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A Study on the Phase Transfer Catalysed Michael Addition.

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Abstract. Solvent-free and liquid-liquid PTC conditions have been used for the Michael addition of several enolates to methyl vinyl ketone, chalcone and methyl acrylate. The solvent-free technique affords high yields whereas the liquid-liquid procedure is less efficient but allows enantioselective reactions.
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The asymmetric Michael addition is a widely used tool in organic synthesis.[1] Three main methodologies have been established: (i) the use of a chiral auxiliary on the Michael donor, (ii) the use of a Michael acceptor bearing a chiral centre and (iii) the use of ligands and other chiral mediators. Two significant results have been reported on the use of chiral phase transfer agents, which both belong to the third methodology. These examples are the Michael addition of the 6,7-dichloro-5-methoxy-1-indanone enolate to methyl vinyl ketone working under liquid-liquid PTC conditions[2] and the Michael addition of diethyl acetamidomalonate enolate to chalcone working under solvent-free solid-liquid PTC conditions.[3] In the first case an enolate-catalyst interaction is invoked to explain the result, whereas the second case is explained by a Michael acceptor-catalyst interaction. Our previous communication in this field,[4] concerning the reaction of 2-phenylcyclohexanone enolate with chalcone, showed a predominance of the enolate-catalyst interaction when both enolate and Michael acceptor bear π-systems. This result was established on the basis of a modification of the regioselectivity of the reaction, but no enantiomeric excesses were obtained.

We have now extended the study of the Michael addition under PTC conditions to the reactions of the enolates of 2-phenylcyclohexanone **1**, ethyl and benzyl 2-oxocyclohexancarboxylate (**2** and **3**, respectively), 2-propyl and 2-phenyl 6,7-dichloro-5-methoxy-1-indanone (**4** and **5**, respectively) towards methyl vinyl ketone (**6**), chalcone (**7**) and methyl acrylate (**8**).

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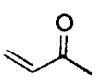
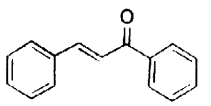
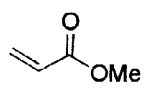
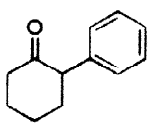
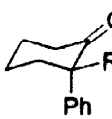
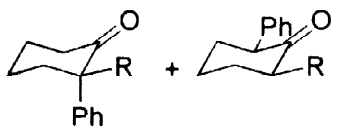
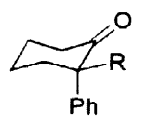
Results and Discussion

The reactions of the enolates of **1**, **2** and **3** with all Michael acceptors under liquid-liquid and solvent-free solid-liquid PTC conditions and the reactions of the enolates of **4** and **5** with the Michael acceptors **6** and **7** under liquid-liquid PTC conditions were performed (see Experimental Section). In all cases *N*-benzyl *N*-methylephedrinium bromide (solvent-free solid-liquid PTC conditions) and *N*-(4-trifluoromethylbenzyl)cinchoninium bromide (liquid-liquid PTC conditions) were used as catalysts. The best results, in terms of yields and enantiomeric excesses, are summarised in Tables 1 to 3.

Table 1. Reactions with 2-phenylcyclohexanone **1**.

	PTC conditions	 **6**	 **7**	 **8**
 **1**	Without solvent	 **9** racemic 95%	 **10** **11** racemic 41%	 **12** racemic 92%
	Liquid-liquid	ee: 46 % yield: 95 %	ee: 14 % yield: 31 %	ee: 20 % yield: 13 %

The reaction yields are highest in the absence of solvent and this could be considered an excellent technique when using small Michael acceptors. However, ee's were never obtained in this manner. This result indicates the ineffectiveness of both types of interaction in terms of obtaining enantioselectivity. The enolate-catalyst interaction does not differentiate between the enolate faces, showing again[5] the low importance of the hydrogen bond between the enolate and the hydroxy group of the catalyst. The catalyst-chalcone interaction has been shown to be ineffective when using enolates both with and without phenyl moieties. The existence of the uncatalysed reaction cannot be excluded due to the increase in the reactivity often observed when solvent-free conditions are used.[6] In the case of the reaction of the enolate of 2-phenylcyclohexanone, the enolate-catalyst interaction was shown to control the regioselectivity.[4]

Table 2. Reactions with 2-oxocyclohexancarboxylates.

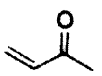
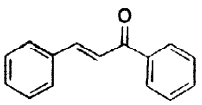
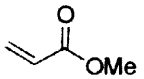
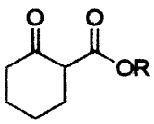
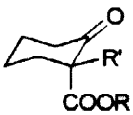
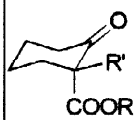
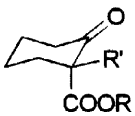
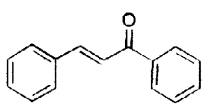
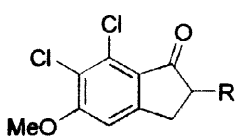
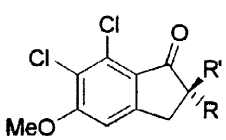
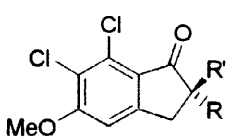
	PTC conditions	 6	 7	 8
 2, 3	Without solvent	 R= Et R= Bn **13** **14** racemic yield: 94% 91%	 R= Et R= Bn **15** **16** racemic yield: 54% 40%	 R= Et R= Bn **17** **18** racemic yield: 80% 97%
	Liquid-liquid	R= Et R= Bn ee: 4 % 20% yield: 55 % 25%	No reaction	R= Et R= Bn ee: 6 % 28 yield: 5 % 9%

Table 3. Reactions with 6,7-dichloro-5-methoxy-1-indanones.

	PTC conditions	 6	 7
 4, 5	Liquid-liquid	 R= Pr R= Ph **19** **20** ee: 70% 52% yield: 97% 50%	 R= Pr R= Ph **21** **22** ee: 0% 10% yield: 43% 10%

The use of liquid-liquid PTC conditions (aq. NaOH / toluene) led to different results in all reactions. As expected, lower yields were obtained and, in the case of the esters, no reaction with chalcone was observed

after 24 hours. However, in these reactions enantiomeric excesses were achieved. When a complete series can be compared (Table 4) it becomes evident that a relationship can be established between the existence of a π-system on the enolate and the enantiomeric excesses obtained. The distance between the π-system and the centre with a high charge density also plays a significant role. The results obtained (enantio- and diastereoselectivity) in the reactions with chalcone can be rationalised by considering that the approach of the chalcone to the enolate with the phenyl group on the ring (Figure 1) is less hindered than those in which the phenyl group is near to the 2-substituent. A similar explanation has been used to justify the diastereoselectivity obtained in the reaction of **1** and 7.[4]

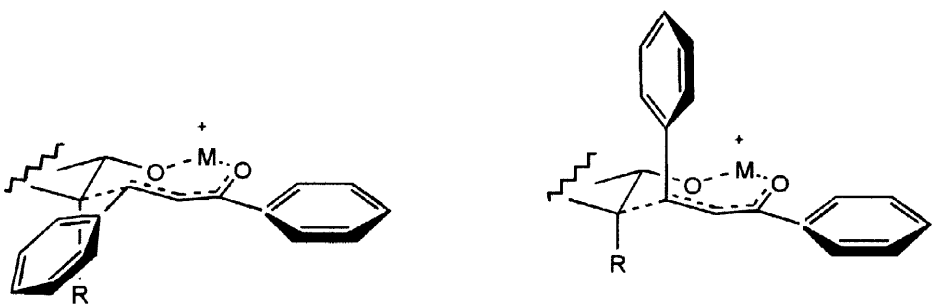


Figure 1

Table 4. Enantiomeric excesses in the reactions with methylvinylketone (liquid-liquid conditions)

Enolate	**1**	**2**	**3**	**4**	**5**
ee (%)	46	4	20	70	52

A set of four experiments was performed in order to gain more information about the role of the hydrogen bond between the catalyst and the enolate. The reaction of 2-phenylcyclohexanone and methyl vinyl ketone was performed in the presence of *N*-(4-trifluoromethylbenzyl)cinchoninium bromide, *N*-(4-trifluoromethylbenzyl)cinchonidinium chloride and their respective *O*-benzyl derivatives. As expected, each catalyst affords enantiomeric excesses (46 and 58%) of different enantiomers, but a change in the sense of the enantioselectivity and a decrease in the enantiomeric excesses were observed on using the *O*-benzyl derivatives. The *O*-benzylated catalysts discriminate poorly between the enolate faces (ee: 20 and 16%). This means that the hydrogen bond plays a determinant role in defining the enolate face which is blocked.

Previously, we reported the structure and stereochemical elucidation of isomers (products **10**, **11**) obtained in the reaction of 2-phenylcyclohexanone and chalcone, based on a combination of NMR

spectroscopy, NOE experiments and coupling constants, and molecular mechanics.[7] In the case of the ester **3**, the stereochemistry of the resultant products are again examined.

NMR study

Assignment of the ^{13}C-NMR NMR signals in the cyclohexane ring and the exocyclic chain was achieved using data from the DEPT spectra which shows six methylenes, one methine and one quaternary carbon atom. One bond CH correlation experiments permitted the assignment of the ^{1}H-NMR spectra and these assignments were confirmed by means of the H,H COSY spectra and the multiplicity and coupling constants in the ^{1}H-NMR spectra. Differentiation between equatorial and axial protons was possible due to the larger coupling constants in axial protons and that equatorial protons are usually less shielded. Differentiation between H-2' and H-2'' was performed by comparing the experimental coupling constants with H-1' and the values calculated from the molecular modelling.

Molecular mechanics calculations

The two isomers **16a** (1*S*-1'*R*) and **16b** (1*S*-1'*S*) were subjected to a conformational search by means of molecular mechanics calculations using the MMX-type force field,[8] which has proved to be a reliable method in conformational analysis.[9] The nine staggered conformations around the CH–CH_2 and CH-cyclohexyl bonds for both isomers are shown in Figure 2.

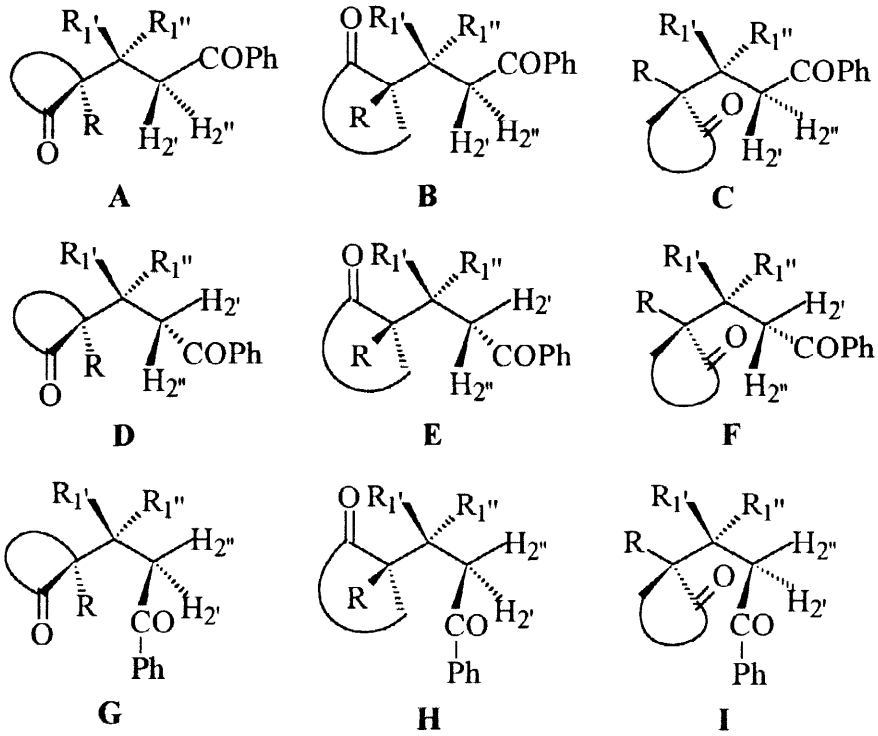
Table 5 shows the MMX energies (Kcal/mol) and calculated conformational populations for the conformers A–I of isomers **16a** and **16b**. The conformational population of conformers A–I for each isomer was calculated by application of the Boltzmann equation using the energy of conformers determined by the MMX force field.

The vicinal coupling constants (^{3}J) were calculated for all conformations using the Karplus-type empirical equation proposed by Altona *et al.*[10] for H–C(sp^3)–C(sp^3)–H and the dihedral angles provided by the geometrical optimisation established with the MMX force field. These coupling constants were averaged by a weight factor proportional to the relative populations of conformations (see Table 5) as shown in Table 6. In this way the coupling constants could be compared directly with the observed values (Table 7).

Both isomers can be considered to be monoconformational, as the relative population is higher than 0.7 for conformer A in **16a** and higher than 0.5 for conformer C in **16b**. Bearing this fact in mind, it is possible to compare the NOE detected in the NMR spectra with the interatomic distances in the most stable conformer. The good agreement between differences in interatomic distances and NOE enhancements is illustrated by the data in Table 8.

Table 5. MMX Calculated Energies (Kcal/mol) and Calculated Conformational Populations (in brackets) for Conformers A-I of Compounds 16a and 16b

Isomer	Conformer								
	A	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**
16a	44.16	45.47	45.36	48.02	49.38	51.14	46.96	46.10	47.06
	(0.77)	(0.08)	(0.10)	(0.00)	(0.00)	(0.00)	(0.01)	(0.03)	(0.01)
16b	45.82	45.38	44.82	46.87	46.54	46.18	51.64	48.85	49.23
	(0.10)	(0.22)	(0.57)	(0.02)	(0.03)	(0.06)	(0.00)	(0.00)	(0.00)



R = CO_2CH_2Ph **16a** $R_1'=H_1'$ $R_1''=Ph$

16b $R_1'=Ph$ $R_1''=H_1'$

Figure 2. Conformations for isomers **16a** and **16b**

Table 6. Calculated Vicinal Coupling Constants for Conformers A-I of Compounds 16a and 16b

Isomer	16a		16b	
Conformer	$J_{1'-2'}$	$J_{1'-2''}$	$J_{1'-2'}$	$J_{1'-2''}$
A	2.53	12.33	12.34	3.38
B	3.08	12.36	12.36	3.05
C	3.20	12.35	12.29	2.36
D	4.47	2.23	1.33	11.59
E	6.31	1.30	1.17	11.36
F	1.80	5.43	2.96	12.32
G	12.17	1.74	4.91	2.48
H	11.75	1.43	1.89	5.08
I	11.10	1.12	1.55	5.58
J_{ijXn}	**3.03**	**11.87**	**11.23**	**3.63**

Table 7. Observed ($CDCl_3$) and Calculated Vicinal Coupling Constants for compounds **16a** and **16b**

	Observed		Calculated	
	$J_{1'-2'}$	$J_{1'-2''}$	$J_{1'-2'}$	$J_{1'-2''}$
16a	3.2	10.3	3.03	11.87
16b	10.9	3.0	11.23	3.63

Table 8. Compounds **16a** and **16b**. Calculated Distances (Å) for the Major Conformer.

Isomer	16	16a[a]	16b
o-H-Ph-1'; H2'	3.82	3.57	2.21□
o-H-Ph-1'; H2''	2.24□	2.14	3.81
H-1'; H-2'	2.50□	2.37	3.08
H-1'; H-2''	3.08	3.07	2.49□

[a] X-ray crystallographic data.
□ NOE detected

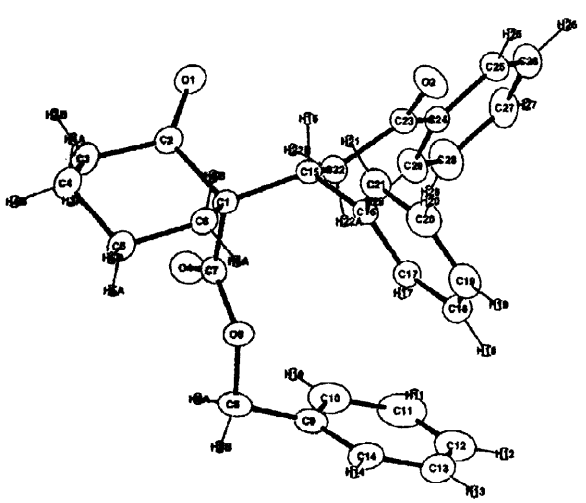


Figure 3. Isomer **16a**. X-ray structure of enantiomer SR (ORTEP representation)

Conclusions

In conclusion, solvent free PTC is an efficient tool to perform Michael additions with a variety of Michael donors and Michael acceptors. However, enantioselective Michael additions require reactions to be carried out in liquid-liquid conditions. The existence of π-moieties on the catalyst and on the Michael donor is also needed.

Experimental Section

NMR spectra were recorded in $CDCl_3$ using a VARIAN UNITY 300 spectrometer operating at 299.980 MHz for proton and 75.423 MHz for carbon-13 at a temperature of 293 K. NOE difference spectra used a 7 second presaturation period for each transient, with blocks of 16 transients per irradiation site. This was cycled to give a total of 128 transients per irradiation frequency. H,H COSY spectra were acquired using a 2.3 kHz spectral width; 8 transients of 1 K data points were collected for each 380 t_1 increments. A 1 second relaxation delay was used. The data were processed using sine-bell functions in both dimensions before Fourier Transformation. C,H COSY spectra were acquired using a 16.5 kHz spectral width; 250 transients of 1 K data points were collected for each 256 t_1 increments. A 1 second relaxation delay was used. The data were processed using sine-bell functions in both dimensions before Fourier Transformation. The 2D NOE spectra were acquired in the phase sensitive mode with 2D hypercomplex data (States-Haberkorn method).[11] The relaxation delay was 0.5 seconds and mixing times were 500 milliseconds. Typically, 1024 real t_2 data points were acquired for each 512 t_1 increments of 16 transients, each with a spectral width of 2.6 kHz. Experiments were recorded on a static sample at 293 K. The free induction decays were processed with square cosine-bell filters in both dimensions, and zero filling was applied in the F_1 dimension prior to double Fourier Transformation. Chemical shifts are reported in δ units (ppm) relative to tetramethylsilane and coupling constants expressed in Hz. Enantiomeric excesses of the Michael adducts were determined by NMR chiral shift using $Eu(hfc)_3$.

General procedure for the Michael addition

Liquid / Solid Phase-Transfer System without solvent: A mixture of the Michael donor (1.5 mmol) and catalytic quantities (6 mol%) of base (KOH) and the catalyst [(–)-*N*-benzyl, *N*-methylephedrinium bromide] was stirred for 5 min. The Michael acceptor (1.5 mmol) was then added and the mixture was stirred at 20 °C for 24 h. The crude mixture was extracted with dichloromethane (20 mL) and filtered. The solvent was removed under reduced pressure and purified by column chromatography (silica gel 230–400 mesh) to give the pure products.

Liquid / Liquid Phase-Transfer System: The catalyst *N*-(4-trifluoromethylbenzyl)cinchoninium bromide (5.6 % mol) and 3.75 mL of 50% aqueous NaOH were added to a solution of the corresponding Michael donor (1.5 mmol) in 11 mL of toluene. The mixture was stirred at 20 °C and a solution of the Michael acceptor (1.5 mmol) in 4 mL of toluene was added dropwise over 0.5 h. The reaction was stirred for

the required time. The organic layer was separated and washed with 10 mL of 1 N HCl. The toluene solution was dried over $MgSO_4$, filtered, and the solvent removed in vacuo.

2-phenyl-2-(3'-oxobutyl)cyclohexanone (9). Colorless oil. ^{1}H-NMR ($CDCl_3$) δ 7.36-7.12 (5H, m), 2.67 (1H, dt, J = 8.0, 3.0 Hz), 2.00 (3H, s), 2.46-1.77 (11H, m). ^{13}C-NMR ($CDCl_3$) δ 213, 208, 140.32, 128.87, 126.92, 126.84, 56.82, 40.14, 38.84, 36.03, 34.02, 29.59, 28.22, 21.55.

Methyl 3-(2'-oxo-1'-phenylcyclohexyl)propanoate (12). Colorless oil. Eluent: hexane : ethyl acetate 10 : 1. ^{1}H-NMR ($CDCl_3$) δ 7.36-7.14 (5H, m), 3.56 (3H, s), 2.69 (1H, dt, J = 11.5, 3.0 Hz), 2.44-1.72 (11H, m). ^{13}C-NMR ($CDCl_3$) δ 212.92, 173.87, 139.69, 128.83, 126.85, 126.83, 56.60, 51.32, 39.96, 35.43, 34.92, 29.07, 28.23, 21.44.

Ethyl 2-oxo-1-(3'-oxobutyl)cyclohexancarboxylate (13). Colorless oil. Eluent: hexane : ethyl acetate 10 : 1). ^{1}H-NMR ($CDCl_3$) δ 4.16 (2H, dq, J = 7.1, 1.6 Hz), 2.60-2.34 (5H, m), 2.09 (3H, s), 2.05-1.38 (7H, m), 1.24 (3H, t, J = 7.1 Hz). ^{13}C-NMR ($CDCl_3$) δ 207.93, 207.70, 171.92, 61.33, 59.88, 40.94, 38.73, 36.61, 29.87, 28.30, 27.46, 22.48.

Ethyl 2-oxo-1-(3'-methoxycarbonylethyl)cyclohexancarboxylate (17). Colorless oil. Eluent: hexane : ethyl acetate 10 : 1). ^{1}H-NMR ($CDCl_3$) δ 4.21 (2H, dq, J = 7.1, 2.8 Hz), 3.66 (3H, s), 2.54-1.41 (12H, m), 1.28 (3H, t, J = 7.2 Hz). ^{13}C-NMR ($CDCl_3$) δ 207.43, 173.35, 171.54, 61.33, 59.85, 51.54, 40.90, 36.24, 29.57, 29.23, 27.42, 22.43.

(1S-1'R/1R-1'S) Ethyl 1-(1',3'-diphenyl-3'-oxopropyl)-2-oxo-cyclohexancarboxylate (15a). White solid. m.p. 141-143°C (from ethanol). Eluent: hexane : ethyl acetate 10 : 1. ^{1}H-NMR ($CDCl_3$) δ 7.92 (2H, d, J = 8.6 Hz), 7.51 (1H, t, J = 7.4 Hz), 7.40 (2H, t, J = 7.4 Hz), 7.20 (5H, m), 4.23 (2H, dq, J = 7.1, 1.1 Hz), 3.99 (1H, dd, J = 10, 3.8 Hz), 3.60 (1H, dd, J = 17.2, 3.8 Hz), 3.52 (1H, dd, J = 17, 10 Hz), 2.52 (2H, m), 2.11 (1H, dd, J = 13.4, 2.9 Hz), 1.99 (1H, m), 1.60 (4H, m), 1.28 (3H, t, J = 7.2 Hz). ^{13}C-NMR ($CDCl_3$) δ 208.04, 198.17, 170.90, 139.34, 136.99, 132.76, 129.87, 128.37, 128.04, 127.81, 126.96, 64.31, 61.31, 44.94, 41.60, 36.85, 27.88, 22.52, 14.08.

(1S-1'S/1R-1'R) Ethyl 1-(1',3'-diphenyl-3'-oxopropyl)-2-oxo-cyclohexancarboxylate (15b). White solid. m.p. 141-143°C (from ethanol). Eluent:hexane : ethyl acetate 10 : 1). ^{1}H-NMR ($CDCl_3$) δ 7.94 (2H, d, J = 8.4 Hz), 7.52 (1H, t, J = 7.3 Hz), 7.41 (2H, t, J = 7.3 Hz), 7.20 (5H, m), 4.19 (1H, dd, J = 10.6, 3.0 Hz), 4.00 (2H, dq, J = 7, 4.6 Hz), 3.69 (1H, dd, J = 16.7, 10.6 Hz), 3.40 (1H, dd, J = 16.7, 3 Hz), 2.58 (1H, td, J = 9.8, 2.8 Hz), 2.43 (2H, m), 1.98 (1H, m), 1.68 (4H, m), 1.14 (3H, t, J = 7.1 Hz). ^{13}C-NMR ($CDCl_3$) δ 206.89, 197.90, 170.67, 139.53, 137.04, 132.73, 129.65, 128.38, 128.07, 128.01, 127.00, 65.05, 61.45, 44.71, 41.77, 40.73, 32.37, 26.56, 22.42, 13.85.

Benzyl 1-(3'-methoxycarbonylethyl)-2-oxo-cyclohexancarboxylate (14). Colorless oil. Eluent: hexane : ethyl acetate 15 : 1. ^{1}H-NMR ($CDCl_3$) δ 7.35 (5H, m), 5.17 (2H, s), 2.02 (3H, s), 2.49-1.40 (12H, m). ^{13}C-NMR ($CDCl_3$) δ 207.62, 207.51, 171.75, 135.21, 128.57, 128.49, 128.46, 66.99, 59.97, 40.93, 38.61, 36.74, 29.74, 28.39, 27.46, 22.46.

Benzyl 2-oxo-1-(3'-oxobutyl)cyclohexancarboxylate (18). Colorless oil. Eluent: hexane : ethyl acetate 15 : 1. ^{1}H-NMR ($CDCl_3$) δ 7.35 (5H, m), 5.22 (1H, d, J = 12.2 Hz), 5.13 (1H, d, J = 12.2 Hz), 3.62 (3H, s), 2.52-1.40 (12H, m). ^{13}C-NMR ($CDCl_3$) δ 207.25, 173.38, 171.50, 135.15, 128.61, 128.46, 128.29, 67.10, 60.07, 51.61, 40.96, 36.30, 29.65, 29.27, 27.45, 22.45.

(1S-1'R/1R-1'S) Benzyl 1-(1',3'-diphenyl-3'-oxopropyl)-2-oxo-cyclohexancarboxylate (16a). White solid. m.p. 122-123°C (from methanol). Eluent: hexane : ethyl ether 10 : 1. ^{1}H-NMR ($CDCl_3$) δ 7.74 (2H, d, J = 8.6 Hz), 7.49 (1H, dt, J = 7.4, 1.5 Hz), 7.41 (5H, m), 7.35 (2H, dt, J = 7.4, 1.3 Hz), 7.14 (5H, m), 5.29 (1H, d, J = 12 Hz), 5.17 (1H, d, J = 12 Hz), 4.03 (1H, dd, J = 10.3, 3.2 Hz), 3.51 (1H, dd, J = 17.5, 3.2 Hz), 3.40 (1H, dd, J = 17.5, 10.3 Hz), 2.49 (2H, m), 2.09 (1H, m), 1.95 (1H, m), 1.58 (4H, m). ^{13}C-NMR ($CDCl_3$) δ 207.70, 197.81, 170.69, 139.29, 136.93, 135.01, 132.68, 129.79, 128.98, 128.70, 128.28, 127.97, 127.84, 126.93, 67.18, 64.23, 44.62, 41.53, 41.50, 36.85, 27.94, 22.38.

(1S-1'S/1R-1'R) Benzyl 1-(1',3'-diphenyl-3'-oxopropyl)-2-oxo-cyclohexancarboxylate (16b). White solid. m.p. 133-135°C (from methanol). Eluent: hexane : ethyl ether 10 : 1. ^{1}H-NMR ($CDCl_3$) δ 7.90 (2H, d, J = 8.3 Hz), 7.51 (1H, t, J = 7.3 Hz), 7.40 (2H, dt, J = 7.5, 1.3 Hz), 7.33-7.13 (10H, m), 4.99 (1H, d, J = 12.2 Hz), 4.96 (1H, d, J = 12.2 Hz), 4.20 (1H, dd, J = 10.7, 3 Hz), 3.70 (1H, dd, J = 16.9, 10.7 Hz), 3.34 (1H, dd, J = 16.9, 3 Hz), 2.58 (1H, d, J = 9.9 Hz), 2.43 (1H, d, J = 14 Hz), 2.33 (1H, td, J = 13, 6 Hz), 1.94

(1H, m), 1.76 (1H, m), 1.64 (3H, m) ^{13}C-NMR ($CDCl_3$) δ 206.69, 197.75, 170.57, 139.42, 136.93, 134.89, 132.73, 129.63, 128.51, 128.45, 128.38, 128.35, 128.06, 127.02, 67.02, 65.08, 44.75, 41.77, 40.61, 32.46, 26.46, 22.34.

6,7-dichloro-2,3-dihydro-5-methoxy-2-(3'-oxobutyl)-2-phenyl-1H-inden-1-one (20). White solid. m.p. 112-114°C (from ethanol).Eluent: hexane : ethyl acetate 15 : 1). ^{1}H-NMR ($CDCl_3$) δ 7.20-7.38 (5H, m), 6.58 (1H, s), 3.88 (3H, s), 3.48 (1H, d, J = 17.6 Hz), 3.25 (1H, d, J = 17.6 Hz), 2.52-2.32 (4H, m), 2.06 (3H, s). ^{13}C-NMR ($CDCl_3$) δ 207.93, 202.33, 161.09, 153.63, 141.29, 132.27, 128.75, 126.98, 126.54, 125.75, 124.66, 123.20, 106.39, 56.92, 41.55, 38.94, 32.20, 29.99.

(2R-1'S/2S-1'R) 6,7-dichloro-2,3-dihydro-5-methoxy-2-(1',3'-diphenyl-3'-oxopropyl)-2-propyl-1H-inden-1-one (21a). White solid. m.p. 164-166°C (from ethanol). Eluent: hexane : ethyl acetate 15 : 1) .^{1}H-NMR ($CDCl_3$) δ 7.84 (2H, d, J = 7.3 Hz), 7.51 (1H, t, J = 7.3 Hz), 7.40 (2H, t, J = 7.8 Hz), 7.25 (2H, d, J = 6.6 Hz), 7.14 (3H, m), 6.76 (1H, s), 3.95 (3H, s), 3.75 (1H, dd, J = 13.1, 0.9 Hz), 3.62 (1H, dd, J = 17.1, 0.9 Hz), 3.60 (1H, dd, J = 17.1, 13.1 Hz), 3.20 (1H, d, J = 18.1 Hz), 2.84 (1H, d, J = 18.1 Hz), 1.94 (1H, m), 1.59 (1H, m), 1.02 (2H, m), 0.83 (3H, t, J = 7 Hz). ^{13}C-NMR ($CDCl_3$) δ 204.55, 198.32, 160.85, 154.39, 140.27, 137.15, 132.84, 129.54, 128.44, 127.94, 127.92, 126.79, 122.70, 106.13, 56.83, 56.78, 46.76, 39.36, 37.45, 35.90, 17.69, 14.59.

(2R-1'R/2S-1'S) 6,7-dichloro-2,3-dihydro-5-methoxy-2-(1',3'-diphenyl-3'-oxopropyl)-2-propyl-1H-inden-1-one (21b). White solid. m.p. 207-208°C (from ethanol). Eluent: hexane : ethyl acetate 15 : 1). ^{1}H-NMR ($CDCl_3$) δ 7.86 (2H, d, J = 7.7 Hz), 7.51 (1H, t, J = 7.3 Hz), 7.40 (2H, t, J = 7.3 Hz), 7.13 (5H, m), 6.74 (1H, s), 3.95 (3H, s), 3.84 (1H, dd, J = 10.7, 3.4 Hz), 3.59 (1H, dd, J = 16.6, 3.4 Hz), 3.39 (1H, dd, J = 16.6, 3.4 Hz), 3.26 (1H, d, J = 18.4 Hz), 2.83 (1H, d, J = 18.4 Hz), 1.66 (1H, m), 1.46 (1H, m), 1.09 (2H, m), 0.77 (3H, t, J = 7.2 Hz). ^{13}C-NMR ($CDCl_3$) δ 205.83, 198.35, 160.68, 155.05, 140.28, 136.83, 132.86, 129.01, 128.40, 128.10, 128.03, 126.79, 122.70, 106.23, 57.00, 56.79, 46.80, 40.31, 39.90, 35.82, 17.62, 14.45.

(2S-1'R/2R-1'S) 6,7-dichloro-2,3-dihydro-5-methoxy-2-(1',3'-diphenyl-3'-oxopropyl)-2-phenyl-1H-inden-1-one (22). White solid. m.p. 199-201°C (from ethanol). Eluent: hexane : ethyl acetate 15 : 1. ^{1}H-NMR ($CDCl_3$) δ 7.81 (2H, d, J = 7.8 Hz), 7.46 (3H, m), 7.28 (7H, m), 7.05 (3H, m), 6.55 (1H, s), 4.24 (1H, dd, J = 11, 2.1 Hz), 4.10 (1H, dd, J = 17.4, 11 Hz), 3.85 (3H, s), 3.56 (1H, d, J = 17.9 Hz), 3.34 (1H, d, J = 17.9 Hz), 3.23 (1H, dd, J = 17.5, 2.1 Hz). ^{13}C-NMR ($CDCl_3$) δ 203.12, 198.36, 160.85, 153.89, 142.39, 139.57, 136.95, 132.76, 131.48, 129.49, 128.74, 128.30, 128.01, 127.26, 127.10, 126.93, 122.80, 106.03, 61.33, 56.74, 50.04, 40.57, 40.12.

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REFERENCES

1. Leonard, J. *Contemporary Organic Synthesis* **1994**, 387.
2. Conn, R.S.E.; Lovell, A.V.; Karady, S.; Weinstock, L.M. *J. Org. Chem.* **1986**, *51*, 4710.
3. (a) Loupy, A.; Sansoulet, J.; Zaparucha, A.; Merienne, C. *Tetrahedron Lett.* **1989**, *30*, 333. (b) Loupy, A.; Zaparucha, A. *Tetrahedron Lett.* **1993**, *34*, 473.
4. Díez-Barra, E.; de la Hoz, A.; Merino, S.; Sánchez-Verdú, P. *Tetrahedron Lett.* **1997**, *38*, 2359.
5. O'Donnell, M.J.; Wu, S.; Huffman, J.C. *Tetrahedron* **1994**, *50*, 4507.
6. Bram, G.; Loupy, A.; Sansoulet, J. *Isr. J. Chem.* **1985**, *26*, 291.
7. de la Hoz, A.; Díez-Barra, E.; Langa, F.; Merino, S.; Rodríguez, A.; Sánchez-Verdú, P. *Tetrahedron* **1997**, *53*, 11693.
8. PCMODEL molecular modeling software, version 5.0 from Serena Software, Bloomington, IN, was used for these calculations. For each structure, the minimum energy was determined after reminimization.
9. (a) Alvarez-Ibarra, C.; Cuervo-Rodríguez, R.; Fernández-Monreal, M.C.; Ruiz, M.P. *J. Org. Chem.* **1994**, *59*, 7284. (b) Alvarez-Ibarra, C.; Cuervo-Rodríguez, R.; Fernández-Monreal, M.C.; Ruiz, M.P. *Tetrahedron* **1996**, *52*, 11239.
10. Haasnoot, C.A.G.; de Leeuw, F.A.A.M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783.
11. States, D.J.; Haberkorn, R.A.; Ruben, D.J. *J. Magn. Reson.* **1982**, *48*, 286.