

Conformation, Stereodynamics, and Chiral Separation of the Rotational Enantiomers of Hindered Naphthyl Ketones¹

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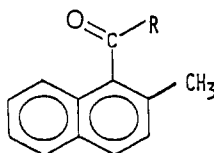
Abstract: A number of α -naphthyl ketones bearing a methyl group in the 2-position of the naphthalene ring adopt a twisted conformation, yielding a pair of rotational enantiomers owing to the restricted rotation about the naphthalene-carbonyl bond. NOE measurements indicate that the twisted conformation is almost exactly orthogonal. The enantiomerization barriers were determined by variable-temperature dynamic NMR spectroscopy, with monitoring of either the anisochronous signals of prochiral substituents or the pairs of signals of the enantiomers themselves, made detectable at low temperature by the addition of a chiral auxiliary agent. The free energies of activation cover a range of 8–20 kcal mol⁻¹, depending on the steric hindrance of the various acyl groups. Molecular mechanics calculations suggest that enantiomerization occurs through a pathway where the carbonyl function passes position 2, rather than position 8, of the naphthalene ring. In the case of a 1,5-disubstituted acyl derivative containing the *tert*-butyl moiety (7), the expected meso and racemic conformers were both observed in solution, whereas only the meso structure was present in the crystals (obtained by the usual slow crystallization procedure) as judged by CP MAS solid-state NMR spectra and by low-temperature solution spectra in nonequilibrium conditions. Low-temperature (-15 °C) chiral high-performance liquid chromatography (LT-ChirHPLC) was employed to separate and identify the two enantiomers of 6 as well as the three conformers (meso, *SS*, and *RR*) of 7. The low-temperature CD spectra of the rotational enantiomers of 6 and 7 were obtained and the absolute configurations assigned by connecting on-line a CD spectrometer to the LT-ChirHPLC apparatus. Respectively, the *S* and *SS* configurations were found to correspond to the conformational enantiomers with the shorter retention times ((*R,R*)-DAC-DNB column).

Introduction

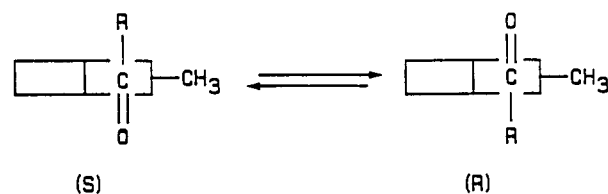
Hindered aromatic ketones can adopt conformations in which the plane of the aromatic ring and that containing the carbonyl moiety are not coplanar. The conformational ground state is therefore twisted, whereas the rotational transition state is almost coplanar. When the energy difference between the twisted ground state and the planar transition state is sufficiently high (≥ 5 kcal mol⁻¹), the NMR spectrum can, in principle, demonstrate that a twisted, rather than planar, conformation is actually adopted.^{3,4} The existence of a twisted conformation, lacking a molecular plane of symmetry, can be revealed when prochiral probes⁵⁻⁷ (i.e., substituents of the type CH₂R or CRMe₂) are present in the molecule. When the temperature is high enough to produce a fast rotation about the Ar-CO bond, a dynamic plane of symmetry is created: the diastereotopic groups of the prochiral probe display NMR signals that broaden and eventually coalesce, allowing one to determine the rate constants for the process.⁴

Naphthyl ketones 1–6 having an acyl moiety at position 1 and bearing a methyl substituent at position 2 are expected to offer good examples of this situation:

- R = Me (1)
 = Et (2)
 = CH₂-Bu^t (3)
 = Prⁱ (4)
 = CHEt₂ (5)
 = Bu^t (6)



Scheme I



If the plane containing the carbonyl function is twisted with respect to the naphthalene ring, no element of symmetry is left in the molecule, which should consequently display a pair of torsional conformers enantiomerically related as shown in Scheme I.

The existence of this equilibrium can be detected by NMR spectroscopy at appropriate temperatures, if the R group is a prochiral probe such as, for instance, an ethyl or an isopropyl substituent.

Results and Discussion

Dynamic NMR Investigation. A typical example of this behavior is offered by the ¹H NMR spectrum of 3 (R = CH₂Bu^t) in CD₂Cl₂. At -80 °C the two protons of the CH₂ group display an AB-type spectrum with a chemical shift separation of 13.2 Hz (200 MHz) and a geminal coupling constant *J*_{HH} = -19.4 Hz; at this temperature the geminal protons are in fact anisochronous. When the temperature is raised (Figure 1), the signals broaden and coalesce reversibly into a single sharp line; the rapid interconversion between the two enantiomers, *S* and *R*, of Scheme I generates a "dynamic" plane of symmetry which makes the methylene hydrogens homotopic (and isochronous) above -49 °C. Computer simulation⁶ of the line shape allows one to determine the rate constants at various temperatures and, hence, the free energy of activation (ΔG^*) for the enantiomerization process (Table I). It has often been observed for conformational processes that the ΔG^* values at different temperatures are equal⁸ within the experimental error (± 0.2 kcal mol⁻¹), suggesting negligible ΔS^* values and an enthalpy of activation ΔH^* almost coincident with ΔG^* . Behavior analogous to that of 3 was observed for both 4 (R = Prⁱ) and 5 (R = CHEt₂), where the process could be followed by ¹³C NMR in that the two carbons of the methyl groups

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(2) (a) University of Bologna. (b) Taken, in part, from the following: Pasquali, F. Doctoral Thesis, Faculty of Industrial Chemistry, University of Bologna, 1988. (c) University of Rome.

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Table I. Free Energies of Activation (ΔG^*) for the Enantiomerization of 1-7^a

compd	ΔG^* (kcal mol ⁻¹)	solvent	method	frequency (MHz)	temp (°C)
1, R = Me	8.1	CHF ₂ Cl	CA, ¹ H	200	-110, -103
	7.9	CHF ₂ Cl/CD ₂ Cl ₂	CA, ¹ H	200	-110, -108
2, R = Et	9.3	CD ₂ Cl ₂	CA, ¹ H	200	-92
3, R = CH ₂ Bu ^t	11.3	CHF ₂ Cl	¹ H	200	-60, -58
	10.7	CD ₂ Cl ₂	¹ H	200	-63, -57
4, R = Pr ⁱ	11.3	CHF ₂ Cl	¹³ C	75.5	-55, -51
	10.7	CD ₂ Cl ₂	¹³ C	50.3	-67, -66
	11.3	CD ₂ Cl ₂	CA, ¹ H	200	-60, -50
5, R = CHEt ₂	11.3	CHF ₂ Cl	¹³ C	50.3	-54, -49
	10.9	CD ₂ Cl ₂	¹³ C	50.3	-61, -56
	20.0	C ₂ Cl ₄	CA, ¹ H	200	+78, +90
7	19.8	C ₂ Cl ₄	¹ H	200	+61, +82

^a When a chiral auxiliary agent was employed, it has been indicated with the term CA. The temperatures (°C) given are those where the line shape simulation has been performed.

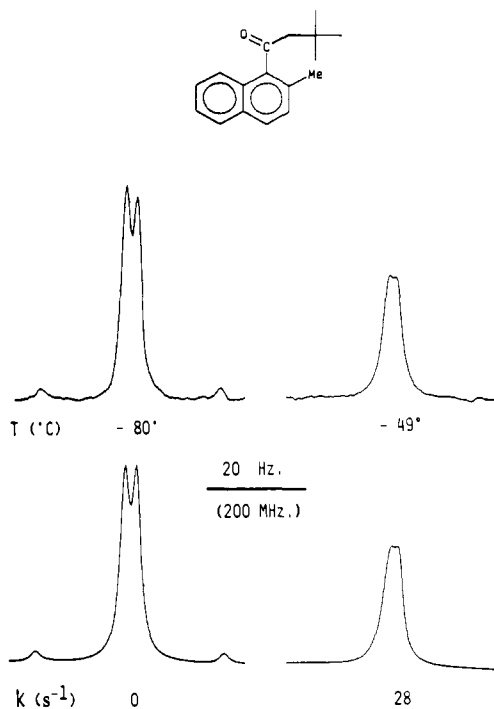


Figure 1. Top spectra: experimental 200-MHz signals of the methylene hydrogens of 3 in CD₂Cl₂ at -80 °C (left) and -49 °C (right), showing the coalescence of the AB-type spectrum. Bottom spectra: computer-simulated spectra obtained with the rate constants (k , s⁻¹) indicated and with the shift difference and J_{HH} given in the text.

in 4, or of the methylene groups in 5, also become anisochronous at low temperature. In the latter cases the use of ¹³C NMR spectra is more advantageous since the low-temperature proton spectra have small shifts (4) or great complexity (5). In the case of derivatives 1 (R = Me) and 6 (R = Bu^t) the absence of prochiral probes prevents direct detection of the dynamic process so spectra were recorded in the presence of a chiral auxiliary agent. For instance, when in 1 Pirkle's alcohol,⁹ (*R*)-1-2,2,2-trifluoro-1-(9-anthryl)ethanol, is added, both the acetyl methyl and the methyl in position 2 of the naphthalene ring (Me-2) split at -120 °C into a pair of 1/1 lines, due to the short-lived pair of diastereomeric solvates¹⁰ (they are the result of the association of the *R* and *S* torsional enantiomers with the *R* configuration of the enantiomerically pure Pirkle's alcohol). When the temperature is raised, the increasing enantiomerization rate of the ketone, due to bond rotation, broadens this pair of lines, which eventually coalesce into a single signal,¹¹ allowing the ΔG^* value to be determined by

computer line shape analysis. The same effect is observed for 6 in the presence of the chiral agent, albeit in a much higher temperature range (above room temperature),¹⁰ because of the higher enantiomerization barrier of 6 with respect to 1 (see Table I). In the case of derivative 2 (R = Et), contrary to the expectation, the methylene signal is not split, even at the lowest attainable temperature (-120 °C); as the ethyl moiety is a prochiral group, this was attributed to an accidental degeneracy of the chemical shifts of the two methylene hydrogens (the same degeneracy was also observed for the ¹H NMR signal of the methyl hydrogens of 4 but not in the corresponding ¹³C NMR spectrum). Indeed, when the ¹H NMR spectrum of 2 was taken in the presence of Pirkle's alcohol, two lines for the Me-2 group were detected at -100 °C, thus indicating that the *R* and *S* conformational enantiomers of 2 are actually present; in this way the enantiomerization barrier of 2 could be determined also (Table I).

To check whether the addition of the chiral agent significantly modifies the ΔG^* values, derivative 4 was examined both in the presence and in the absence of Pirkle's alcohol. The introduction of the latter, apparently, increases the ΔG^* of 4 only by 0.5 kcal mol⁻¹, a modification similar to that caused by a solvent effect (see the ΔG^* values of 4 and 5 in CD₂Cl₂ and CHF₂Cl reported in Table I).

The enantiomerization barriers of Table I increase when larger substituents are involved; this is consistent with a planar transition state destabilized by steric effects more than the twisted ground state. The lowest value is that for R = Me (1); for R = Et (2) the barrier increases by 1 kcal mol⁻¹, and it increases further by 2 kcal mol⁻¹ when substituents with secondary carbons (such as R = Prⁱ and R = CHEt₂) or with a primary carbon bonded to the bulky *tert*-butyl group (R = CH₂Bu^t) are examined (derivatives 4, 5, and 3, respectively). A much larger additional increase (9 kcal mol⁻¹) is observed when R is a tertiary carbon (6, R = Bu^t); the ΔG^* for 6 is as much as 12 kcal mol⁻¹ higher than for 1, and it is close to the value (about 23 kcal mol⁻¹) which would allow the physical separation of the enantiomers to be achieved at room temperature.

Conformational Analysis by NOE. In Scheme I the simplifying assumption was made that the plane of the carbonyl group is orthogonal to the plane of the naphthalene ring. An X-ray investigation in a similar compound¹² indicates that the angle is indeed very close to 90° (76° in the solid), but it is possible that in solution, particularly when R is a less bulky moiety, the angle deviates significantly, to yield a twisted conformation far from being orthogonal. Differential NOE measurements were thus carried out on derivative 2 (R = Et) to estimate the torsion angle in solution. The NOE effect is sensitive, in fact, to the sixth power of the interproton distances¹³ and thus to the value of the torsion angle. It is quite obvious that changes in the Ar-CO dihedral

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Table II. NOE Values (η)^a Determined for Derivative 2 in CDCl₃

obsd	irradiated	NOE (η)
Me-2	CH ₂	0.9 ₅
Me-2	CH ₃	0.4
CH ₂	H-8	1.6 ₅
CH ₂	Me-2	1.2 ₅
CH ₃	H-8	0.6 ₅
CH ₃	Me-2	0.5

^a Expressed as a percent of the original signals.

angle will substantially modify both the distance between the methyl protons (CH₃) of the ethyl moiety and H-8 and that between the same CH₃ group and the methyl group in position 2 (Me-2) of the naphthalene ring. Similar changes are also expected for the distances CH₂-H-8 and CH₂-Me-2. Accordingly, the H-8 and Me-2 signals of 2 were irradiated while the enhancement of the quartet and of the triplet of the CH₂ and the CH₃ groups, respectively, of the ethyl moiety were being observed. The reverse experiment (i.e., irradiation of the CH₂ and CH₃ groups of the ethyl moiety while the H-8 and Me-2 signals are observed) should yield consistent results. Unfortunately the signals of the aromatic hydrogen H-8 are superimposed on those of other aromatic protons; a quantitative determination of the enhancement in the reverse experiment was, as a consequence, too inaccurate. Therefore only the NOEs observed on Me-2 (upon irradiation of the CH₂ and CH₃ ethyl signals) were used, in addition to the NOE values obtained from the first experiment. In this way three independent NOE ratios could be employed to determine the unknown value of the torsion angle. It has to be remembered, however, that the measured NOEs (Table II) cannot be directly used to yield the needed ratios. The theory of the NOE experiment¹³ indicates that when an observed proton (or group of equivalent protons) essentially relaxes through mechanisms that do not involve the protons being irradiated, the observed NOE increases proportionally with the number of irradiated protons. In these cases irradiation of CH₃, CH₂, or CH groups will give NOE effects approximately proportional to 3/2/1. This prediction has been experimentally verified by deuterium substitution of some of the irradiated protons in a related molecule.¹⁴ In the present case the protons of the ethyl group and of the Me-2 group essentially relax through their geminal interactions. Accordingly, the measured NOEs have to be divided by 3 or 2 when generated, respectively, by the irradiation of a methyl or a methylene group. The corrected NOE values are indicated as η/n , where $n = 1, 2, \text{ or } 3$, depending whether 1, 2, or 3 protons were irradiated.

To obtain reliable values of the interproton distances, MM calculations¹⁵ were carried out for 2, assuming different torsion angles. The molecule displays a flat energy minimum corresponding to values of the dihedral angle O,C=C-1,C-10 (α) in the range 80–100°. The averaged interproton distances for the various dihedral angles were obtained through the relationships $\bar{r} = (\sum r_i^6/m)^{1/6}$, where r_i is the individual distance between a pair of protons and m represents the number of distances that enter into the average (thus, for instance, $m = 9$ for averaging the proton distances between two methyl groups). The computed \bar{r} values obtained in this way yielded the three required reciprocal ratios that, elevated to the sixth power, were compared to the ratios of the corresponding corrected NOE values (Table III). A quite satisfactory agreement with experiment is obtained when the mentioned dihedral angle (α) is about 95°. Angles deviating more than $\pm 15^\circ$ from the optimum value yield much less acceptable results. It is gratifying to observe that the perpendicular conformation, which corresponds to a minimum of the computed

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(15) The molecular mechanics calculations were performed using the MMX force field as implemented in PC Model, Serena Software, Bloomington, IN 47402-3076. (See also: Gajewski, J. J.; Gilbert, K. K.; McKelvey, J. In *Advances in Molecular Modeling*; JAI Press: Greenwich, 1990; Vol. 2. Burkert, U.; Allinger, N. L. In *Molecular Mechanics*; Caserio, M. C., Ed.; ACS Monograph Series 177; American Chemical Society: Washington, DC, 1982).

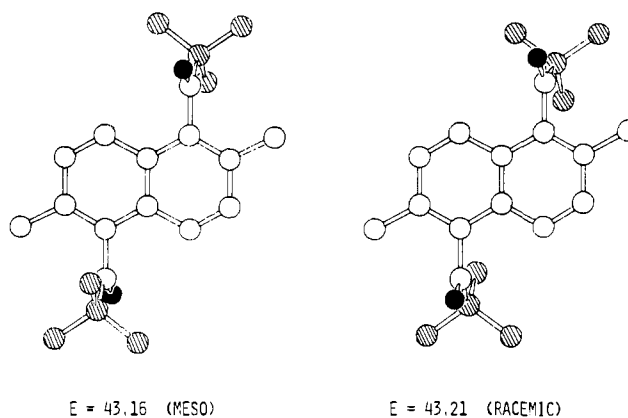
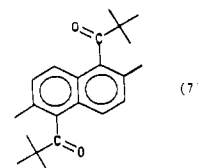
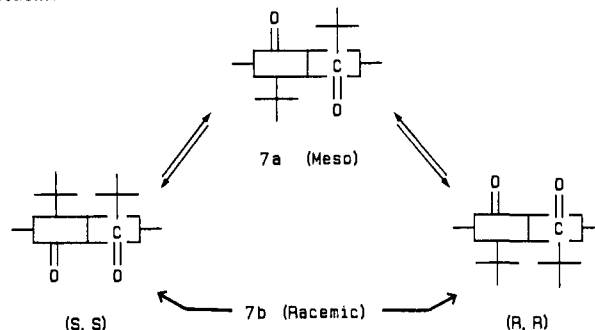


Figure 2. Conformation of derivative 7 as obtained by MM-X calculations. The H-atoms have been omitted for simplicity, the oxygen atoms are black, and the carbon atoms of the *tert*-butyl groups are striped. In both conformers the averaged Ar-CO torsional angle is 89.4°. The meso conformer (7a) is predicted to be slightly more stable, having a computed energy (E , kcal mol⁻¹) 50 cal mol⁻¹ lower than that of the racemic conformer (7b).

Scheme II



energy, also has distances that agree with the experimental NOE results. Even in solution the preferred conformation of these ketones is therefore almost orthogonal.

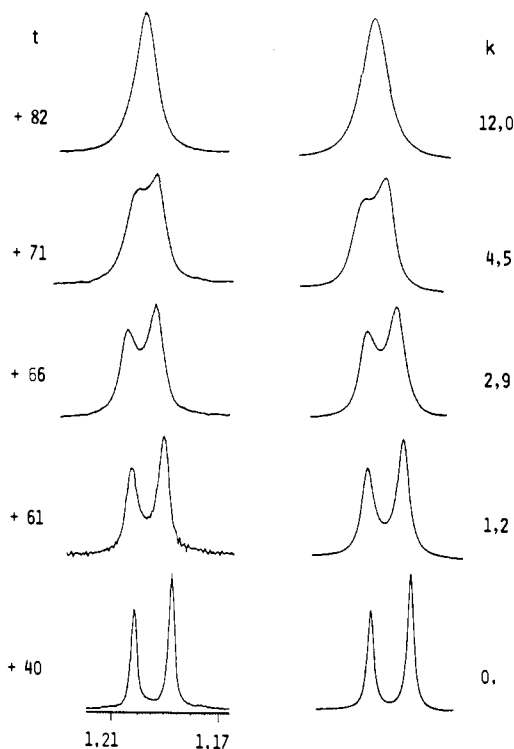
Detection of Meso and Racemic Conformers. If two RCO groups are introduced in the 1- and 5-positions and, at the same time, two methyl groups are present in the 2- and 6-positions, a meso and a racemic conformer are expected to be generated. When R = Bu^t, for instance, one obtains derivative 7, which should generate conformers 7a (meso) and 7b (racemic), as shown in Scheme II.

Molecular mechanics calculations¹⁵ (Figure 2) suggest that the meso form (7a) is more stable (by 0.05 kcal mol⁻¹) than the racemic form (7b), the computed torsional angle being 88° for both 7a and 7b. At room temperature in C₂Cl₄ the proton NMR spectrum of 7 displays signals corresponding to a pair of species with slightly different intensities (the more stable being 57 ± 2%); the observed ratio is similar to that obtainable from the computed energy difference.

Line shape analysis of spectra (Figure 3) yields the free energy of activation ($\Delta G^\ddagger = 19.8 \pm 0.2$ kcal mol⁻¹) for the interconversion of the meso into the racemic conformer. The similarity with the barrier of 6 (Table I) indicates that substitution at positions 5 and 6 does not affect the dynamic process (in the case of 7 the rate constants were divided by 2 because the rotation of *only one* of the two Bu^t-CO groups is needed to transform the meso 7a into the racemic 7b conformer).

Table III. Ratios of the Corrected (See Text) NOE Values (η/n) Compared with the Sixth Power of the Reciprocal Ratios of the Interprotonic Distances Computed (Molecular Mechanics) as a Function of the Ar-CO Torsion Angle (α) of Derivative 2

obsd	irradiated	ratio of η/n	6th power of distance ratios				
			$\alpha = 70^\circ$	$\alpha = 80^\circ$	$\alpha = 95^\circ$	$\alpha = 110^\circ$	$\alpha = 120^\circ$
Me-2	CH ₂ , CH ₃	3.6	4.8	4.1	3.5	3.5	2.7
CH ₂	H-8, Me-2	4.0	1.4	2.2	4.0	4.6	10.9
CH ₃	H-8, Me-2	3.9	2.6	3.0	4.2	5.3	6.0

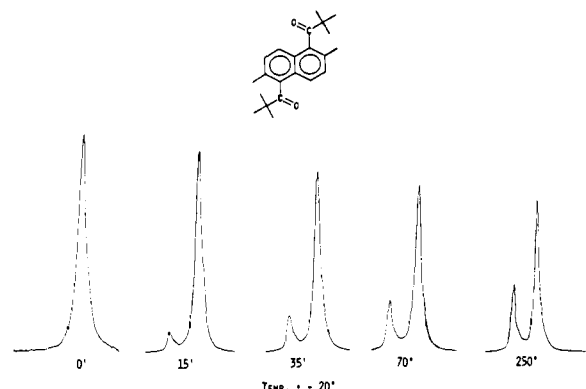
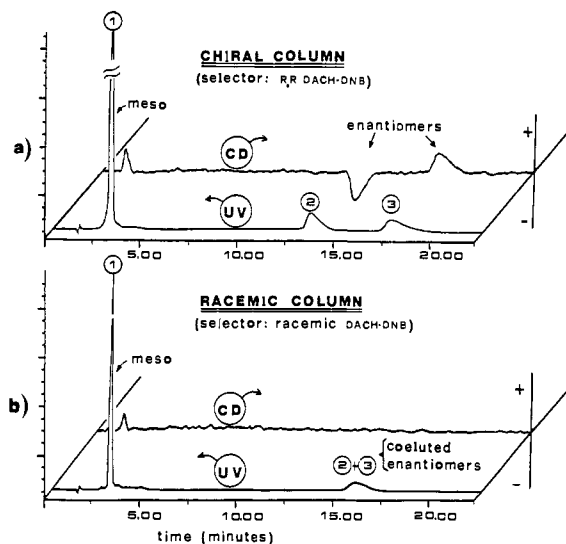
**Figure 3.** Experimental proton spectrum (left) of the *tert*-butyl group of 7 (200 MHz in C₂Cl₄) as a function of temperature (°C). On the right-hand side are shown the computer-simulated spectra obtained with the rate constants (k , s⁻¹) indicated.

The barrier for this process is sufficiently high so that the transformation of the more stable into the less stable conformer should be directly observed, provided only one of the two conformers is present in the solid state. Solid-state NMR spectra (¹³C CP MAS) of 7 suggest that indeed this is the case as only nine lines for the nine pairs of carbons are observed. Accordingly, when derivative 7 was dissolved at -40 °C in CDCl₃ and the NMR spectrum recorded at that temperature, only the signals corresponding to the more stable conformer were visible. When the temperature was raised to -20 °C, the signals of the less abundant conformer (particularly the *tert*-butyl singlet) began to appear and their intensity increased (Figure 4) until the equilibrium between the conformers (74/26 in CDCl₃ at -20 °C) was reached (about 4 h). The kinetic process could thus be followed by monitoring the change of the relative intensities; the rate constant obtained in this way ($k/2 = 5.0 \times 10^{-5} \text{ s}^{-1}$) corresponds to a ΔG^\ddagger of 19.7 kcal mol⁻¹ at -20 °C, in agreement with that (19.8 kcal mol⁻¹) obtained from line shape analysis in the range +60° to +80 °C.

The rotation of the R-CO moiety can occur in two possible ways, depending on whether the C=O moiety is directed toward position 8 or toward position 2. Molecular mechanics calculations carried out for the two possible transition states of 6 and 7 suggest that rotation of the C=O past Me-2 corresponds to the pathway with the lower energy. Computed barriers (for 6 or 7) are in fact 21 and 25.6 kcal mol⁻¹ for the first and the second situation, respectively; the lower barrier also matches better those determined experimentally (i.e., 19.8–20.0 kcal mol⁻¹).

Chiral Separation and Dynamic HPLC (DHPLC) Investigations.

The enantiomerization barriers determined via NMR spectroscopy for 6 and 7 indicate that the enantiomeric conformers have too

**Figure 4.** Proton signal (200 MHz in CDCl₃) of the *tert*-butyl group of 7, obtained by dissolving the compound at -40 °C and recording the spectrum at -20 °C as a function of time. The single signal initially observed (meso conformer) decreases as that due to the racemic conformer increases, a proof that in the solid state only a single conformer (meso) is present.**Figure 5.** (a) Chromatograms of 7 (chiral column) at -15 °C obtained by using both CD and UV detection. The UV detector displays the intense peak (76%) of the meso conformer (peak 1) and the two weak peaks (12% each) of the conformational enantiomers (peaks 2 and 3) of the racemic conformer (7b). The CD detector displays only the latter peaks, with opposite polarity. (b) Chromatograms of 7 (racemic column) obtained at -15 °C under the same conditions. The UV detector displays the intense peak (76%) of the meso conformer (peak 1) and that (24%) of the two coeluted conformational enantiomers. As expected, the CD detector does not yield any peak in the achiral environment.

short a racemization lifetime at room temperature ($t_{1/2} = 34 \text{ s}$ for 7 at +20 °C) to allow an easy physical separation. At -15 °C the lifetimes of both 6 and 7 are more conveniently long ($t_{1/2} \approx 1 \text{ h}$). Using a HPLC apparatus equipped with a chiral column ((*R,R*)-DACH-DNB stationary phase)¹⁶ cooled at -15 °C, the two enantiomers of 6, as well as the meso conformer (7a) and the pair of enantiomers of the racemic conformer (7b), could be separated. As shown in Figure 5a the three peaks expected for 7 are clearly visible by UV detection and their assignment to the

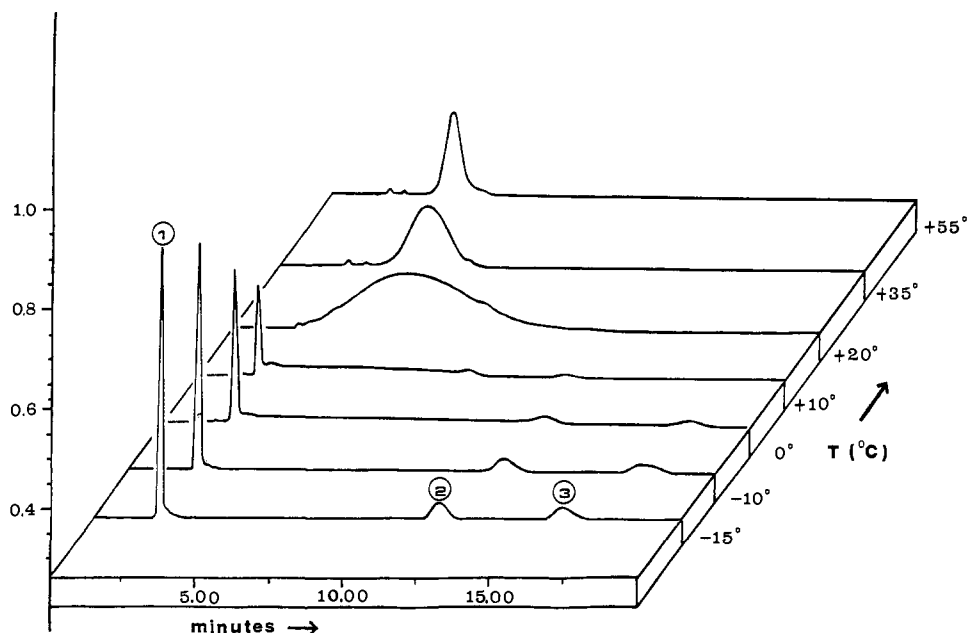


Figure 6. Chromatograms of **7** obtained by UV detection on a chiral column at various temperatures. At a high temperature (+55 °C) a single peak is observed, which broadens considerably on lowering the temperature to 20 °C and eventually splits into three peaks below 0 °C.

meso conformer and to the pair of enantiomers was unambiguously achieved by simultaneous UV and CD detection. The two equally intense weaker UV peaks yield CD traces opposite in sign, and at the same time, the stronger UV signal does not result in a meaningful CD detection. Consequently, the intense peak (76%) due to the first eluate corresponds to the meso conformer **7a** and the other two peaks (12% each) correspond to the enantiomers of **7b**.¹⁷ This conclusion also agrees with the HPLC separation obtained when a racemic version of the chiral column was employed (Figure 5b). Under these conditions no signal is observed by CD monitoring, and only two peaks (with relative intensities 76% and 24% for the first and second eluates, respectively) were observed by UV monitoring. As the diastereoselectivity of the column is unaffected on passing from the chiral to the racemic form, the intense peak (corresponding to **7a**, meso conformer) appears at the same position for both columns; on the other hand, the two peaks due to the pair of enantiomers coalesce¹⁸ to a position midway between those of the chiral column. Therefore the hypothesis derived from calculations,¹⁵ that the meso (**7a**) is more stable than the racemic conformer (**7b**), is clearly proven.

The effect of temperature on the peak elution profiles of an eluate that undergoes on-column isomerization (DHPLC) is better illustrated in Figure 6 by the resolution of **7**, as the simultaneous presence of three stereoisomeric species further complicates the chromatographic pattern encountered in the presence of dynamic processes. At a temperature of -15 °C the extent of isomerization during chromatography is negligible, whereas in the temperature range -5 °C to +10 °C the extreme peaks of the chromatogram are separated by an intermediate interconversion zone that does not reach the zero base line (Figure 6). The extent of on-column isomerization increases with the temperature, yielding extensive peak broadening and eventually complete coalescence¹⁸ of the three peaks near +20 °C. Resharpener of the peak containing the three coeluted conformers occurs at temperatures above 55 °C, when

(17) It has to be pointed out that the relative amounts of the three isomers can be obtained from digital integration of the corresponding peaks only in the case of identical UV spectra for **7a** and **7b**. Low-temperature HPLC with diode array detection allowed us to acquire the UV spectra of the meso (**7a**) and chiral conformers (**7b**), which were found to be identical; they are also identical to the UV spectrum of the mixture of conformers obtained at room temperature.

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Table IV. Free Energies of Activation (ΔG^*) for the Interconversion of Compounds **6** and **7**, As Obtained by HPLC Methods

compd	ΔG^* (kcal mol ⁻¹)	solvent	method	temp (°C)
6	20.0 ± 0.2	3% dioxane in hexane	I ^a	-5
7a	19.8 ± 0.2	CDCl ₃	II ^b	-20

^a On-line monitoring of the CD signal (327 nm) for the thermal racemization after chiral separation. ^b The reaction rate constant for the meso (**7a**) to racemic (**7b**) transformation in bulk CDCl₃ solvent was measured by sampling the reaction mixture from a batch reactor (-20 °C) followed by chiral chromatography in the HPLC system (eluent: *n*-hexane/dioxane, 93/7 v/v) at different reaction times.

the rotation about the ArCO bond is much faster.

At a given temperature, the shape of the chromatographic band profiles depends on the characteristic time of the separation process, so that the appearance of peak coalescence becomes recognizable at lower temperatures or on lowering the eluent flow rate. On the other hand, increasing the flow rate allows complex chromatograms with anomalous peak profiles due to dynamic processes to be simplified. For example, using a quite short column packed with 3- μ m spherical chiral silica and delivering the mobile phase at very high linear velocities (ultrafast HPLC), it is possible to separate the three conformers of **7** even at +20 °C, since complete resolution occurs in less than 30 s, i.e., less than the lifetime (34 s at +20 °C) predicted by the NMR measurements.

Thermal racemization of **6** has also been carried out using a stopped-flow procedure, the flow of the eluent being stopped when the CD cell (kept at -5 °C) contained the maximum amount of a single enantiomer. The disappearance of the CD signal was monitored on-line at 327 nm over a period of 6-7 half-lives (method HPLC-I). Racemization of **6** displays first-order kinetics with the interconversion barrier listed in Table IV. In the case of **7**, kinetic data could be obtained with the same method previously reported using NMR spectroscopy. Crystals of **7a** dissolved at -20 °C (in CDCl₃) and rapidly injected into the cooled HPLC display only the single peak of the meso conformer. The subsequent slow appearance of the peak due to the racemic conformer **7b** was then monitored over a period of about 4 h (method HPLC-II). The interconversion barrier obtained (Table IV) agrees well with the values of the two NMR determinations.

Finally, the CD spectra of the two enantiomeric conformers of **7b** were obtained at -20 °C. The spectrum of the first eluted peak displays a positive band (dotted trace) at about 335 nm, followed by a broad, negative band with a maximum at about 290

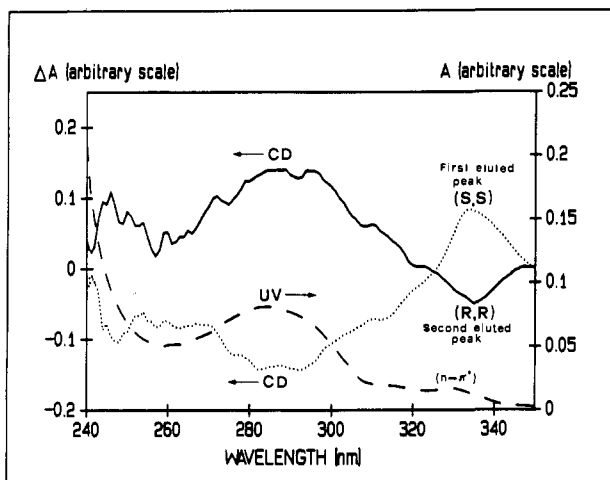
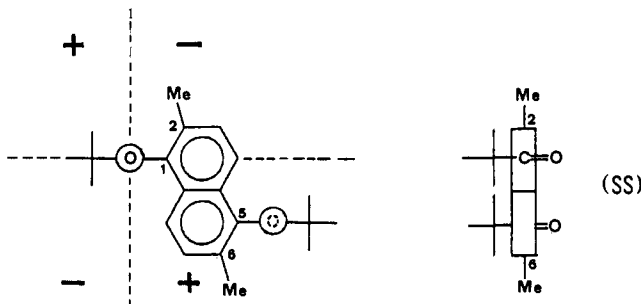


Figure 7. Low-temperature ($-20\text{ }^{\circ}\text{C}$) CD spectra of the two rotational enantiomers of the racemic conformer **7b**, obtained by connecting the spectrometer to the cooled chiral chromatographic column. The full trace (negative Cotton effect) corresponds to the spectrum of the more retained rotational enantiomer; the dotted trace (positive Cotton effect) corresponds to the spectrum of the less retained enantiomer. To the latter, the *SS* absolute configuration can be assigned on the basis of the octant rule (Scheme III).

Scheme III^a



^aRight: Top view of the *SS* enantiomer of **7b**. Left: The same enantiomer projected along the $\text{C}=\text{O}$ bond to apply the octant rule.

nm; the second eluted peak displays mirror-image behavior (Figure 7). The first band is due to the $n-\pi^*$ carbonyl transition, whereas the second one is related to the first two transitions of the naphthalene chromophore.

On the basis of the octant rule for carbonyl derivatives (Scheme III), the absolute *SS* configuration could be assigned to the conformational enantiomer having the shorter retention time. From Scheme III it is quite evident that, in the case of *SS*, the larger substituent occupies a region which entails a positive Cotton effect, as observed for the first eluate. Such an empirical application of the octant rule can be rationalized and supported by the dynamic coupling mechanism.¹⁹ The magnetically allowed $n-\pi^*$ carbonyl transition is associated with a rotatory charge displacement around the $\text{C}=\text{O}$ bond (Scheme IV, a) giving rise to a magnetic moment along the z -direction ($-m_z$) with the orbital phase depicted in Scheme IV, a) and with a quadrupolar charge distribution in the xy plane (Scheme IV, b).

The potential field of the electric quadrupole couples with the electric transition dipoles of the naphthalene chromophore, giving to the $n-\pi^*$ transition the electric dipole component necessary to generate the CD intensity. For the orthogonal conformation (Scheme IV, b) the long-axis polarized transition of the naphthalene ($-\mu_x$) is perpendicular to the magnetic moment ($-m_z$) and does not give any contribution to CD. The short-axis polarized transition, on the contrary, has a component along the $-z$ direction and gives a positive contribution to the carbonyl $n-\pi^*$ transition.

Scheme IV

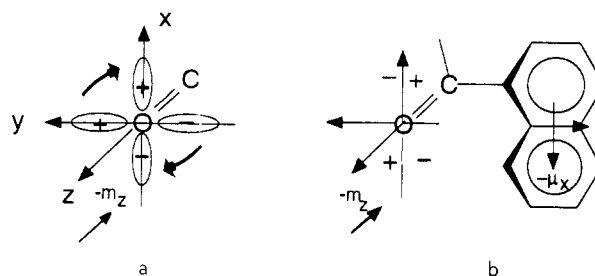


Table V. Low-Temperature Chiral HPLC Separations of Compounds **6** and **7^a**

compd	$k'_1{}^b$	$k'_2{}^b$	α^c	eluent
6	5.43	6.03	1.11	hexane/dioxane, 97/3
7a	3.85	—	18.66 ^d	hexane/dioxane, 97/3
7b	57.70	85.97	1.49	hexane/dioxane, 97/3
7a	1.55	—	9.10 ^d	hexane/dioxane, 93/7
7b	11.75	16.45	1.40	hexane/dioxane, 93/7

^aSee Experimental Section for chromatographic conditions. ^bThe term k' represents the chromatographic capacity factor and is defined as $(t - t_0)/t_0$, where t and t_0 are the retention times of the sample (1 and 2 refer to the first and second eluted enantiomers) and of an unretained compound, respectively. ^cEnantioselectivity factor (α), defined as k'_2/k'_1 . ^dDiastereoselectivity factor, defined as $(k'_1 + k'_2)/2k'_{\text{meso}}$.

Conversely, the CD corresponding to short-axis naphthalene transition (1L_a) should be of opposite sign. The experimental spectrum agrees with this interpretation; in particular, the relevant CD intensity in the naphthalene absorption is negative and is mainly observed in the region corresponding to the short-axis polarized (1L_a) transition.²⁰ The dynamic coupling mechanism thus confirms that the molecule adopts an orthogonal conformation and gives rational support to the application of the octant rule to this case. Similar CD spectra and the same elution order (*S* before *R*) were obtained for compound **6**.

From the data of capacity factors (k') listed in Table V one can see that **7a** is the less retained conformer, even when the same eluent (hexane/dioxane, 97/3) used for **6** is employed. In these conditions the averaged capacity factor of **7b** is equal to 71.82, which yields a diastereoselectivity factor (column selectivity between the meso and the chiral form) of 18.65. This value corresponds, at $-15\text{ }^{\circ}\text{C}$, to a difference in the free energies of adsorption ($\Delta\Delta G^{\circ}$) onto the chiral stationary phase between **7a** and **7b** of 1.5 kcal mol⁻¹. Such a large difference between two closely related diastereoisomers can be explained on the basis of a dual, simultaneous interaction (H-bond) of the chiral stationary phase (CSP) with the two carbonyl groups of **7b**. Assuming a face to face approach of the solute toward the chiral, planar array of the functional groups of CSP, a dual interaction is available only to conformer **7b**, as here the two $\text{C}=\text{O}$ moieties point toward the same side of the naphthalene ring. The difference in retention between **6** and **7a**, which has a single interaction of $\text{C}=\text{O}$ with CSP (according to this interpretation), might be accounted for by the lower dipole moments of **7a** with respect to **6** (the MM-computed dipole moments of **6**, **7a**, and **7b** are 2.8, 0.0, and 4.6 D, respectively).

Conclusion

When interconversion rates are known from dynamic NMR spectra, conditions for physical separation of conformational enantiomers by chiral HPLC at low temperature can be obtained. It is also possible to obtain the low-temperature circular dichroism spectrum of each conformational enantiomer and so to attempt the assignment of the absolute configuration by connecting on-line a CD spectrometer to the chiral column. We used some hindered 1-naphthyl ketones (which yield conformational enantiomers owing

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to the restricted Ar-CO rotation) to exemplify this procedure.

Experimental Section

Materials. Ketones 1-6 were prepared according to a general method described in detail for the case of 1.

2-Methyl-1-ethanoylnaphthalene (1). To a cooled (-10 °C) solution (kept under a N₂ atmosphere) of acetyl chloride (2.5 g, 32 mmol) in dried THF (50 mL) was added dropwise with stirring, the temperature of the exothermic reaction being kept below 0 °C, a THF (70 mL) solution of 2-methylnaphthylmagnesium bromide, obtained from 1-bromo-2-methylnaphthalene (7 g, 32 mmol) and Mg turnings (1 g, 42 mmol). The reaction mixture was left at room temperature overnight and then quenched by dropwise addition of water. After removal of the organic solvent at low pressure, the residue was extracted (ether, 3 × 30 mL), washed, dried (sodium sulfate), concentrated, and distilled (bp 156-157 °C, 0.5 mm), to yield 3.4 g of 1: ¹H NMR (CDCl₃) δ 2.35 (s, 3 H, CH₃Ar), 2.55 (s, 3 H, CH₃CO), 7.2 (d, 1 H, Ar), 7.42 (m, 2 H, Ar), 7.6-7.8 (m, 3 H, Ar); ¹³C NMR (CDCl₃) δ 17.77 (CH₃Ar), 31.26 (CH₃CO), 122.72 (CH, Ar), 124.25 (CH, Ar), 125.67 (CH, Ar), 127.12, (CH, Ar), 127.39 (CH, Ar), 127.53 (CH, Ar), 127.76 (C, Ar), 128.69 (C, Ar), 130.62 (C, Ar), 137.72 (C, Ar), 206.7 (C, CO); HRMS calcd for C₁₃H₁₂O (M⁺) 184.088 81, found 184.089 16.

Derivatives 2-6 were identified as follows.

2-Methyl-1-propanoylnaphthalene (2): ¹H NMR (CDCl₃) δ 1.3 (t, 3 H, CH₃CH₂), 2.4 (s, 3 H, CH₃Ar), 2.95 (q, 2 H, CH₂CH₃), 7.29 (d, 1 H, Ar), 7.46 (m, 3 H, Ar), 7.76 (m, 2 H, Ar); ¹³C NMR (CDCl₃) δ 7.40 (CH₃CH₂), 19.02 (CH₃Ar), 38.36 (CH₂CH₃), 123.96 (CH, Ar), 125.41 (CH, Ar), 126.80 (CH, Ar), 128.26 (CH, Ar), 128.53 (CH, Ar), 128.63 (CH, Ar), 129.30 (C, Ar), 130.09 (C, Ar), 131.77 (C, Ar), 211.29 (C, CO); HRMS calcd for C₁₄H₁₄O (M⁺) 198.104 46, found 198.104 76.

2-Methyl-1-(3,3-dimethylbutanoyl)naphthalene (3): ¹H NMR (CDCl₃) δ 1.15 (s, 9 H, Me₃C), 2.40 (s, 3 H, CH₃Ar), 2.75 (s, 2 H, CH₂Me₂), 7.30 (d, 1 H, Ar), 7.45 (m, 2 H, Ar), 7.65 (m, 1 H, Ar), 7.75 (d, 1 H, Ar), 7.85 (m, 1 H, Ar); ¹³C NMR (CDCl₃) δ 19.18 (CH₃Ar), 29.42 (Me₂C), 40.35 (CH₂CO), 57.43 (CMe₂), 124.01 (CH, Ar), 125.44 (CH, Ar), 126.87 (CH, Ar), 128.38 (CH, Ar), 128.65 (CH, Ar), 128.77 (CH, Ar), 129.37 (C, Ar), 130.01 (CH, Ar), 131.97 (C, Ar), 139.30 (C, Ar), 209.65 (C, CO); HRMS calcd for C₁₇H₂₀O (M⁺) 240.151 41, found 240.151 83.

2-Methyl-1-(2-methylpropanoyl)naphthalene (4): ¹H NMR (CDCl₃) δ 1.25 (d, 6 H, Me₂CH), 2.42 (s, 3 H, CH₃Ar), 3.18 (m, 1 H, CHMe₂), 7.28 (d, 1 H, Ar), 7.45 (m, 2 H, Ar), 7.78 (m, 2 H, Ar); ¹³C NMR (CDCl₃) δ 17.83 (Me₂CH), 19.69 (CH₃Ar), 42.75 (CHMe₂); 124.62 (CH, Ar), 125.46 (CH, Ar), 126.78 (CH, Ar), 128.32 (CH, Ar), 128.69 (CH, Ar), 131.16 (C, Ar), 131.91 (C, Ar), 132.90 (C, Ar), 140.80 (C, Ar), 211.50 (C, CO); HRMS calcd for C₁₅H₁₆O (M⁺) 212.120 11, found 212.120 58.

2-Methyl-1-(2-ethylbutanoyl)naphthalene (5): ¹H (CDCl₃) δ 0.97 (t, 6 H, CH₃CH₂), 1.62 (m, 2 H, CH₂CH₃), 1.80 (m, 2 H, CH₂CH₃), 2.45 (s, 3 H, CH₃Ar), 2.95 (m, 1 H, CHET₂), 7.27 (d, 1 H, Ar), 7.44 (m, 2 H, Ar), 7.64 (m, 1 H, Ar), 7.78 (m, 2 H, Ar); ¹³C NMR (CDCl₃) δ 11.58 (CH₃CH₂), 19.78 (CH₃Ar), 21.9 (CH₂CH₃), 55.99 (CHET₂), 124.64 (CH, Ar), 125.40 (CH, Ar), 126.72 (CH, Ar), 128.34 (CH, Ar), 129.06 (CH, Ar), 130.39 (CH, Ar), 131.70 (C, Ar), 132.00 (C, Ar), 138.27 (C, Ar), 212.54 (C, CO); HRMS calcd for C₁₇H₂₀O (M⁺) 240.151 41, found 240.151 14.

2-Methyl-1-(2,2-dimethylpropanoyl)naphthalene (6): ¹H NMR (CDCl₃) δ 1.25 (s, 9 H, Me₃C), 2.40 (s, 3 H, CH₃Ar), 7.27 (d, 1 H, Ar), 7.45 (m, 3 H, Ar), 7.72 (d, 1 H, Ar), 7.80 (m, 1 H, Ar); ¹³C NMR (CDCl₃) δ 20.32 (CH₃Ar), 27.75 (Me₃C), 45.27 (CMe₂), 125.08 (CH, Ar), 125.34 (CH, Ar), 126.32 (CH, Ar), 128.12 (CH, Ar), 128.20 (CH, Ar), 128.52 (CH, Ar), 129.64 (C, Ar), 130.0 (C, Ar), 131.66 (C, Ar), 138.43 (C, Ar), 218.63 (C, CO); HRMS calcd for C₁₆H₁₈O (M⁺) 226.135 76, found 226.136 17.

2,6-Dimethyl-1,5-bis(2,2-dimethylpropanoyl)naphthalene (7). To a benzene (200 mL) solution of 1,5-dibromo-2,6-dimethylnaphthalene²¹ (6 g, 19.2 mmol) kept under N₂ was slowly added under continuous stirring a 2 M solution of butyllithium (25 mL, 50 mmol). The reaction was completed in 5 h, and after cooling to -40 °C, pivaloyl chloride (5 g, 50 mmol) was added dropwise, the temperature being kept below -20 °C. After 1 h the reaction was quenched, and the organic layer was separated, washed, dried, and concentrated. The solid residue was purified by chromatography on silica gel (light petroleum/ethyl acetate, 95/5 v/v). In room-temperature solutions 7 appears as a solvent dependent equilibrium mixture of the meso (major) and racemic (minor) conformers (see text): ¹H NMR (CDCl₃) δ 1.25 and 1.27 (major and minor s, 9 H, Me₃C), 2.35 and 2.37 (minor and major s, 3 H, CH₃Ar), 7.30 (d, 1 H,

Ar), 7.38 (d, 1 H, Ar); ¹³C NMR (CDCl₃) δ major 19.46 (CH₃Ar), 27.13 (Me₃C), 44.68 (CMe₂), 124.57 (CH, Ar), 127.17 (C, Ar), 128.36 (CH, Ar), 129.01 (C, Ar), 138.14 (C, Ar), 217.97 (CO), minor 19.42 (CH₃Ar), 27.13 (Me₃C), 44.68 (CMe₂), 124.62 (CH, Ar), 127.17 (C, Ar), 128.25 (CH, Ar), 128.92 (C, Ar), 138.03 (C, Ar), 217.17 (CO); HRMS calcd for C₂₂H₂₈O₂ (M⁺) 324.208 93, found 324.208 66.

NMR Spectroscopy. The samples for the very low temperature measurements were prepared by connecting the NMR tubes containing the compounds to a vacuum line and condensing the gaseous CHF₂Cl by means of liquid nitrogen. The tubes were sealed in vacuo and allowed to reach room temperature before being introduced in the precooled probe of the spectrometer. The temperatures were determined by means of the calibrated chemical shift differences of methanol (low temperature) or ethylene glycol (high temperature). For temperatures below the freezing point of methanol, an appropriate sample thermometer²² was employed. The differential NOE experiments were carried out in N₂-saturated CDCl₃ solutions at 200 MHz. The signals to be irradiated were presaturated for a time equal to about 3T₁-5T₁ before acquiring the spectra with the decoupler having been turned off. To obtain good selectivity the irradiation was carried out by setting the decoupler at the frequencies of the various lines of the multiplet to be saturated and cycling it over these lines (about 50 cycles). A program that accumulates the difference between the two FIDs (the one corresponding to the preirradiated spectrum and the one where irradiation is kept away from any signal) was employed. Usually 128 scans (corresponding to 64 differential FIDs) were accumulated after four dummy scans, with the probe temperature maintained constant at 25 °C. The resulting FID, acquired with 16K (sweep width 3000 Hz), was transformed with 32K (zero filling) using a line broadening of 3-4 Hz. A control spectrum, with half the number of scans (i.e., 64), was subsequently obtained under the same conditions, and the NOE values were determined by comparing the line intensities of the two spectra. The ¹³C solid-state NMR spectrum of 7 (mixed with NaCl) was taken under the cross polarization (CP) magic angle spinning (MAS) conditions using a double bearing probe with a 7-mm-diameter Zr₂O rotor spinning at 2750 Hz; the recycle time was 3 s, the contact time 2 ms, and the number of accumulations 600.

HPLC Separation. Chromatography was performed on a micro-HPLC Carlo Erba System 20 equipped with a Micro UVIS20 detector and a Rheodyne Model 8125 5-μL loop injector; on-line simultaneous UV and CD detections were carried out using a modified JASCO A 500 spectropolarimeter equipped with a homemade flow cell suitable for low-temperature measurements. Subambient temperature chromatography was performed placing the chiral column in a homemade temperature control module (TCM); cooling of the CD flow cell and TCM was provided by the expansion of liquid CO₂, controlled by a solenoid valve. Temperatures were maintained within ±0.2 °C by means of an electronic controller. UV spectra of the resolved conformers of 6 and 7 were obtained using a Waters 990 diode array detector and a standard analytical (150 × 4 mm i.d.) chiral column ((R,R)-DACH-DNB). The latter is a HPLC chiral stationary phase (CSP) containing, as chiral moiety, the N,N'-bis(3,5-dinitrobenzoyl) derivative of (R,R)-1,2-diaminocyclohexane covalently bonded to silica microparticles. The CSP has been obtained by reacting first the glycidoxypolymer silica gel (GPSG) with (R,R)-(-)-1,2-diaminocyclohexane and then derivatizing the so prepared matrix with 3,5-dinitrobenzoyl chloride, as previously reported.¹⁶ The chromatographic parameters pertinent to the resolutions of 6 and 7 at -15 °C on a column (150 × 1 mm i.d.) packed with (R,R)-DACH-DNB (Lichrosorb Si-100, 5 μm)²⁴ as CSP are presented in Table V. The flow rate was 125 μL/min, and the UV and CD detections were set at 280 nm for 6 and 284 nm for 7. In the separation of 7, a more polar mobile phase has been employed in order to obtain a good global resolution in a reasonable time.

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