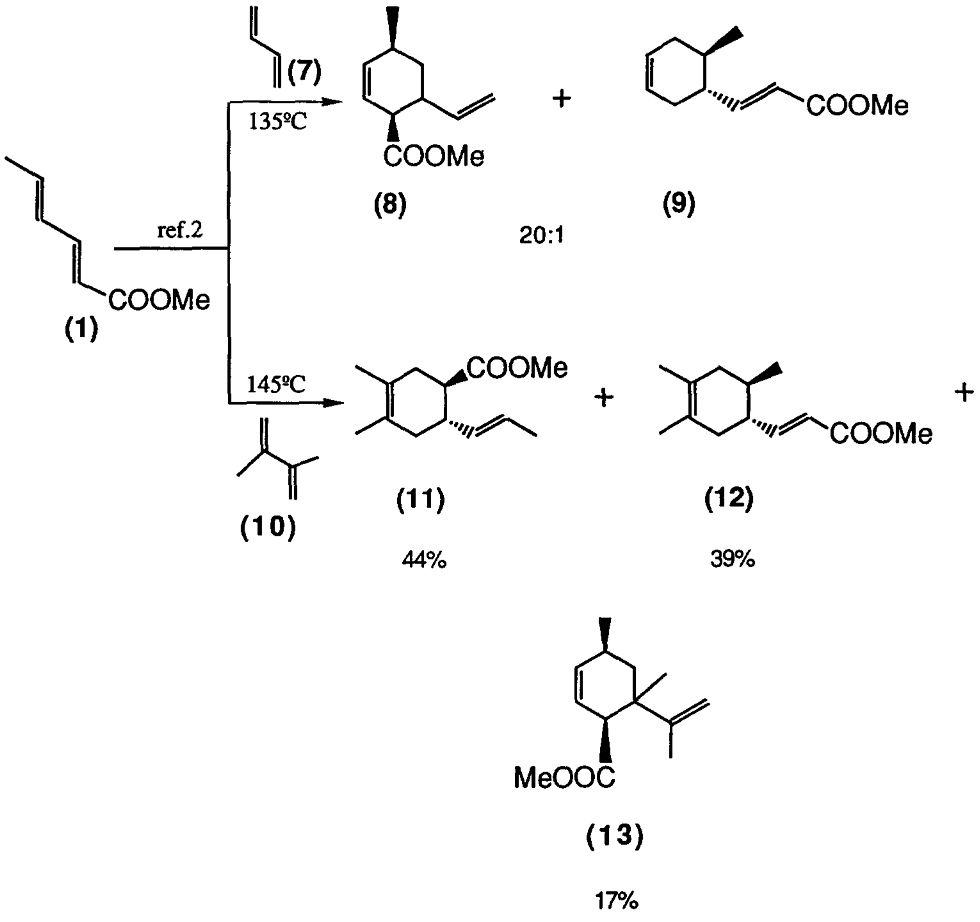


R^1 = Ac, R^2 = Me (5)
R^1 = R^2 = H (5a)



(6)

Garratt *et al.*[2] have described the uncatalyzed Diels-Alder reaction between methyl (*E*)-sorbate (1) and butadiene (7) at 135 °C to afford a 20:1 mixture of adducts (8) and (9), the major isomer corresponding to the addition of sorbate (1) as diene to butadiene (7) as dienophile (Scheme 1). When the reaction between (1) and the electron-richer 2,3-dimethylbutadiene (10) was performed, a 44:39:17 mixture of compounds (11), (12), and (13) was obtained, the major products becoming from addition to (1) which behaves now as the dienophile. In this case, only slight regioselectivity was observed.



Scheme 1

The transition states for the cycloadditions of dienes (7) and (10) to dienophiles (1a)-(3a) at every C-C double bond are represented in Fig. 1. Table 1 shows the AM1 calculated bond distances and the values of the imaginary frequency ($\tilde{\nu}\sqrt{-1}$) corresponding to the only negative eigenvalue of the force constant matrix (negative vibration), at the transition states. The enthalpy barriers ($\Delta H^{\neq}$) for the reactions of dienes (7) and (10) with dienophiles (1a)-(3a) at each C-C double bond are given in Table 2. From these results, pentadienoic acid (2a) should be the most reactive

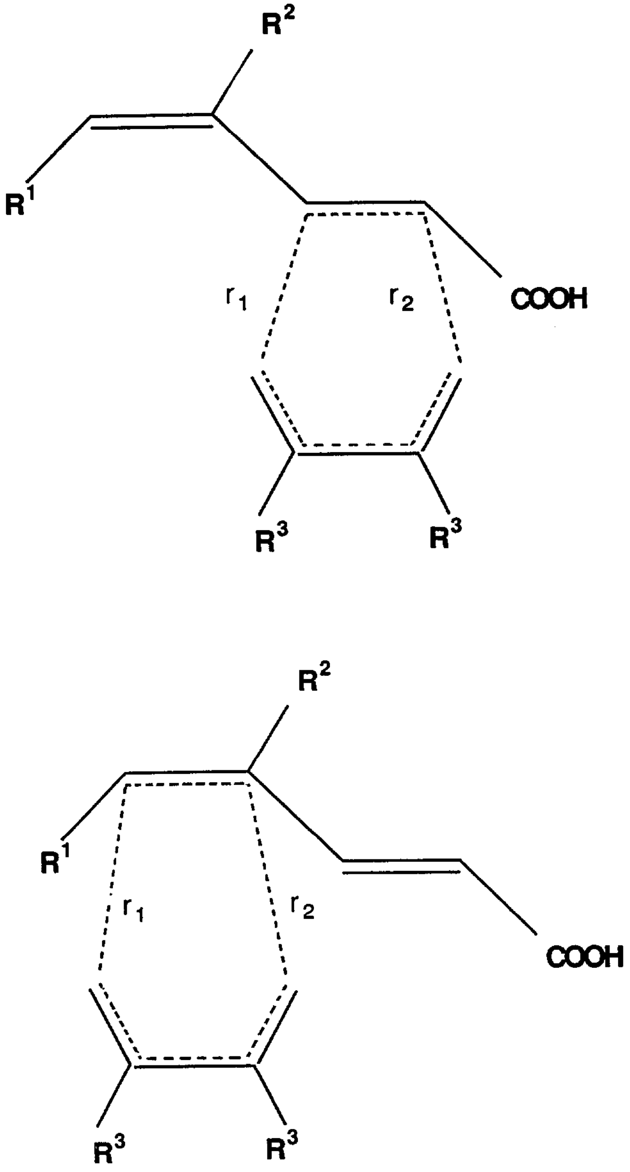


Fig 1. Cycloadditions of dienes **(7)** (R^3=H) and **(10)** (R^3=Me) to dienophiles **(1a)** (R^1=Me, R^2=H), **(2a)** (R^1=R^2=H), and **(3a)** (R^1=H, R^2=OH), respectively, at: (a) the C_2-C_3 bond, (b) the C_4-C_5 bond. r Values are given in Table 1.

dienophile toward butadiene, the predictable regioselectivity being converse respect to that of sorbic acid **(1a)** (entries 1 and 3). A very low regioselectivity would be expected for the reaction involving acid **(3a)** (entry 4).

Table 1. AM1 Calculated lengths of the two forming bonds (r, Å), and negative vibrations ($\bar{\nu}$, cm^{-1}) (see the text and Fig. 1 for their definition), for the transition states corresponding to the cycloadditions of dienes **(7)** and **(10)** to dienophiles **(1a)-(3a)**, respectively, at every C-C double bond.

Diene	Dienophile	C_2-C_3			C_4-C_5		
		r_1	r_2	$\bar{\nu}$	r_1	r_2	$\bar{\nu}$
(7)	(1a)	2.105	2.148	887	2.078	2.183	864
(10)	(1a)	2.109	2.153	840	2.076	2.194	852
(7)	(2a)	2.103	2.108	851	2.038	2.232	904
(7)	(3a)	2.126	2.141	844	1.987	2.335	863

In the case of **(1a)**, the enthalpy barrier was smaller when it was reacted with diene **(10)** than with butadiene **(7)** by a difference of about 1 Kcal/mol (compare entries 1 and 2). The C_2-C_3 double bond was shown to be

Table 2. AM1 Calculated enthalpy barriers ($\Delta H^{\#}$, kcal/mol) for the cycloadditions of dienes **(7)** and **(10)** to dienophiles **(1a)-(3a)**, respectively, at every C-C double bond.

Entry	Diene	Dienophile	$\Delta H^{\#}(C_2-C_3)$	$\Delta H^{\#}(C_4-C_5)$
1	(7)	(1a)	27.4	28.8
2	(10)	(1a)	26.2	27.5
3	(7)	(2a)	27.6	24.8
4	(7)	(3a)	27.1	27.2

the most reactive in both cases, in agreement with the experimental results (Scheme 1). Otherwhise, inspection of Table 3 (entries 1 and 2) reveals that the barrier for the cycloaddition of diene **(1a)** to dienophile **(10)** is much higher (c.f. 4.5 kcal/mol) than that for the addition of **(1a)** to **(7)**, thus explaining the low yield in adduct **(8)** obtained from the reaction between sorbate **(1)** and 2,3-dimethylbutadiene **(10)**. Orientation of the reactants for the cycloadditions of diene **(1a)** to dienophiles **(7)** and **(10)** are indicated in Fig. 2, the lengths of the two forming bonds and the negative vibrations for each transition state being given in Table 3.

Table 3. AM1 Calculated $\Delta H^{\#}$ (kcal/mol), lengths of the two forming bonds (r, Å), and negative vibrations ($\bar{\nu}$, cm^{-1}) (see the text and Fig. 2 and 3 for their definition), for the transitions states corresponding to the cycloadditions of dienes **(1a)** and **(7)** to several dienophiles

Entry	Diene	Dienophile	$\Delta H^{\#}$	r_1	r_2	$\bar{\nu}$
1	**(1a)**	**(7)**	29.0	2.030	2.228	896
2	**(1a)**	**(10)**	33.5	1.976	2.333	889
3	**(7)**	**(4a)**	23.2	2.043	2.219	863
4	**(7)**	**(5a)**	25.8	2.026	2.284	854

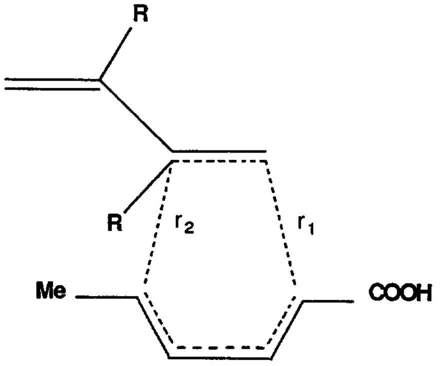


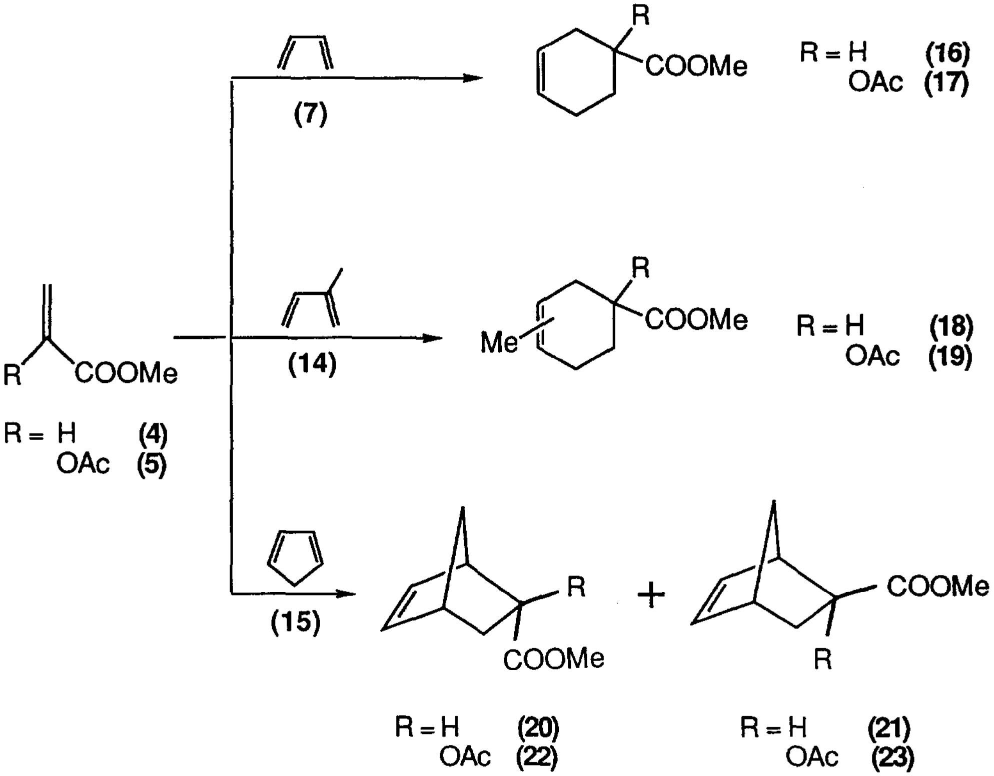
Fig 2. Cycloadditions of diene **(1a)** to dienophiles **(7)** (R=H) and **(10)** (R=Me), respectively. r Values are given in Table 3.

Regioselectivity in the reactions of dienoic acids **(2a)** and **(3a)** were also investigated (Table 2, entries 3 and 4). In the case of pentadienoic acid **(2a)**, the C_4-C_5 double bond was expected to be more reactive than the C_2-C_3 double bond. This theoretical prediction was confirmed by the fact of the exclusive formation of adduct **(6)** (Chart I) resulting of the self-cycloaddition of methyl (E)-2,3-pentadienoate (2).[3] These results emphasize the influence of the methyl substitution at C_5 on the decrease of the reactivity at the C_4-C_5 bond, then reversing the regiochemistry of the cycloaddition. Moreover, calculations show that the presence of the methyl group destabilizes the LUMO of the dienophile by 0.018 eV.

In the case of acid **(3a)** reactivity of the two double bonds was calculated to be almost the same, the C_4-C_5 bond being less reactive than the C_4-C_5 bond in the parent acid **(2a)**, probably due to the cross conjugation to the hydroxyl group. Unfortunately, we did not find similar acids or derivatives described in the literature, and we were not able to synthesize them. For instance, all attempts to prepare **(3)** or its methyl ester from levulinic acid failed.

Then, we studied the effect of cross conjugation to an acetoxyl group on the reactivity of methyl ester **(5)** compared with the reactivity of methyl acrylate **(4)**. Although many examples exist in the bibliography on the Diels-Alder reactions of acrylic acid **(4a)** and simple ester derivatives with current dienes,[4] we carried out several experiments in our laboratory in order to be sure that reaction conditions were comparable for both dienophiles **(4)** and **(5)**. The results obtained are listed in Table 4, and the structures of the adducts are shown in Scheme 2.

Methyl 2-acetoxyacrylate **(5)**[5] was easily prepared in 90% yield by treating comercial methyl pyruvate with acetic anhydride and p-toluenesulfonic acid.[5a] Ester **(5)** was reacted with butadiene at 140 °C for 8 hours to afford a mixture of adduct **(17)** and starting dienophile (Table 4, entry 2). Yield in adduct **(17)** was estimated to be 25% by GC and ^{1}H NMR of this mixture, since column chromatography allowed the obtention of fractions enriched in about 95% of **(17)**, but its total isolation could not be achieved. ^{1}H NMR and IR spectra of these fractions confirmed the structure expected for this compound (Scheme 2). Thus, ^{1}H NMR spectrum showed significant signals at 2.0 and 3.7 ppm as singlets corresponding to the two methyl groups, and double doublets at 5.2 and 5.9 ppm, respectively, with J=6.7 Hz, J'=2 Hz, for the olefinic protons. Moreover, the IR spectrum showed typical absorptions of saturated ester at 1750 and 1755 cm^{-1}, while the absorption corresponding to C-C double bond stretching was not observed. Other reaction conditions were also tried for the



Scheme 2

addition of (5) to butadiene, the results being similar to those described above.

Reaction of (5) with isoprene in the optimal conditions found (Table 4, entry 4) gave a 70:30 mixture of regioisomeric adducts (19) in 50% yield. These isomers could not be separated by chromatographic techniques. ^{1}H NMR and IR spectra as well as microanalysis of the mixture confirmed their structures (see Experimental Section).

Finally, ester (5) was reacted with cyclopentadiene at 90 ^oC for 2.2 hours to afford a 60:40 mixture of endo/exo adducts (22) and (23) in 29% yield (Table 4, entry 6) (Scheme 2). This yield was increased to 63% when the reaction was carried out at 120 ^oC for 4 hours. The two isomers are liquid that could be separated by column chromatography and characterized.

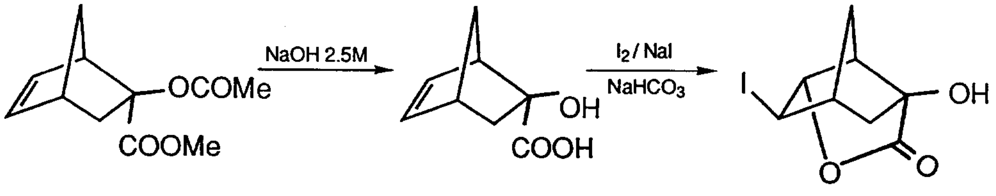
The major reaction product (22) produced the hydroxy carboxylic acid

Table 4. Reaction conditions and results obtained in selected Diels-Alder cycloadditions of dienophiles (4) and (5) to butadiene (7), isoprene (14), and cyclopentadiene (15), respectively.

Entry	Dienophile	Diene	Temperature[a]	Time[b]	Adduct(s)	% Yield
1	(4)	(7)	140	8	(16)	58[c]
2	(5)	(7)	140	8	(17)	25[d]
3	(4)	(14)	120	16	(18)	90[c]
4	(5)	(14)	140	16	(19)	50[d]
5	(4)	(15)	90	2.2	(20)+(21)	50[c]
6	(5)	(15)	90	2.2	(22)+(23)	29[d]

[a] In ^{o}C. [b] In hours. [c] Isolated yield. [d] Determined by CG and ^{1}H NMR of the reaction crude.

(24) through saponification. This compound was transformed into the tricyclic lactone (25) when treated with sodium iodide/iodine in sodium bicarbonate solution.[6] Lactonization confirmed the *endo* orientation of the carbonyl moiety in the stereoisomer (22).



(22) (24) (25)

Scheme 3

In turn, methyl acrylate (4) was also reacted with dienes (7), (14) and (15) in the conditions listed in Table 4. Physical and spectroscopic data of the adducts obtained in each case agree with those previously described in the literature for these compounds[4] (Scheme 2).

Comparison of the yields in adducts prepared in the reactions of (4) or (5) with each diene (observe entries 1/2, 3/4, and 5/6 in Table 4) leads to establish methyl acrylate (4) as a more reactive dienophile than (5). This result is in accordance with the theoretical prediction resulting by comparing the calculated enthalpy barriers for the reactions of acids (4a) and (5a) with butadiene (7) (Table 3, entries 3 and 4). Fig. 3 represents the transitions states corrsponding to the cycloaddition of butadiene to dienophiles (4a) and (5a). Bond distances and negative vibrations for these TS's are given in Table 3.

These experimental and theoretical results verify that geminal substitution on an olefin by both an electron-withdrawing and an electron-releasing groups, such as alkoxycarbonyl and acetoxyl groups, respectively, contribute to the lower reactivity of dienophile (5a) belonging to the so-called captodative olefin-class,[7] respect to that of the parent acrylic ester. This result agrees with and complements those reported by Tamariz and Vogel[8] for the Diels-Alder reactions of 1-acetylvinyl acetate, which was found to be less reactive than the related dienophile methyl vinyl ketone.

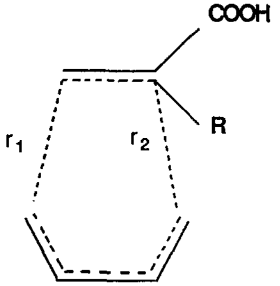


Fig 3. Cycloadditions of butadiene to dienophiles (4a) (R=H) and (5a) (R=OH), respectively. r Values are given in Table 3.

In conclusion, the presence of a methyl group at the C-5 position of a pentadienoic acid derivative, decreases the reactivity of the C_4-C_5 bond toward dienes and directs the addition to the C_2-C_3 bond, probably due to both electronic and steric effects. On the other hand, an electron-releasing substituent, cross-conjugated to an unsaturated acid or ester group, diminishes the reactivity of the resulting captodative systems respect to the parent pentadienoic or acrylic acids.

EXPERIMENTAL SECTION

Melting points were determined on a hot stage and are uncorrected. Distillation of small amounts was effected on a rotary distillation apparatus (only the oven temperature is given). The electron-impact mass spectra were recorded at 70 eV.

General Procedures for Theoretical Calculations. The calculations were performed by using the AM1[9] method. Complete geometry optimization was performed throughout. Transition states were directly located through minimization of the root mean square gradient of the energy and have been characterized through the computation of the force constant matrix.[10] For a transition state this matrix must have only one negative eigenvalue. In all cases, both endo and exo approaches were considered and the corresponding transition states were calculated. Only the enthalpy barriers associated to the most favourable approach have been presented. All calculations were carried out with the AMPAC program[11] implemented on a VAX 6410 and a HP 9000/835 computers.

General Procedures for the Diels-Alder Cycloadditions. The dienophile (5 mmol), the diene (10 mL), and a trace of hydroquinine were introduced into a glass reactor fitted with a teflon stopper, and heated in an oil bath (see Table 3 for the specific reaction temperature and time conditions). The reaction mixture was cooled, diluted with CH_2Cl_2 and filtered to remove hydroquinone and polymeric materials. The solvent and excess diene were evaporated under reduced pressure. The residue was chromatographed on silica gel (mixtures of hexane ethyl acetate as eluents) to afford the corresponding adducts. The relative proportions of regioisomers and stereoisomers in the reactions with isoprene and cyclopentadiene, respectively, were determined by means of capillary GLC and/or ^1H NMR spectra analysis. The adduct resulting from the reaction between ester **(5)** and butadiene could not be isolated satisfactorily, being contaminated by some remaining starting material which precluded the satisfactoy microanalysis.

1-Acetoxy-1-methoxycarbonyl-3-cyclohexene (17): entry 2, Table 4; yield, 277 mg (25%); oil; IR (film) 1733, 1750, 1755 cm^{-1}; 80 MHz ^1H NMR ($CDCl_3$) δ 2.1 (3 H, s), 2.4 (4 H, m), 3.7 (3 H, s), 3.9 (2 H, m), 5.19 (1 H, m), 5.9 (1 H, dd, J = 6.7 Hz, J' = 2.0 Hz). This compound was contamined with ester **(5)** and we could not get a sample suitable for microanalysis.

Mixture of 1-acetoxy-1-methoxycarbonyl-3-methyl-3-cyclohexene and 1-acetoxy-1-methoxycarbonyl-4-methyl-3-cyclohexene (19): entry 4, Table 4; 30:70 mixture of regioisomers (capillary GLC); yield 450 mg (52%); oil, oven temperature 100-105 °C (0.1 Torr); IR (film) 1744 cm^{-1}; 80 MHz ^1H NMR ($CDCl_3$) δ 1.5 (3 H, s), 2.1 (3 H, s), 2.4 (4 H, m), 3.7 (3 H, s), 3.9 (2 H, m), 5.0 (1 H, m). Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.28; H, 7.74. Found: C, 62.25; H, 7.60.

endo- and exo-2-Acetoxy-2-methoxycarbonylbicyclo(2.2.1)-5-heptene, (22) and (23): entry 6, Table 4; these compounds were obtained as a 62:38 mixture of stereoisomers (capillary GLC) that were separated by column chromatography and characterized; total yield, 340 mg (29%).

endo-isomer (22): liquid, oven temperature 95 °C (0.03 Torr); IR (film) 1733, 1750, 1755 cm^{-1}; 400 MHz ^1H NMR ($CDCl_3$) δ 1.3 (H-7, dd, Jgem = 12 Hz, J' = 1 Hz), 1.5 (2 x H-3, d, Jgem = 12 Hz), 2.0 (MeCOO, s), 2.7 (H-7', dd, Jgem = 12 Hz, J' = 1 Hz), 2.9 (H-4, m), 3.3 (H-1, m), 3.8 (MeO, s), 6.1 (H-6, m), 6.4 (H-5, m); 100 MHz ^{13}C NMR ($CDCl_3$) δ 20.7, 39.8, 41.9, 47.3, 50.7, 52.5, 86.5, 132.8, 139.9, 170.7, 173.1.

exo-isomer (23): liquid, oven temperature 97 °C (0.03 Torr); IR (film) 1733, 1750, 1755 cm^{-1}; 400 MHz ^1H NMR ($CDCl_3$) δ 1.6 (2 x H-3, dq, Jgem = 9 Hz, J' < 1 Hz), 1.8 (H-7, m), 2.1 (MeCOO, s), 2.3 (H-7', m), 2.9 (H-4, m), 3.1 (H-1, m), 3.8 (MeO, s), 5.9 (H-6, m), 6.4 (H-5, m).

Anal. of the mixture (22)/(23). Calcd. for $C_{12}H_{16}O_4$: C, 62.85; H, 6.71. Found: C, 62.79; H, 6.50.

2-Hydroxybicyclo(2.2.1)-5-heptenyl-2-carboxylic acid (24). A mixture of diester **(22)** (700 mg, 3.3 mmol) and 2.5 M NaOH (12 mL, 30 mmol) was heated to reflux for 2 h. The solution was acidified with 5 N HCl, then saturated with ammonium sulfate and extracted with chloroform (5 x 25 mL). The extracts were dried and the solvent was removed at reduced pressure to afford 275 mg of hydroxyacid **(24)** (62% yield), m.p. 47-49 °C; IR (KBr) 1706, 1668, 3426 cm^{-1}; 400 MHz ^{1}H NMR ($CDCl_3$ + CF_3COOH) δ 1.2 (H-7, d, Jgem = 12 Hz), 1.6 (H-3, d, Jgem = 9 Hz), 2.0 (H-3', m), 2.5 (H-7', d, J = 12 Hz), 2.9 (H-4, m), 3.1 (H-1, m), 6.0 (H-6, m), 6.4 (H-5, m), 6.5 (acid H's, br s). Anal. Calcd. for $C_8H_{10}O_3$: C, 62.38; H, 6.32. Found: C, 62.35; H, 6.52.

1-Hydroxy-5-iodotricyclo(3.2.1.1^{6,8})-3-oxanonan-2-one (25). A solution of **(24)** (150 mg, 1.0 mmol) in 0.5 N aqueous sodium bicarbonate (9 mL) was added to a solution of iodine (571 mg, 2.2 mmol) and potassium iodide (1.5 g) in 11 mL of water. The mixture was light-protected and stirred at room temperature for 38 h. After this period of time, sodium thiosulfate was added until color disappeared from the solution which was then extracted with ether (5 x 15 mL). The organic solution was dried and the solvent evaporated to give 120 mg of **(24)** (48% yield), m.p. 72-73 °C; IR (KBr) 1771, 3480 cm^{-1}; 400 ^{1}H NMR ($CDCl_3$) δ 1.7 (H-7, d, J =12 Hz), 2.1 (2 x H-3, m), 2.4 (H-7', d, J = 12 Hz), 2.8 (H-4, br s), 3.2 (H-1 + OH, br s), 3.8 (H-5, s), 5.2 (H-6, s); 100 MHz ^{13}C NMR ($CDCl_3$) δ 28.11, 35.96, 44.61, 46.84, 51.60, 75.10, 86.36, 179.25. Anal. Calcd. for $C_8H_9IO_3$: C, 34.31; H, 3.24; I45.31. Found: C, 34.31; H, 3.21; I, 45.22.

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