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Structural Determination by NMR Spectroscopy and Molecular Mechanics of the Regio and Diastereoisomers obtained in the Addition of 2-Phenylcyclohexanone to Chalcone.

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Abstract: The structure and stereochemistry of the six regio and stereoisomers obtained in the reaction of 2-Phenylcyclohexanone **1** with chalcone **2** by solvent-free phase transfer catalysis has been determined by a combination of NMR techniques and molecular mechanics calculations. The validity of the method has been confirmed by the X-ray structure determination of isomer 7.

The Michael addition reaction is one of the most fundamental C-C bond forming reactions in the synthesis of to 1,5-dicarbonyl compounds.[1] This method has been widely used for the preparation of both carbocyclic and heterocyclic compounds, it being one of the most important structure building reactions in organic synthesis. Asymmetric versions of this reaction have been extensively studied.[1]

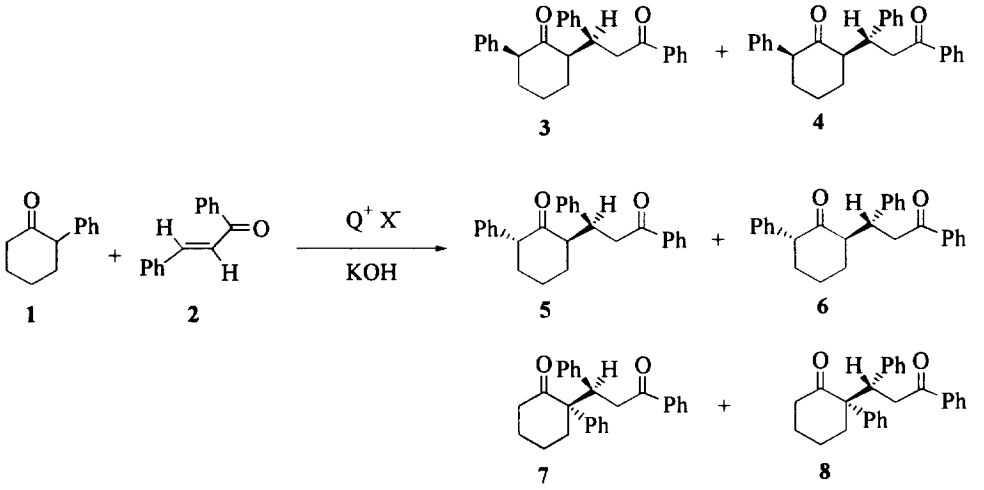
During our investigation into the application of solvent-free phase transfer catalysis we became interested in studying the influence of the absence of solvent on regio and diastereoselectivities in the reaction of 2-phenylcyclohexanone **1** with chalcone **2**[2] and on the enantioselectivity in this reaction when using enantiomerically pure phase transfer agents.

2-Phenylcyclohexanone **1** reacts with chalcone **2** under solvent-free phase transfer catalysis to give products **3-8** (Scheme 1).[2] The regio and diastereoselectivity are controlled by a careful choice of the reaction conditions, counterion, temperature or phase transfer agent.[2] In order to show the influence of several factors on the regio, diastereo and enantioselectivity, the structure of the six products must be accurately determined.

Several approaches have been used for the configurational and conformational analysis of organic compounds. They include, molecular mechanics and ^{1}H-NMR, chemical shifts and coupling constants for β-hydroxysulphoxides,[3] cembrene derivatives,[4] N-nitrosopiperidines,[5] and spirocyclic oxaziridines,[6] CP-MAS ^{13}C-NMR for microcrystalline samples,[7] NOE transfer due to restricted rotation for (9-Anthryl)carbinol derivatives,[8] and DNMR spectroscopy for arylmethoxyacetates,[9] and N-naphtylimines,[10] CD and ^{1}H-NMR studies for β-glucopyranosides,[11] NOE enhancements and molecular modelling of β-sulfinylenamines,[12] long-

range carbon-proton coupling constants in the three dimensional structure of okadaic acid,[13] and 1D HOHAHA and NOE enhancements in the study of N-nitroso compounds.[14]

The choice of one of these techniques is based essentially on the structure of the compounds to be studied.



Scheme 1

Isomers **3-8** have a cyclic structure with one or two chiral centres in the ring and an additional chiral centre in the exocyclic chain. This short exocyclic chain can be analysed by conformational analysis because rotation of the C-6-C-1' and C-1'-C-2' bonds gives nine conformers whose stability can be compared.

We now present the structure and stereochemical elucidation of isomers **3-8**, based on a combination of NMR spectroscopy, NOE experiments and coupling constants, and molecular mechanics, using PCMODEL.[15] The validity of the method has been confirmed by X-ray crystal structure determination of isomer **7**.

Results

NMR study

The most significant NMR signals of compounds **3-8** and correlations observed in the H,H-COSY, C,H-COSY and NOESY spectra are collected in tables 1-6. The spectra of isomer **3** were recorded in $CDCl_3$, DMSO-d_6 and acetone-d_6 to observe the influence of solvent polarity on the conformational equilibrium (see experimental part). The small differences shown in chemical shifts and coupling constants in the NMR spectra

Table 1. Compound **3**. Correlation Experiments

One bond C,H correlations

		H-2	H-1'	H-2'	H-2"	H-6	H-3eq	H-3a	H-5eq H-4	H-5a
		3.75	3.69	3.60	3.12	2.94	2.26	1.97	1.77	1.32
C-2	58.63	■								
C-6	56.16					■				
C-2'	44.35			■	■					
C-1'	41.90		■							
C-3	37.35						■	■		
C-5	34.50								■	■
C-4	25.81								■	

H,H correlations, COSY ■, NOESY □

H-2	H-1'	H-2'	H-2"	H-6	H-3eq	H-3a	H-5eq H-4	H-5a		
3.75	3.69	3.60	3.12	2.94	2.26	1.98	1.79	1.30		
		□	□						7.88	**COPh**
□						□			7.22	**Ph-2**
	□		□	□			□	□	7.12	**Ph-1'**
			□	■	■□		□		3.75	**H-2**
		■□	■	■					3.69	**H-1'**
			■□						3.60	**H-2'**
									3.12	**H-2"**
							■□	■	2.94	**H-6**
						■□	□		2.26	**H-3eq**
							■□		1.98	**H-3a**
								■□	1.79	**H-4, H-5eq**

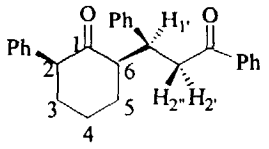


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Table 2. Compound **4**. Correlation Experiments

One bond C,H correlations

		H-1'	H-2"	H-2	H-2'	H-6	H-3eq H-5eq	H-3a H-4eq	H-4a	H-5a
		3.92	3.63	3.59	3.42	2.92	2.26	2.01	1.82	1.67
C-2	58.19			■						
C-6	55.87					■				
C-2'	40.76		■		■					
C-1'	40.25	■								
C-3	36.06						■	■		
C-5	31.02						■			■
C-4	25.75							■	■	

H,H correlations, COSY ■, NOESY □

H-1'	H-2"	H-2	H-2'	H-6	H-3eq H-5eq	H-3a H-4eq	H-4a	H-5a		
3.92	3.63	3.59	3.42	2.92	2.26	2.01	1.82	1.67		
		□	□						7.93	**COPh**
□		□	□	□	□				7.29	**Ph-1'**
		□			□	□			7.11	**Ph-2**
■□		■□	■□						3.92	**H-1'**
		■							3.63	**H-2"**
			□	■□	■	□			3.59	**H-2**
							□		3.42	**H-2'**
					■□		□	■	2.92	**H-6**
						■□		■□	2.26	**H-3eq H-5eq**
							■	■□	2.01	**H-3a H-4eq**
								■	1.82	**H-4a**

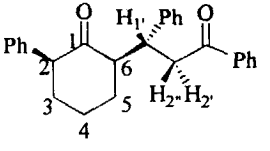

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Table 3. Compound **5**. Correlation Experiments

One bond C,H correlations

		H-1' 3.77	H-2' 3.53	H-2" 3.09	H-3e 3.01	H-2 2.99	H-6 2.80	H-3a 1.76	H-5eq H-4 1.68	H-5a 1.25
C-2	59.61					■				
C-6	52.56						■			
C-2'	43.77		■	■						
C-1'	41.37	■								
C-3	39.99				■			■		
C-5	34.47								■	■
C-4	22.63								■	

H,H correlations, COSY ■, NOESY □

H-1' 3.77	H-2' 3.53	H-2" 3.09	H-3eq 3.01	H-2 2.99	H-6 2.80	H-3a 1.76	H-5eq H-4 1.68	H-5a 1.25	
□	□	□							7.92 **COPh**
	□		□	□	□		□		7.31 **Ph-2**
□		□			□				7.03 **Ph-1'**
	■□	■		■	■				3.77 **H-1'**
		■			□				3.53 **H-2'**
									3.09 **H-2"**
						■□	■		3.01 **H-3eq**
						■□			2.99 **H-2**
							■□		2.80 **H-6**
									1.76 **H-3a**
								■□	1.68 **H-5eq H-4**

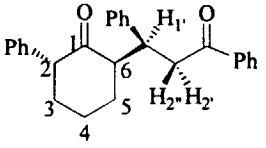

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Table 4. Compound **6**. Correlation Experiments

One bond C,H correlations

		H-1' 3.99	H-2 3.69	H-2" 3.49	H-2' 3.39	H-6 2.92	H-3 2.20	H-4eq H-5 2.07	H-4a 1.84
C-6	54.85					■			
C-2	54.55		■						
C-2'	42.87			■	■				
C-1'	40.74	■							
C-3	32.44						■		
C-5	30.38							■	
C-4	21.06							■	■

H,H correlations, COSY ■, NOESY □

H-1' 3.99	H-2 3.69	H-2" 3.49	H-2' 3.39	H-6 2.92	H-3 2.20	H-4eq H-5 2.07	H-4a 1.84	
		□	□					7.90 **COPh**
□			□	□				7.26 **Ph-1'**
	□				□			6.84 **Ph-2**
		■	■□	■				3.99 **H-1'**
			□		■□			3.69 **H-2**
			■					3.49 **H-2"**
								3.39 **H-2'**
						■		2.92 **H-6**
						■□	■□	2.20 **H-3**
							■□	2.07 **H-4eq H-5**

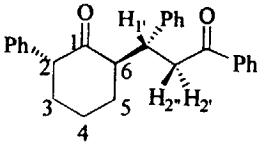

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Table 5. Compound 7. Correlation Experiments

One bond C,H correlations

		H-1' 3.98	H-2' 3.68	H-2" 2.88	H-6a 2.54	H-6eq 2.31	H-3eq 2.18	H-5eq 1.90	H-3a 1.68	H-5a 1.64	H-4 1.57
C-1'	47.57	■									
C-2'	41.84		■	■							
C-6	40.60				■	■					
C-3	37.32						■		■		
C-5	29.10							■		■	
C-4	21.37										■

H,H correlations, COSY ■, NOESY □

H-1' 3.98	H-2' 3.68	H-2" 2.88	H-6a 2.54	H-6eq 2.31	H-3eq 2.18	H-5eq 1.90	H-3a 1.68	H-5a 1.64	H-4 1.57	
□	□	□								7.84 **PhCO**
		□	□		□				□	6.99 **Ph-2**
□		□			□		□	□		6.74 **Ph-1'**
■□		■					□			3.98 **H-1'**
	■□	■□								3.68 **H-2'**
										2.88 **H-2"**
			■□			■□		■	■□	2.54 **H-6a**
				■□		■□		■□		2.31 **H-6eq**
							■	■□	■	2.18 **H-3eq**
							■		□	1.90 **H-5eq**
									■	1.68 **H-3a**
									■	1.64 **H-5a**

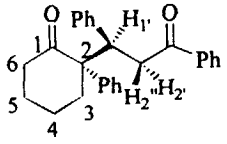

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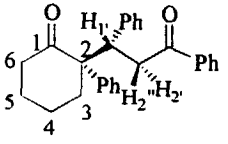
Table 6. Compound **8**. Correlation Experiments

One bond C,H correlations

		H-1' 3.99	H-2' 3.67	H-2" 3.44	H-3eq 2.66	H-6 2.34	H-3a 2.03	H-5eq 1.89	H-4 1.71	H-5a 1.65
C-1'	49.49	■								
C-6	40.87					■				
C-2'	40.61		■	■						
C-3	30.51				■		■			
C-5	27.07							■		■
C-4	21.14								■	

H,H correlations, COSY ■, NOESY □

H-1' 3.99	H-2' 3.67	H-2" 3.44	H-3eq 2.66	H-6 2.34	H-3a 2.03	H-5eq 1.89	H-4 1.71	H-5a 1.65	
	□	□							7.92 **PhCO**
□			□	□				□	6.90 **Ph-2**
□	□		□						6.75 **Ph-1'**
	■	■□							3.99 **H-1'**
		■□			□				3.67 **H-2'**
									3.44 **H-2"**
					■□		□		2.66 **H-3eq**
						■□	■	□	2.34 **H-6**
							■	□	2.03 **H-3a**
							■□	□	1.89 **H-5eq**
								■	1.71 **H-4**



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indicates that they are produced by the influence of the solvent polarity in these parameters. Changes in the conformational equilibria must produce larger differences, specially in coupling constants. Similarly, no temperature effects were observed at 120°C in DMSO-d_6.

Assignment of the NMR spectra of isomers **3-8** has been performed by using several NMR techniques and molecular mechanics. The use of one or other technique depended on the isomer to be differentiated, that is the number and position of the chiral centres and the configuration of the asymmetric carbon.

The ^{1}H-NMR spectra are too complex to be assigned without the help of other NMR techniques. Moreover, some signals that correspond to the cyclohexane protons overlap and they were assigned by correlation experiments. In these cases, coupling constants could not be adequately measured.

Assignment of the NMR signals in the cyclohexane ring and the exocyclic chain was performed on the basis of the ^{13}C-NMR spectra. Cyclohexane and exocyclic chain carbons were assigned considering the multiplicity deduced from the DEPT spectra and the influence of the substituent in position 6 on the chemical shifts of 2-phenylcyclohexanone.

One bond CH correlation experiments permitted the assignment of the ^{1}H-NMR spectra and these assignments could be 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 hydrogens was performed considering the larger coupling constants in axial hydrogens and that equatorial hydrogens are usually less shielded.[16]

Differentiation between H-2' and H-2" was performed by comparison of the experimental coupling constants with H-1' with the values calculated from the molecular modelling.

Regioisomers **3-6**, which have the exocyclic chain in position 6, could be differentiated from isomers **7-8** where the exocyclic chain in position 2, using DEPT experiments. Isomers **3-6** show four methylenes and three methines whilst isomers **7-8** show five methylenes and only one methine and one quaternary carbon atom.

The relative configuration of carbons 2 and 6, and consequently, differentiation of epimers **3** and **4** from **5** and **6** was performed by NOE difference experiments. In both **3** and **4** the phenyl and alkyl groups are to be found in a *cis* diequatorial conformation and thus irradiation of H-2 produces enhancements in H-6 in both isomers. On the contrary **5** and **6** show a *trans* configuration, and a NOE enhancement between the H_{ortho}-Ph-2 and the axial H-4 and H-6 is observed, showing that the phenyl and not the alkyl group is situated in the axial position.

Finally, differentiation between pairs of epimers **3** and **4**, **5** and **6**, and **7** and **8**, which have opposite configurations in the exocyclic chiral centre, was performed by 1D NOE difference spectroscopy and NOESY spectra and comparison of detected NOE with interatomic distances calculated by molecular mechanics.

Isomers **3**, **5** and **7** which have the same relative configuration at C-1' show a NOE between H_{ortho}-Ph-1' and H-2" and between H-1' and H-2'. These relationships are inverted in **4**, **6** and **8**, in which NOE enhancements between H_{ortho}-Ph-1' with H-2' and H-1' with H-2" are observed.

Analysis of the ^{1}H-NMR spectra of **3-8** shows some differences in chemical shifts and coupling constants. From the value of coupling constants important structural information could be deduced, in particular information which confirmed the assignment of the NOE difference and NOESY spectra.

The axial position of H-6 is confirmed in the four isomers **3-6** by the existence of a J_{gauche} with the equatorial H-5 (4.7-5 Hz) and a J_{trans} with the axial H-5 (12-14.4 Hz).

The relative configuration at C-2 is also confirmed, in **3** and **4**, from the J_{gauche} which H-2 shows with the equatorial H-3 (5-5.7 Hz) and the J_{trans} with the axial H-3 (11.7-13 Hz). In **5** and **6** two J_{gauche} are observed with the equatorial and axial H-3 (7.6 Hz).

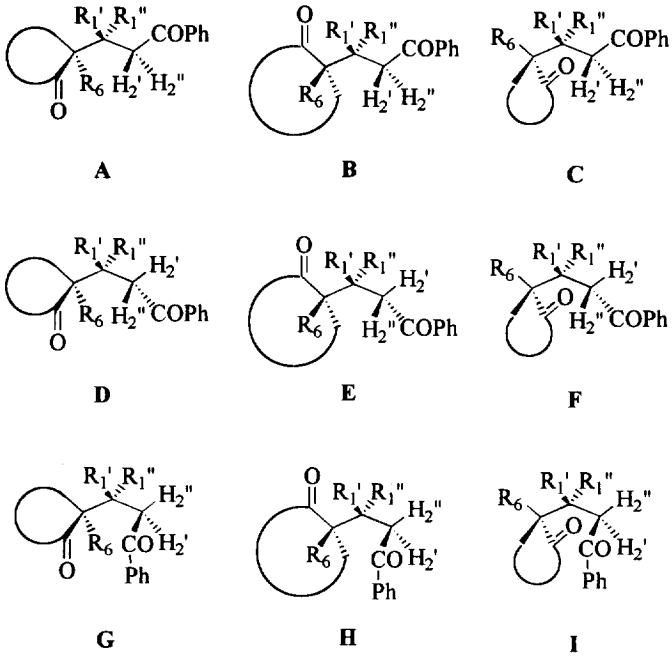
Coupling constants in the exocyclic chain give important information regarding the relative configuration at C-1'. In **3**, **5** and **7**, which have the same relative configuration at C-1', $J_{1'-2'}$ is always smaller than $J_{1'-2"}$ ($J_{1'-2'}$ =3-3.9 Hz; $J_{1'-2"}$=8.8-11.4 Hz) while this relationship is reversed in **4**, **6** and **8** ($J_{1'-2'}$ =8.9-11.2 Hz, $J_{1'-2"}$=2.7-5.1 Hz).

Finally, $J_{6-1'}$ is always large, it being 8.3-9.9 Hz in all cases except in **4** where it is reduced to 4.7 Hz.

Molecular mechanics calculations

The six isomers **3** (2R-6S-1'R), **4** (2R-6S-1'S), **5** (2S-6S-1'R), **6** (2S-6S-1'S), **7** (2S-1'S) and **8** (2S-1'R) were subjected to a conformational search, by means of molecular mechanics calculations using the MMX-type force field,[15] which has proved to be a reliable method in conformational analysis.[3] The nine staggered conformations around the CH-CH_2 and CH-Cyclohexyl bonds for all isomers are shown in Figure 3. The energy minima were found by complete geometrical optimisation; rotations, with increments of 10°, of both phenyl groups were carried out and, based on the frequency in the IR spectra ($\nu_{C=O}$ 1680 cm^{-1} in **3**) the CO-Ph dihedral angle was forced to 0°.

Table 7 shows the MMX energies (Kcal/mol) and calculated conformational populations for the conformers **A-I** of isomers **3-8.** As depicted in Table 7, structure A is the most stable in isomers **3**, **5** and **8**, whilst B is the minimum energy conformer for isomers **4**, **6** and **7**. The conformational population of conformers A-I for each isomer was calculated by application of the Boltzmann equation using the energy of conformers, as determined by the MMX force field.[17]



3, 5: $R_1' = H_1$; $R_1'' = Ph$; $R_6 = H$ **7:** $R_1' = H_1$; $R_1'' = Ph$; $R_6 = Ph$

4, 6: $R_1' = Ph$; $R_1'' = H_1'$; $R_6 = H$ **8:** $R_1' = Ph$; $R_1'' = H_1'$; $R_6 = Ph$

Figure 3. Conformations for isomer **3-8**

The vicinal coupling constants (^3J) were calculated for all conformations using the Karplus type empirical equation proposed by Altona et al.[18] for H-C(sp^3)- C(sp^3)-H and the dihedral angles provided by the geometrical optimisation established with the MMX force field.[17] These coupling constants were averaged by a weight factor proportional to the relative populations of conformations (see Table 7) as shown in Table 8. In this way the coupling constants could be compared directly with the observed values. The results are presented in Table 9. As depicted in Table 7, conformations with an energy more than 3 Kcal/mol higher than the optimum conformation do not contribute to the conformational population and, consequently, to the average coupling constants. When the calculated and experimental coupling constants are compared, it is evident that molecular mechanics method is capable of correctly predicting the stereochemistry of each pair of stereoisomers.

Table 7. MMX Calculated Energies (Kcal/mol) and Calculated Conformational Populations (in brackets) for Conformers **A-I** of Compounds **3-8**

Isomer	Conformer								
	A	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**
3	42.99	44.39	44.06	44.62	46.71	48.27	44.13	44.61	45.25
	(0.64)	(0.06)	(0.11)	(0.04)	(0.00)	(0.00)	(0.09)	(0.04)	(0.01)
4	44.17	43.70	43.79	44.72	44.38	43.95	48.32	44.43	48.01
	(0.12)	(0.27)	(0.23)	(0.05)	(0.08)	(0.17)	(0.00)	(0.08)	(0.00)
5	43.22	45.48	44.88	44.84	48.51	51.09	44.89	45.28	46.46
	(0.81)	(0.02)	(0.05)	(0.05)	(0.00)	(0.00)	(0.05)	(0.02)	(0.00)
6	44.85	44.16	45.06	45.07	44.93	49.21	45.72	45.00	50.18
	(0.13)	(0.43)	(0.09)	(0.09)	(0.12)	(0.00)	(0.03)	(0.10)	(0.00)
7	49.46	48.06	52.50	54.23	58.51	60.11	54.57	49.74	53.82
	(0.08)	(0.87)	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)	(0.05)	(0.00)
8	48.12	52.22	50.70	50.04	53.66	56.81	55.22	57.01	57.06
	(0.95)	(0.00)	(0.01)	(0.04)	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)

Table 8. Calculated Vicinal Coupling Constants for Conformers **A-I** of Compounds **3-8.**

Isomer	**3**			**4**			**5**			**6**			**7**		**8**	
Conformer	$J_{6\text{-}1'}$	$J_{1'\text{-}2'}$	$J_{1'\text{-}2''}$	$J_{6\text{-}1'}$	$J_{1'\text{-}2'}$	$J_{1'\text{-}2''}$	$J_{6\text{-}1'}$	$J_{1'\text{-}2'}$	$J_{1'\text{-}2''}$	$J_{6\text{-}1'}$	$J_{1'\text{-}2'}$	$J_{1'\text{-}2''}$	$J_{1'\text{-}2'}$	$J_{1'\text{-}2''}$	$J_{1'\text{-}2'}$	$J_{1'\text{-}2''}$
A	12.04	3.03	12.36	2.72	12.36	2.87	12.07	2.74	12.36	2.84	12.27	3.61	2.49	12.32	12.36	3.12
B	2.21	3.11	12.36	12.28	12.26	3.87	1.67	3.15	12.35	12.26	12.27	3.78	3.08	12.36	12.35	2.84
C	2.38	3.36	12.33	2.17	12.36	2.80	2.68	3.24	12.34	1.73	12.35	3.12	3.17	12.36	12.28	2.32
D	12.14	2.86	4.05	5.05	4.78	11.64	12.31	3.08	3.49	5.77	3.92	12.12	4.34	2.41	10.95	1.06
E	4.07	5.92	1.43	12.24	1.18	11.34	3.27	6.13	1.36	12.33	1.01	10.79	7.45	0.96	10.78	1.00
F	1.84	5.58	1.93	1.54	3.13	12.32	1.02	8.34	0.97	0.52	3.23	12.34	8.94	1.12	12.28	3.42
G	11.1	12.30	3.15	1.50	5.92	1.73	11.69	12.33	2.20	1.00	4.58	2.19	4.40	2.85	2.85	4.40
H	1.83	12.18	2.05	12.29	4.23	2.53	0.70	11.95	1.76	12.33	4.12	2.61	2.81	3.98	3.98	2.81
I	1.67	12.33	2.26	4.76	5.47	2.06	3.17	11.11	1.14	7.77	6.80	1.22	7.20	1.11	1.11	7.20
$J_i x_n$	**9.76**	**4.45**	**10.57**	**6.59**	**8.78**	**5.88**	**11.11**	**3.51**	**11.11**	**9.34**	**9.25**	**5.21**	**3.43**	**11.78**	**12.31**	**3.03**

Table 9. Observed ($CDCl_3$) and Calculated Vicinal Coupling Constants for Compounds **3-8**.

	Observed			Calculated		
	$J_{6\text{-}1'}$	$J_{1'\text{-}2'}$	$J_{1'\text{-}2''}$	$J_{6\text{-}1'}$	$J_{1'\text{-}2'}$	$J_{1'\text{-}2''}$
3	9.0	3.6	10.0	9.76	4.45	10.52
4	4.7	9.3	5.1	6.59	8.78	6.01
5	9.7	3.9	10.0	11.11	2.73	11.88
6	8.3	8.9	5.1	9.34	9.25	5.21
7	-	3.0	11.7	-	3.43	11.78
8	-	11.2	3.0	-	12.31	3.03

X-ray structure determination of isomer 7

An x-ray structure determination of isomer 7 confirms the stereochemical assignment deduced from the NMR spectra and molecular mechanics calculations.

Isomer 7 crystallises as a racemic mixture, the enantiomer SS being represented in Figure 1. Bond lengths and angles are collected in table 11.

Table 10. Bond Lenghts (Å) and Angles (deg) for compound 7

O(1)-C(1)	1.212(2)	C(7)-C(8)	1.393(2)	C(17)-C(18)	1.369(3)
O(2)-C(21)	1.211(2)	C(8)-C(9)	1.384(2)	C(18)-C(19)	1.385(2)
C(1)-C(2)	1.509(2)	C(9)-C(10)	1.376(2)	C(20)-C(21)	1.515(2)
C(1)-C(6)	1.542(2)	C(10)-C(11)	1.376(2)	C(21)-C(22)	1.495(2)
C(2)-C(3)	1.526(2)	C(11)-C(12)	1.381(2)	C(22)-C(23)	1.388(2)
C(3)-C(4)	1.521(2)	C(13)-C(14)	1.518(2)	C(22)-C(27)	1.396(2)
C(4)-C(5)	1.528(2)	C(13)-C(20)	1.549(2)	C(23)-C(24)	1.386(2)
C(5)-C(6)	1.559(2)	C(14)-C(15)	1.393(2)	C(24)-C(25)	1.381(3)
C(6)-C(7)	1.524(2)	C(14)-C(19)	1.388(2)	C(25)-C(26)	1.373(3)
C(6)-C(13)	1.574(2)	C(15)-C(16)	1.393(2)	C(26)-C(27)	1.383(2)
C(7)-C(12)	1.391(2)	C(16)-C(17)	1.372(3)		
O(1)-C(1)-C(2)	121.47(11)	C(1)-C(6)-C(13)	110.18(9)	C(14)-C(13)-C(20)	111.66(10)
O(1)-C(1)-C(6)	122.36(11)	C(5)-C(6)-C(13)	109.31(9)	C(14)-C(13)-C(6)	112.67(9)
C(2)-C(1)-C(6)	115.70(11)	C(12)-C(7)-C(8)	117.50(11)	C(20)-C(13)-C(6)	112.15(10)
C(1)-C(2)-C(3)	108.80(12)	C(12)-C(7)-C(6)	121.71(11)	C(15)-C(14)-C(19)	117.88(13)
C(4)-C(3)-C(2)	110.96(11)	C(8)-C(7)-C(6)	120.70(11)	C(15)-C(14)-C(13)	119.40(12)
C(3)-C(4)-C(5)	111.35(11)	C(9)-C(8)-C(7)	121.29(13)	C(19)-C(14)-C(13)	122.72(12)
C(4)-C(5)-C(6)	113.56(11)	C(8)-C(9)-C(10)	120.21(14)	C(14)-C(15)-C(16)	120.8(2)
C(7)-C(6)-C(1)	110.79(10)	C(11)-C(10)-C(9)	119.26(13)	C(17)-C(16)-C(15)	120.2(2)
C(7)-C(6)-C(5)	111.95(9)	C(10)-C(11)-C(12)	120.77(14)	C(18)-C(17)-C(16)	119.6(2)
C(1)-C(6)-C(5)	102.51 (10)	C(11)-C(12)-C(7)	120.96(12)	C(17)-C(18)-C(19)	120.8(2)
C(79-C(6)-C(13)	111.73 (9)				

The carbonyl group C-21-O-2 and the phenyl group to which it is attached may be considered to be planar when the experimental error is taken into account, thus confirming the data deduced from the IR spectrum which was used in the calculations.

Two diffrerences are observed when comparing with molecular mechanics calculations: i) conformation of the benzoyl group, i.e. the conformation around the C-2"-CO bond. In the solid state the benzoyl is twisted by 74.86° relative to the plane of the exocyclic chain defined by C-6, C-1' and C-2'. From molecular mechanics calculations the benzoyl group is almost planar, showing a deviation of 9.18° relative to the plane of the exocyclic chain, ii) The A conformer is predominant in the solid state while the B conformer is predominant in the gas phase.

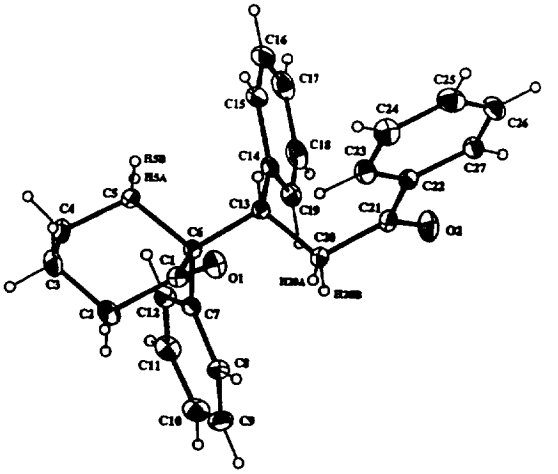


Figure 1. Isomer 7. X-ray structure of enantiomer SS (ORTEP representation)

Molecular mechanics calculations on isomer 7 after forcing the angle to 74.86°, as determined by X-ray crystallography, increases the calculated energy by 2 Kcal.mol^{-1} in most conformers. The relative stability of conformers **A-I** is not affected by this variation but a comparison of the calculated and experimental coupling constants shows a better concordance in the previous case (angle 9.18°), showing that this conformation is the most stable in solution. These differences can be explained by considering that molecular mechanics calculate the energy in the gas phase and not in the solid state.

Discussion

From the data in Table 7 it can be deduced that the relative conformer stability strongly depends on the absolute configuration at C-1'. Conformer A is the most stable in isomers **3**, **5** and **8** which have the same absolute configuration at C-1' and similarly conformer B is the most stable in isomers **4**, **6** and 7. Most isomers can be considered to be monoconformational, as the relative population is higher than 0.6 for conformer A in **3**, **5** and **8**, higher than 0.8 for conformer B in 7, the only exception being isomer **4**, where conformers A, B, C and F have similar stabilities and, in a lesser extend **6** where conformer B has a population higher than 0.4.

Considering this fact it is possible to compare the NOE detected in the NMR spectra with the interatomic distances in the most stable conformer, and in this way, important differences in a given interatomic distance between two isomers should be reflected in the observed NOE.

Tables 11 and 12 show respectively selected NOE enhancements and inter-atomic distances for isomers **3-6** and **7-8**.

A good agreement between differences in inter-atomic distances and NOE enhancements is shown. From this data, it is evident that with the use of NMR spectroscopy and molecular mechanics it is possible to elucidate the structure and stereochemistry of the six regio and stereoisomers obtained in the reaction of 2-phenylcyclohexanone with chalcone.

The relative configuration at C-1' affects the NOE observed between H-1' and H_{ortho}-Ph-1'. In isomers **3**, **5** and **7** a NOE between H_{ortho}-Ph-1' and H-2" and between H-1' and H-2' is observed and, in agreement with the calculated inter-atomic distances, the situation is reversed in isomers **4**, **6** and **8**, in which NOE's are detected between H_{ortho}-Ph-1' and H-2' and between H-1' and H-2".

Table 11. Compounds **3-6**. Calculated Distances (Å) for the Major Conformer and Detected NOE's (□)

Isomer	3	4	5	6
o-H-Ph-2; H-3a	2.34 □	2.39 □	3.75	3.75
o-H-Ph-2; H-3eq	3.44	3.54 □	2.21 □	2.21 □
o-H-Ph-2; H-4a	4.72	4.68	2.49 □	2.46
o-H-Ph-2; H-6	4.53	4.73	3.13 □	3.15
o-H-Ph-1'; H-5eq	3.25 □	4.24	3.25	4.46
o-H-Ph-1'; H-5a	3.33 □	4.84	3.32	4.70
o-H-Ph-1'; H-2'	3.87	2.38 □	3.85	2.38 □
o-H-Ph-1'; H-2"	2.32 □	3.95	2.32 □	3.93
H-2; H-6	2.45 □	2.54 □	3.77	3.76
H-1'; H-2'	2.52 □	3.07	2.52 □	3.09 □
H-1'; H-2"	3.09	2.46 □	3.10	2.46 □

Table 12. Compounds **7-8**. Calculated Distances (Å) for the Major Conformer and Detected NOE's (□)

Isomer	7	7[a]	8
o-H-Ph-1'; H-3a	2.45 □	2.78	3.12
o-H-Ph-1'; H-2'	3.82	3.66	2.25 □
o-H-Ph-1'; H-2"	2.23 □	2.29	3.81
H-1'; H-2'	2.44 □	2.34	3.06
H-1'; H-2"	3.07	2.92	2.42 □

[a] X-ray crystallographic data

In isomers **3**, **5** and **7** the Ph-1' ring is close to the adjacent CH_2 of the cyclohexanone ring. This is made evident by a NOE between the H_{ortho}-Ph-1' and the axial and equatorial H-5 in isomers **3** and **5** and with the

axial H-3 in isomer **7**. In isomers **4**, **6** and **8** this relationship is not observed as the phenyl group is close to the C=O group (Figures 3 and 4).

The configuration at C-2 and C-6 affects the NOE observed between H-2 and H_{ortho}-Ph-2. In isomers **3** and **4** a NOE's between H-2 and H-6 and between H_{ortho}-Ph-2 and the axial H-3 are observed while in isomers **5** and **6** NOE's between H_{ortho}-Ph-2 and H-4, H-6 and the equatorial H-3 are to be seen, in agreement with the distances calculated by molecular mechanics.

Conclusions

A combination of several NMR spectroscopic techniques and molecular mechanics calculations permits the regio and stereochemical assignment of the six isomers produced in the reaction of 2-phenylcyclohexanone with chalcone, **3** (2R-6S-1'R/2S-6R-1'S), **4** (2R-6S-1'S/2S-6R-1'R), **5** (2S-6S-1'R/2R-6R-1'S), **6** (2S-6S-1'S/2R-6R-1'R), **7** (2S-1'S/2R-1'R) and **8** (2S-1'R/2R-1'S). The validity of the method has been confirmed by X-ray structure determination of isomer **7**.

Experimental

NMR spectra were recorded on a VARIAN UNITY 300 spectrometer operating at 299.980 MHz for proton and 75.423 MHz for carbon-13 at 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 Transformations.

The 2D NOE spectra were acquired in the phase sensitive mode with 2D hypercomplex data (States-Haberkorn method).[19] The relaxation delay was 0.5 s and mixing times were 500 mseconds.

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 referenced to internal tetramethylsilane (TMS) for $CDCl_3$ and to the residual solvent signal for DMSO-d_6 and acetone-d_6.

Intensity data for 7 were collected on an Enraf-Nonius CAD4 diffractometer equipped with a graphite monochromator using Mo Kα (λ = 0.71073 Å) and a ω /2θ scan technique to a maximum value of 60°. The details of the X-ray data collection, structure solution and refinement are provided in table 13.

Table 13. Crystal Data and Structure Refinement for 7

Identification code	2sts
Empirical formula	$C_{27}H_{26}O_2$
Formula weight	382.48
Temperature	293 (2) K
Wavelength	0.71070 Å
Crystal system	monoclinic
Space group	P 21/n
Unit cell dimensions	a = 9.325 (2) Å alpha = 90 deg b = 15.570 (2) Å beta = 99.930 (10) deg. C= 14.719 (3) Å gamma = 90 deg.
Volume	2105.0 (7) $Å^3$
Z	4
Density (calculated)	1.207 Mg/m^3
Absorption coefficient	0.074 mm^{-1}
F(000)	816
Crystal size	0.6 x 0.4 x 0.4 mm
Theta range for data collection	2.41 to 28.04 deg.
Index ranges	$0 \leq h \leq 12$, $-20 \leq k \leq 20$, $-19 \leq l \leq 19$
Reflections collected	9979
Independent reflections	5082 [R(int) = 0.0140]
Refinement method	Full-matrix least-squares on F^2
Data / restrains /parameters	5082 / 0 / 290
Final R indices [I>2sigma(I)	R1 = 0.0397, wR2 = 0.1201
Largest diff. Peak and hole	0.268 and -0.194 $e.A^{-3}$

Data were collected for Lorentz-polarization effects and for linear decay of the two periodically measured reference reflections. No absorption correction was necessary (μ = 0.7 cm^{-1}). The structure was solved by a combination of direct methods and Fourier synthesis and then refined by full-matrix least-squares (SHELX-93).[20] All non-hydrogen atoms were refined with anisotropic thermal parameters. The hydrogen atoms on C5, C13, C15, C19 and C20 were found by difference Fourier synthesis and refined isotropically. The

rest of the hydrogen atoms were optimised in the final refinement cycles. Table 14 lists the final atomic co-ordinates and equivalent thermal factors for non-hydrogen atoms.

Table 14. Atomic Co-ordinates (x 10^4) and Equivalent Isotropic Displacement Parameters (A^2 x 10^3) for 7. U(eq) is Defined as One Third of the Trace of the Orthogonalized Tensor.

Atom	x	y	z	Ueq	Atom	x	y	z	Ueq
O (1)	7694 (1)	-203 (1)	-157 (1)	51 (1)	C (14)	7911 (1)	-951 (1)	2643 (1)	36 (1)
O (2)	10861 (1)	-2140 (1)	2348 (1)	60 (1)	C (15)	6632 (2)	-1353 (1)	2781 (1)	49 (1)
C (1)	7633 (1)	385 (1)	375 (1)	37 (1)	C (16)	6399 (2)	-1551 (1)	3667 (1)	64 (1)
C (2)	7220 (2)	1281 (1)	36 (1)	48 (1)	C (17)	7437 (2)	-1356 (1)	4418 (1)	65 (1)
C (3)	5729 (2)	1499 (1)	268 (1)	52 (1)	C (18)	8708 (2)	-972 (1)	4291 (1)	60 (1)
C (4)	5710 (2)	1369 (1)	1290 (1)	46 (1)	C (19)	8954 (2)	-774 (1)	3413 (1)	46 (1)
C (5)	6213 (1)	465 (1)	1601 (1)	37 (1)	C (20)	9637 (1)	-997 (1)	1487 (1)	38 (1)
C (6)	7772 (1)	245 (1)	1424 (1)	30 (1)	C (21)	9989 (1)	-1937 (1)	1674 (1)	39 (1)
C (7)	8920 (1)	841 (1)	1951 (1)	32 (1)	C (22)	9297 (1)	-2612 (1)	1019 (1)	39 (1)
C (8)	10207 (2)	1010 (1)	1624 (1)	41 (1)	C (23)	8312 (2)	-2425 (1)	224 (1)	46 (1)
C (9)	11291 (2)	1514 (1)	2121 (1)	53 (1)	C (24)	7696 (2)	-3081 (1)	-350 (1)	58 (1)
C (10)	11115 (2)	1859 (1)	2955 (1)	56 (1)	C (25)	8074 (2)	-3924 (1)	-136 (1)	61 (1)
C (11)	9850 (2)	1699 (1)	3288 (1)	50 (1)	C (26)	9065 (2)	-4118 (1)	640 (1)	57 (1)
C (12)	8766 (1)	1196 (1)	2796 (1)	39 (1)	C (27)	9678 (2)	-3467 (1)	1219 (1)	46 (1)
C (13)	8115 (1)	-726 (1)	1670 (1)	32 (1)					

General procedure for the Michael addition of 2-Phenylcyclohexanone to chalcone

A mixture of 2-phenylcyclohexanone (1.5 mmol), base (6 % mol) and the catalyst (6 % mol) was stirred for 5 min. Chalcone (1.5 mmol) was then added and the mixture was stirred at the 20 or 60°C for 24 h.[2] The crude mixture was extracted with dichloromethane (20 mL) and filtered. The solvent was removed under pressure and the crude products were analysed by HPLC to determine the ratio of isomers. Purification was performed by flash chromatography (hexane : ethyl ether 15 :1) to yield, in sequence products **7**, **8**, **4**, **3**, **6**, **5**.

(2R-6S-1'R/2S-6R-1'S) 2-Phenyl-6-(1',3'-diphenyl-3'-oxopropyl)cyclohexanone (3)

m.p. 184-186 °C (from ethanol) IR (KBr) 1710, 1680 (C=O) ^{1}H-NMR ($CDCl_3$) δ 7.88 (2H, d, *J* = 8.2 Hz), 7.48 (1H, t, *J* = 7.4 Hz), 7.37 (2H, t, *J* = 7.4 Hz), 7.34-7.12 (6H, m), 7.22 (2H, m), 7.12 (2H, m), 3.75 (1H, dd, *J* = 13, 5 Hz), 3.69 (1H, ddd, *J* = 10, 9, 3.6 Hz), 3.60 (1H, dd, *J* = 15, 3.6 Hz), 3.12 (1H, dd, *J* = 15, 10 Hz), 2.94 (1H, ddd, *J* = 12, 9, 5 Hz), 2.26 (1H, dq, *J* = 12.9, 3.6 Hz), 1.97 (1H, qd, *J* = 12.9, 3.6 Hz), 1.77 (3H, m), 1.32 (1H, qd, *J* = 13.4, 5 Hz). ^{1}H-NMR (DMSO-d_6) δ 7.86 (2H, d, *J* = 8.5 Hz), 7.56 (1H, t, *J* = 7.5 Hz), 7.45 (2H, t, *J* = 7.5 Hz), 7.40-7.10 (10 H, m), 3.89 (1H, dd, *J* = 13.2, 5.3 Hz), 3.56 (1H, ddd, *J* = 9.5, 8.8, 5.2), 3.35 (1H, dd, *J* = 16.3, 5.2), 3.35 (1H, dd, *J* = 16.3, 5.2 Hz), 3.06 (1H, ddd, *J* = 13.8, 9.5, 5 Hz),

2.12 (1H, dq, *J* = 10, 5.3 Hz), 1.89 (1H, m), 1.74 (2H, m), 1.58 (1H, dq, *J* = 12. 5 Hz), 1.21 (1H, m). ^{1}H-NMR (Acetone-d_6) δ 7.91 (2H, d, *J* = 8.5 Hz), 7.54 (1H, t, *J* = 7.3 Hz), 7.43 (2H, t, *J* = 7.6 Hz), 7.40-7.10 (10 H, m), 3.94 (1H, dd, *J* = 13, 5.7 Hz), 3.71 (1H, td, *J* = 10.3, 10, 3.5 Hz), 3.53 (1H, dd, *J* = 16.2, 3.5 Hz), 3.34 (1H, dd, *J* = 16.2, 10.3 Hz), 3.16 (1H, ddd, *J* = 14.4, 9.9, 5.5 Hz), 2.24 (1H, dq, *J* = 12.4, 5.7 Hz), 2.0 (1H, m), 1.86 (2H, m), 1.74 (1H, dq, *J* = 13.1, 5.5 Hz), 1.29 (1H, m).^{13}C-NMR ($CDCl_3$) δ 211.02, 198.93, 141.87, 138.19, 136.99, 132.59, 128.76, 128.39, 128.37, 128.32, 128.24, 128.17, 127.03, 126.52, 58.63, 56.16, 44.35, 41.90, 37.35, 34.50, 25.81, Anal. Calc for $C_{27}H_{26}O_2$: C, 84.78; H, 6.85; O, 8.37. Found: C, 84.50; H, 7.06.

(2R-6S-1'S/2S-6R-1'R) 2-Phenyl-6-(1',3'-diphenyl-3'-oxopropyl)cyclohexanone (4)

m.p. 172-174 °C (from ethanol) IR (KBr) 1710, 1680 (C=O) ^{1}H-NMR ($CDCl_3$) δ 7.93 (2H, d, *J* = 8.6 Hz), 7.50 (1H, t, *J* = 7.3 Hz), 7.39 (2H, m), 7.36 (1H, m), 7.32 (2H, m), 7.28-7.22 (4H, m), 7.16 (1H, t, *J* = 7.1 Hz), 7.11 (2H, d, *J* = 8.3 Hz), 3.92 (1H, ddd, *J* = 9.3, 5.1, 4.7 Hz), 3.63 (1H, dd, *J* = 16.4, 5.1 Hz), 3.59 (1H, dd, *J* = 11.7, 5.7 Hz), 3.42 (1H, dd, *J* = 16.4, 9.3 Hz), 2.92 (1H, dt, *J*= 12.7, 4.7 Hz), 2.26 (2H, m), 2.01 (2H, m), 1.82 (1H, qt, *J* = 12.6, 3.4 Hz), 1.67 (1H, qd, *J* = 12.7, 3.4 Hz), ^{13}C-NMR ($CDCl_3$) δ 209.84, 199.19, 142.65, 138.56, 137.05, 132.76, 128.71(2), 128.42, 128.25, 128.21, 128.16, 126.92, 126.34, 58.19, 55.87, 40.76, 40.25, 36.06, 31.02, 25.75, Anal. Calc for $C_{27}H_{26}O_2$: C, 84.78; H, 6.85; O, 8.37. Found: C, 84.52; H, 7.09.

(2S-6S-1'R/2R-6R-1'S) 2-Phenyl-6-(1',3'-diphenyl-3'-oxopropyl)cyclohexanone (5)

m.p. 70-72 °C (from ethanol) IR (KBr) 1710, 1685 (C=O) ^{1}H-NMR ($CDCl_3$) δ 7.92 (2H, d, *J* = 8.6 Hz), 7.54 (1H, t, *J* = 7.3 Hz), 7.44 (3H, m), 7.31 (2H, m), 7.26-7.10 (5H, m), 7.03 (2H, d, *J* = 8.1 Hz), 3.77 (1H, td, *J* = 9.7, 3.9 Hz), 3.53 (1H, dd, *J* = 15.6, 3.9 Hz), 3.09 (1H, dd, *J* = 15.6, 10 Hz), 3.01 (1H, m), 2.99 (1H, m), 2.80 (1H, ddd, *J* = 13.2, 9.7, 4.9 Hz), 1.76 (1H, m), 1.68 (3H, m), 1.25 (1H, m). ^{13}C-NMR ($CDCl_3$) δ 213.79, 198.49, 141.15, 139.76, 136.94, 132.85, 129.35, 128.70, 128.49, 128.40, 128.19, 128.14, 126.72, 126.48, 59.61, 52.56, 43.77, 41.37, 39.99, 34.47, 22.63, Anal. Calc for $C_{27}H_{26}O_2$: C, 84.78; H, 6.85; O, 8.37. Found: C, 84.62; H, 6.95.

(2S-6S-1'S/2R-6R-1'R) 2-Phenyl-6-(1',3'-diphenyl-3'-oxopropyl)cyclohexanone (6)

m.p. 139-141 °C (from ethanol) IR (KBr) 1710, 1685 (C=O) ^{1}H-NMR ($CDCl_3$) δ 7.90 (2H, d, *J* = 8.4 Hz), 7.53 (1H, t, *J* = 7.3 Hz), 7.43 (2H, t, *J* = 7.3 Hz), 7.30-7.10 (6H, m), 7.26 (2H, m), 6.84 (2H, d, *J* = 7.6

Hz), 3.99 (1H, td, J = 8.9, 8.3, 5.1 Hz), 3.69 (1H, t, J = 7.6 Hz), 3.49 (1H, dd, J = 17.1, 5.1 Hz), 3.39 (1H, dd, J = 17.1, 8.9 Hz), 2.92 (1H, m), 2.20 (2H, m), 2.07 (3H, m), 1.84 (1H, m). ^{13}C-NMR ($CDCl_3$) δ 212.34, 198.64, 141.81, 137.84, 136.94, 133.03, 128.59, 128.51, 128.41, 128.36, 128.05, 127.75, 126.79, 126.71, 54.85, 54.55, 42.87, 40.74, 32.44, 30.38, 21.06. Anal. Calc for $C_{27}H_{26}O_2$: C, 84.78; H, 6.85; O, 8.37. Found: C, 84.79; H, 7.25.

(2S-1'S/2R-1'R) 2-Phenyl-2-(1',3'-diphenyl-3'-oxopropyl)cyclohexanone (7)

m.p. 149-151 °C (from ethanol) IR (KBr) 1700, 1675 (C=O) ^{1}H-NMR ($CDCl_3$) δ 7.84 (2H, d, J = 8.4 Hz), 7.47 (1H, t, J = 7.3 Hz), 7.44-7.22 (4H, m), 7.12-7.09 (4H, m), 6.99 (2H, d, J = 8.3 Hz), 6.74 (2H, d, J = 7.6 Hz), 3.98 (1H, dd, J = 11.7, 3 Hz), 3.68 (1H, dd, J = 15.6, 3 Hz), 2.88 (1H, dd, J = 15.6, 11.7 Hz), 2.54 (1H, td, J = 13, 5.8 Hz), 2.31 (1H, d, J = 12.7 Hz), 1.90 (1H, m), 2.18 (1H, dd, J = 11.5, 2.5 Hz), 1.68 (1H, m), 1.64 (1H, m), 1.57 (2H, m), ^{13}C-NMR ($CDCl_3$) δ 213.91, 199.06, 139.50, 137.38, 137.28, 132.40, 130.43, 129.45, 128.25(2), 128.03, 127.35, 127.29, 126.55, 60.89, 47.57, 41.84,40.60, 37.32, 29.10, 21.37, Anal. Calc for $C_{27}H_{26}O_2$: C, 84.78; H, 6.85; O, 8.37. Found: C, 84.51; H, 7.16.

(2S-1'R/2R-1'S) 2-Phenyl-2-(1',3'-diphenyl-3'-oxopropyl)cyclohexanone (8)

m.p. 117-119 °C (from ethanol) IR (KBr) 1700, 1685 (C=O) ^{1}H-NMR ($CDCl_3$) δ 7.92 (2H, d, J = 8.5 Hz), 7.49 (1H, t, J = 7.3 Hz), 7.44-7.32 (3H, m), 7.15 (2H, m), 7-6.96 (2H, m), 7.49 (1H, m), 6.9 (2H, d, J = 8.1 Hz), 6.75 (2H, d, J = 7.6 Hz), 3.99 (1H, dd, J = 11.2, 3 Hz), 3.67 (1H, dd, J = 16.1, 11.2 Hz), 3.44 (1H, dd, J = 16.1, 3 Hz), 2.66 (1H, d, J = 14.4 Hz), 2.34 (2H, m), 2.03 (1H, td, J = 14.4, 4 Hz), 1.89 (1H, m), 1.71 (2H, m), 1.65 (1H, m). ^{13}C-NMR ($CDCl_3$) δ 212.66, 198.6, 139.67, 139.57, 137.15, 132.55, 129.69, 128.43, 128.30, 128.07, 127.26, 127.14, 126.79, 126.06, 61.17, 49.49, 40.87, 40.61, 30.51, 27.07, 21.14, Anal. Calc for $C_{27}H_{26}O_2$: C, 84.78; H, 6.85; O, 8.37. Found: C, 84.48; H, 7.07

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References

1. (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford 1992. (b) Leonard, J. *Contemporary Org. Synth.* **1994**, 387.
2. (a) Díez-Barra, E.; de la Hoz, A.; Merino, S.; Sánchez-Verdú, P. ACS Symposium Series 659, M.E. Halpern Ed. pp. 181-189. (b) Díez-Barra, E.; de la Hoz, A.; Merino, S.; Sánchez-Verdú, P. *Tetrahedron Lett.* **1997**, *38*, 2359.
3. (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.
4. Vorobjev, A.V.; Shakirov, M.M.; Raldugin, V.A.; Heathcock, C.H. *J. Org. Chem.* **1985**, *60*, 63.
5. Gdaniec, M.; Milewska, M.J.; Polonski, T. *J. Org. Chem.* **1995**, *60*, 7411.
6. Usuki, T., Wang, Y., Aubé, J. *J. Org. Chem.* **1995**, *60*, 8028.
7. Svenson, S.; Kirste, B.; Fuhrhop, J.-H. *J. Am. Chem. Soc.* **1994**, *116*, 11969.
8. de Riggi, I.; Virgili, A.; Moragas, M.; Jaime, C. *J. Org. Chem.* **1995**, *60*, 27.
9. Latypov, Sh. K.; Seco, J.M.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **1995**, *60*, 504.
10. Guerra, A.; Lunazzi, L. *J. Org. Chem.* **1995**, *60*, 7959.
11. Morales, E.Q.; Padrón, J.I.; Trujillo, M.; Vázquez, J.T. *J. Org. Chem.* **1995**, *60*, 2537.
12. Kozerski, L.; Kavecki, R.; Krajewski, P.; Gluzinski, P.; Rupek, K.; Hansen, P.E.; Williamson, M.P. *J. Org. Chem.* **1995**, *60*, 3553.
13. Matsumori, N.; Murata, M.; Tachibana, K. *Tetrahedron* **1995**, *51*, 12229.
14. Jeyaram, R.; Senthilkumar, U.P.; Pigler, P. *J. Org. Chem.* **1995**, *60*, 7461.
15. 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.
16. Günther, H. *NMR Spectroscopy*, 2nd ed. John Wiley & Sons, Chichester, 1995, p 80.
17. By solving the system formed by the eight Boltzman equations and $\Sigma n_i=1$.
18. Haasnoot, C.A.G.; de Leeuw, F.A.A.M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783.
19. States, D.J.; Haberkorn, R.A.; Ruben, D.J. *J. Magn. Reson.* **1982**, *48*, 286.
20. SHELX-93, Sheldrick, G.M., program for the refinement of Crystal Structures from Diffraction data, University of Götingen, Göttingen, 1993.

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