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Atropisomerism in Hindered Naphthyl Sulfoxides: Structure, Stereodynamics, and Chiral Resolution[1]

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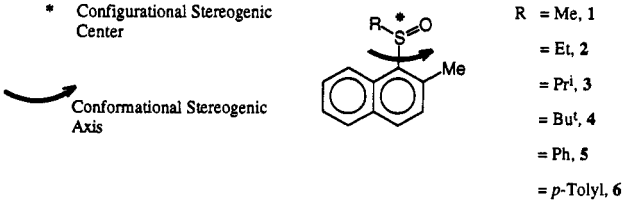
Barriers for the *E,Z* interconversion of atropisomers of 1-naphthyl sulfoxides (ArSOR) having a methyl group at position 2 of the naphthalene moiety were measured by variable-temperature NMR. Their values were found to cover the range 10.6–18.4 kcal mol^{-1}, the extreme values corresponding to derivatives **1** (R = Me) and **4** (R = Bu^t), respectively. NOE and LIS measurements indicated that the *Z* atropisomer is more stable than the *E* but that the absence of the methyl group at position 2 of the naphthalene moiety reverses this trend, rendering *E* more stable than *Z*. Solid-state NMR and X-ray diffraction of **4** established that only the more stable atropisomer (*Z*) is present in the crystalline state. Molecular mechanics calculations suggest that the *Z,E* interconversion process might occur by a rotation pathway having an opposite direction in the case of the more hindered derivatives **3** and **4** (R = Pr^i and Bu^t, respectively) with respect to the less hindered **1** and **2** (R = Me and Et, respectively). The enantiomers, which are due to the presence of the asymmetric sulfur atom, were resolved on a chiral stationary phase (DACH-DNB) having an *SS* configuration. Asymmetric oxidation reactions were employed to assign the absolute *R* configuration to the more retained enantiomers of alkyl aryl sulfoxides. The opposite trend (*S* being retained longer) was observed for diaryl sulfoxides such as **5** (R = Ph). In the case of the derivative with the largest interconversion barrier, sulfoxide **4**, it was also possible to resolve (at −35 °C) the two enantiomeric forms and their associated atropisomers. The use of on-line CD detection and the knowledge of the NMR assignments allowed us to unambiguously assign the elution order of the four species as *ES*, *ER*, *ZS*, *ZR*.

Introduction

Like configurational enantiomers, conformational enantiomers too can be isolated, provided the instrumentation for conducting low-temperature chiral chromatographic (LT-Chir HPLC) separations is available. In favorable circumstances, assignment of the absolute configuration can be achieved simultaneously if the same low temperature is maintained in the cell of a CD spectrometer that is connected to the cooled chiral column. It is of paramount importance to know in advance the temperature range required for a successful separation, and so the interconversion rate constants should be measured in advance by dynamic NMR spectroscopy.

Hindered naphthyl derivatives are forced to stay in nonplanar conformations which gives rise to pairs of atropisomers. We had detected this in 1-naphthylamines,[3] 1-naphthyl ketones,[4] and 1-naphthylimines.[5] In the latter case, we observed that particularly hindered substituents yield atropisomers which are configurationally stable and can be separated at room temperature on a chiral column.[5]

Scheme I



1-Naphthyl sulfoxides, bearing a methyl group at position 2 of the naphthalene ring, are also expected to adopt twisted conformations. These sulfoxides display a configurational stereogenic center (the sulfur atom) in addition to the conformational stereogenic axis (Scheme I). Consequently, at ambient temperature when the Ar–SO rotation is fast, a pair of configurational enantiomers will be observed whereas at lower temperatures a pair of *E,Z* atropisomers for each individual enantiomer should be detected (Figure 1 and Scheme II).

Derivatives **1–6** were chosen for investigation in hopes of verifying this hypothesis and achieving the conformational assignment and chiral separation.

Results and Discussion

Stereodynamics. Derivatives **1–5** display, at appropriate low temperatures, two sets of NMR signals appropriate for a pair of unequally populated atropisomers. In the case of **4**, this is observed even at ambient temperature. A typical spectrum is shown in Figure 2 for the case of derivative **3** (R = Pr^i). At −55 °C, the ^{1}H signal of the 2-methyl group is split into two lines (intensity ratio 1:9) which broaden upon increase of temperature and even-

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(3) (a) Casarini, D.; Lunazzi, L.; Placucci, G.; Macciantelli, D. *J. Org. Chem.* **1987**, *52*, 4721. (b) Casarini, D.; Lunazzi, L.; Macciantelli, D. *J. Org. Chem.* **1988**, *53*, 177. (c) Casarini, D.; Foresti, E.; Lunazzi, L.; Macciantelli, D. *J. Am. Chem. Soc.* **1988**, *110*, 4527. (d) Casarini, D.; Davalli, S.; Lunazzi, L.; Macciantelli, D. *J. Org. Chem.* **1989**, *54*, 4616. (e) Davalli, S.; Lunazzi, L.; Macciantelli, D. *J. Org. Chem.* **1991**, *56*, 1739.

(4) (a) Casarini, D.; Lunazzi, L.; Sgarabotto, P. *J. Crystallogr. Spectrosc. Res.* **1990**, *20*, 507. (b) Casarini, D.; Lunazzi, L.; Pasquali, F.; Gasparrini, F.; Villani, C. *J. Am. Chem. Soc.* **1992**, *114*, 6521.

(5) Casarini, D.; Lunazzi, L.; Macciantelli, D. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1363.

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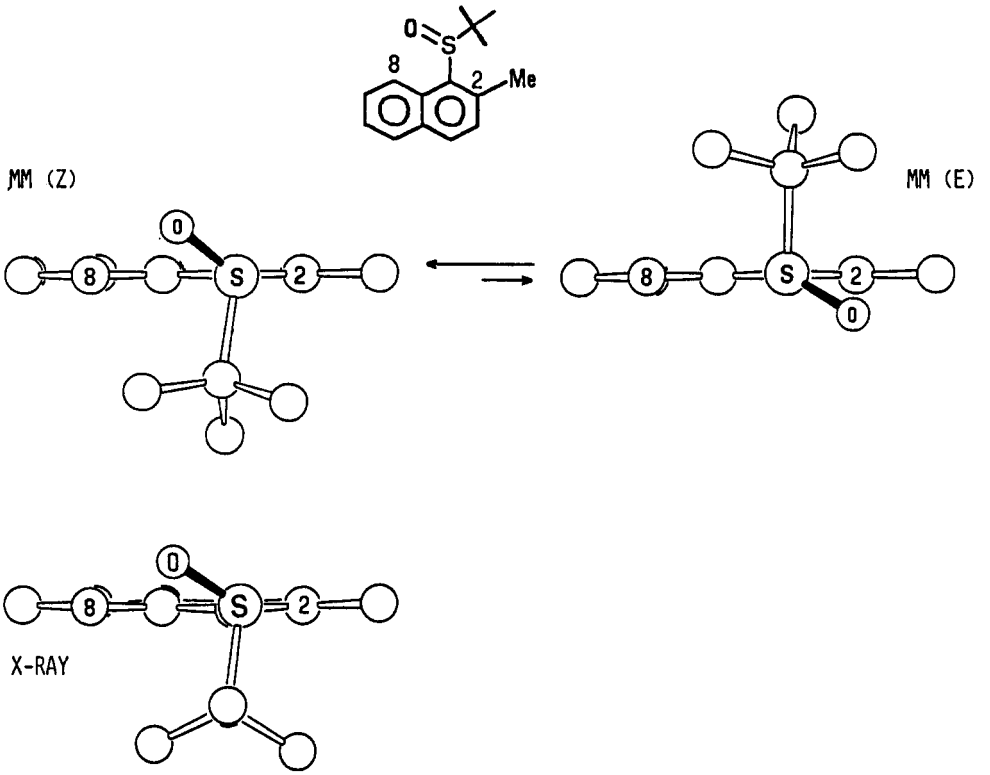
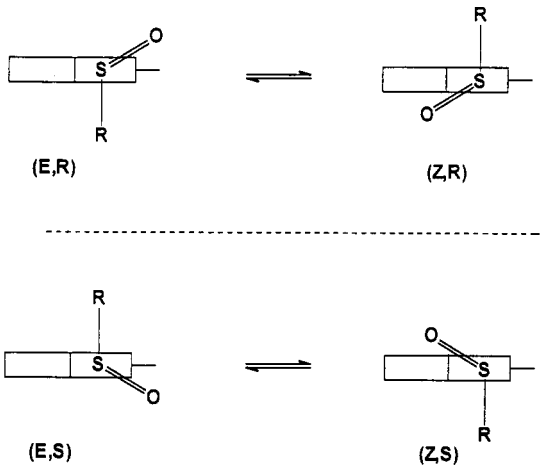


Figure 1. Top: representation of the *Z* (left) and *E* (right) atropisomers of sulfoxide 4 as obtained by MM calculations. Bottom: structure of 4 as obtained by X-ray diffraction.

Scheme II



tually coalesce into a single line in a reversible manner. Computer line shape simulations yield the rate constants (k, in s^{-1}) for the interconversion of the more into the less abundant atropisomer, and hence the corresponding free energy of activation ($\Delta G^* = 13.4$ kcal mol^{-1}) is derived. In Table I are collected the ΔG^* values for the sulfoxides 1–4. They increase with the increasing size of the aliphatic substituent (R = Me, Et, Pr^i, Bu^t, respectively). In the case of R = Ph (5), the ΔG^* value (11.1 kcal mol^{-1}) lies in between those of R = Me (1) and R = Et (2), suggesting a similar steric effect (Table I) .

Such a stereomutation might arise by two possible pathways. The substitutent R could pass over position 8 or, alternatively, over position 2 of the naphthalene ring. Since no available experiment can discriminate between these two possibilities, molecular mechanics (MM) calculations[6] were performed. The computed structures obtained in this way for the two *E* and *Z* atropisomers are shown in Figure 1 for R = Bu^t (4). The two rotational transition states corresponding to the passage of the R groups over C-8 and over C-2 were also calculated,[6] and the energy differences with respect to the most stable of the two possible ground states are given in Table I. It appears that in the more hindered derivatives 3 and 4 (R = Pr^i and Bu^t, respectively) the lowest energy pathway is the one in which the R group crosses position 8. The alternative route (i.e., the R group crossing position 2) seems to be adopted by the less hindered derivatives 1, 2, and 5 (R = Me, Et and Ph, respectively). However, the differences between the two computed barriers for each pair of pathways (0.9–2.4 kcal mol^{-1}) are not large enough to support an unambiguous conclusion.[7] We consider the idea that these sulfoxides follow one pathway or the other, depending on the steric character of the R group, to be a likely possibility but not an established finding.

Whichever pathway is followed, the observed trend in the computed barriers of aliphatic R does parallel that observed experimentally (see the values for derivatives 1–4 in Table I). By contrast, both the computed barriers for R = Ph (5) are smaller than any barrier computed for 1–4, a result at variance with the experimental observa-

(6) We made use of the MMX force field as implemented in the program PC Model, Serena Software, Bloomington, IN. See also: Gajewski, J.J.; Gilbert, K.K.; McKelvey, J. *Advances in Molecular Modelling*; JAI press: Greenwich, 1992; Vol. 2. As no particular parameters were available for sulfoxides those of default were employed. The barriers were computed by driving the Ar–SO torsion angle in 2° steps in the proximity of 0° and 180° and allowing the other angles and bond distances to relax to their minima for each fixed values of the torsion angle.

(7) The steric hindrance due to H-8 (peri position) and that due to the 2-methyl group (ortho-like position) are very similar, thus accounting for the ambiguity in the conclusion. When the absence of a substituent at position 2 makes the energies involved in the two rotation pathways much more different (as in the case of 1-neopentylnaphthalene where the computed barriers differ by 9.4 kcal mole^{-1}) the MM calculations confidently allow us to discern the passage of the *tert*-butyl group over C-2 as the preferred one (cf. Anderson, J. E.; Barkel, D. J. D. *J. Chem. Soc. Perkin Trans. 2* 1984, 1053).

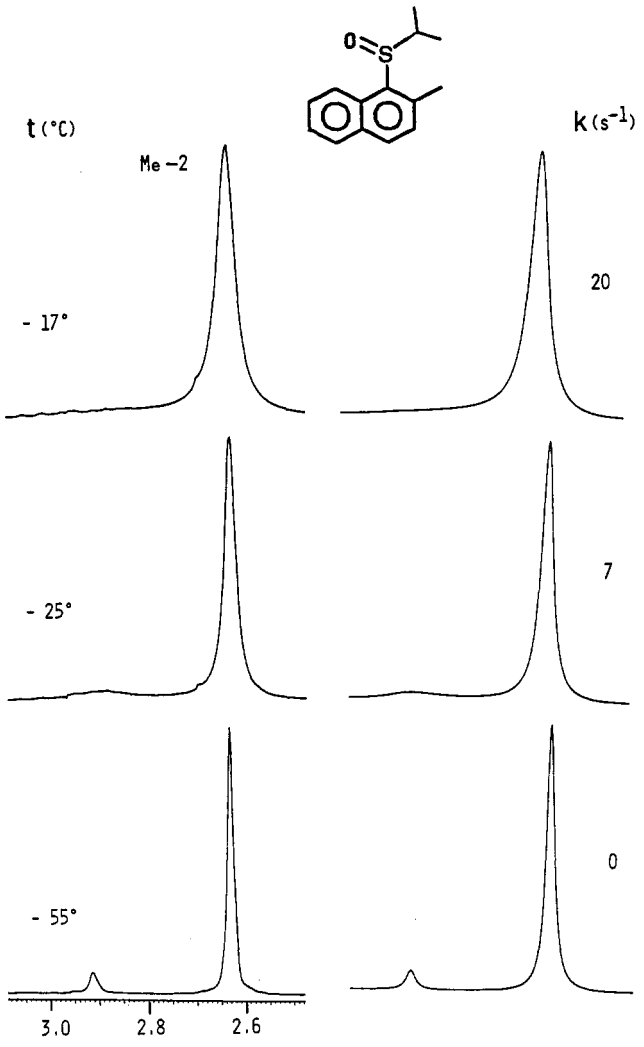


Figure 2. Temperature dependence of the experimental ^1H NMR signal (in $CDCl_3$ at 200 MHz) of the 2-methyl group of sulfoxide **3**, showing the existence of the *E* and *Z* atropisomers in a 1:9 ratio (left). On the right, the simulated spectra with the rate constants (*k*, in s^{-1}) indicated are shown.

tions. A possible explanation for this discrepancy might be that in both of the MM computed transition states of **5**, the phenyl ring is allowed to be twisted by exactly 90° with respect to the plane of the naphthalene moiety, a situation which requires a 30° dihedral angle about the Ph–SO bond. This would make the passage of the phenyl group across the naphthalene ring most facile. However, such a perfect orthogonality between the two aromatic rings is unlikely to occur in reality since the Ph–SO conjugation is conceivably stronger than is predicted by the MM calculations. X-ray structures and *ab initio* calculations of aryl sulfoxides agree in indicating that the Ph–SO dihedral angle is, in fact, considerably smaller (14° and 6°, respectively).[8] The phenyl–naphthalene interactions are consequently greater, thus accounting for the failure of the MM approach in predicting the relatively high barrier observed for **5**. Indeed, if the MM computed transition state of **5** is forced to maintain an almost planar Ph–SO dihedral angle, the calculated barrier for the passage of the phenyl group over C-2 increases from 6.0 to 8.0 kcal mol^{-1}, thus approaching the corresponding values computed for **1** and **2** in Table I.

(8) Ianelli, S.; Musatti, A.; Nardelli, M.; Benassi, R.; Folli, R.; Taddei, F. *J. Chem. Soc., Perkin Trans. 2* **1992**, 49.

Conformational Analysis in Solution. The ^1H NMR signals of the 2-methyl groups in **1–4** appear at higher field in the more stable atropisomer than in the less stable atropisomer (owing to the low interconversion barrier they can be regarded as conformers). The opposite trend is observed for the H-8 signal of the naphthalene moiety (see Experimental Section). Since the SO moiety has often been found to shift the signals of hydrogens close enough to be affected by its anisotropic environment to lower field,[9] the more stable atropisomer should be the one having the S=O moiety close to H-8 (conformer *Z*) and the less stable should be the one with the S=O moiety close to the 2-methyl group (conformer *E*), as shown in Figure 1 for **4** (R = Bu^t). MM calculations suggest that the total energy of the *E* conformers in **1–5** is indeed larger than that of the corresponding *Z* conformers, the energy differences (ΔE_0 in kcal mol^{-1}) being listed in Table I. Both these considerations, however, can hardly be considered conclusive.[10] Two additional experiments were thus performed (in the case of **4**) to reach an unambiguous conformational assignment in solution: (a) a nuclear Overhauser enhancement (NOE) determination and (b) a lanthanide induced shift (LIS) measurement.

(a) NOE Determination. A differential NOE spectrum[11] was produced by simultaneously saturating the hydrogens of the *tert*-butyl group of both atropisomers of **4**. As shown in Figure 3, the H-8 and Me-2 signals were enhanced, whereas those of the other protons disappeared. The NOE effect experienced by the 2-methyl groups is larger for the less than for the more abundant conformer (2.4% vs 1.6%). The opposite occurs for the hydrogens in position 8 (i.e., 9.3% for the less and 11.5% for the more abundant conformer). This suggests that the average interproton distance[12] between the *tert*-butyl and the 2-methyl group is *shorter* in the *less* than in the more abundant conformer, whereas the distance between the *tert*-butyl group and H-8 is *shorter* in the *more* abundant conformer. Accordingly, the ratio of the interproton distances[13] (Table II) between the *tert*-butyl group and H-8 in the *E* and in the *Z* conformer, respectively, must be *larger* than 1 (i.e., 4.68/4.54 = 1.03) whereas the analogous ratio between the proton distances of the *tert*-butyl and 2-methyl groups must be *lower* than 1 (i.e., 5.44/5.54 = 0.98). The ratios of the measured NOE's (elevated to −1/6) [3-5,11] between the *less* and the *more* stable conformer turn out to be, respectively, 1.04 and 0.93. These reproducible results are in agreement with the calculated distance ratios if the *Z* conformer is taken as the more stable (Table II). The opposite assignment (i.e., *Z* being the less stable) would give distance ratios in disagreement with the measured NOE values.

(9) (a) Fraser, R.; Schuber, F. J. *Can. J. Chem.* **1970**, *48*, 633. (b) Lett, R.; Marquet, A. *Tetrahedron* **1974**, *30*, 3379 and references cited therein.

(10) For instance, the ^{13}C chemical shift of the 2-methyl group of **4** is at lower field for the more stable with respect to the less stable conformer: a trend opposite to that observed for the corresponding ^1H signals.

(11) Neuhaus, D.; Williamson, M. *The Nuclear Overhauser Effect in Structural and Conformational Analysis*; VCH Publishers Inc.: New York, 1989.

(12) As the T_1 values for the same type of hydrogens were found to be the same in the two conformers (2.6 ± 0.2 s for both the 2-Me groups and 3.8 ± 0.3 s for both the H-8 hydrogens), the differences within each pair of the NOE values should mainly depend on the interproton distances.

(13) As the NOE values are approximately related to the inverse sixth power of the distances,[11] the average interproton distances were computed according to the relationship: $r = (\sum r_i^6/m)^{1/6}$ where r_i is the individual distance (in Å) between a pair of protons and *m* represents the number of distances that enter into the average [3-5] (thus *m* = 9 for the distance Bu^t, H-8 and *m* = 27 for the distance Bu^t, Me-2).

Table I. Parameters Related to the Interconversion of the More into the Less Stable Atropisomers of 1-5 (the Free Energies of Activation (ΔG^* in kcal mol^{-1}) Have an Error of ±0.15 kcal mol^{-1})

compd	solvent	$\Delta\nu^a$ (Hz)	Z:E ratio	ΔG^*	temp range^b (°C)	$\Delta E_0{}^c$	computed barriers^d (R on C-8)	computed barriers^d (R on C-2)
2 (R = Me)	CD_2Cl_2	68	88:12 (at −90 °C)	10.6	−70 to −60	0.52	10.6	9.0
2 (R = Et)	CD_2Cl_2	59	90:10 (at −70 °C)	12.2	−40 to −35	0.64	11.3	9.6
3 (R = Pr^i)	$CDCl_3$	56	90:10 (at −55 °C)	13.4	−25 to −17	0.44	12.6	13.5
4 (R = Bu^t)	C_2Cl_4	89	64:36 (at +25 °C)	18.4	+80 to +100	0.42	18.3	19.8
5 (R = Ph)	CD_2Cl_2	96	92:8 (at −85 °C)	11.1	−55 to −47	0.20	8.4	6.0

[a] Shift differences (at 200 MHz) between the signals of the 2-methyl groups of the more (*Z*) abundant (upfield) and the less (*E*) abundant (downfield) atropisomer. Only in 5 is the more intense signal (due to the *Z* conformer) downfield with respect to the less intense one. [b] Temperature interval where line shape simulations were performed for determining the ΔG^* values. [c] Computed (MM) energy difference (kcal mol^{-1}) between the ground state of the less (*E*) and the more (*Z*) stable atropisomer. [d] Computed (MM) energy difference (kcal mol^{-1}) between the two possible rotational transition states and the more stable (*Z*) ground state.

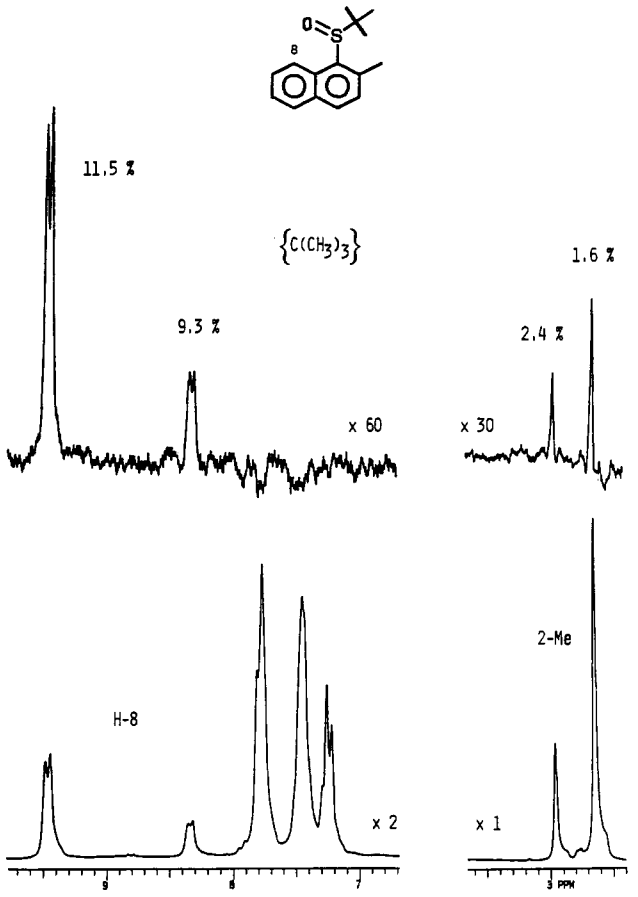


Figure 3. Lower trace: ^{1}H spectrum (in $CDCl_3$ at 200 MHz) of the aromatic region (left) and of the 2-methyl group (right) of sulfoxide 4,showing the presence of the *E* and *Z* atropisomers in a 1:3 ratio (for convenience the vertical scale of the aromatic region has been amplified by a factor of 2). Upper trace: NOE difference spectrum (vertically amplified by a factor of 30) obtained by simultaneously saturating the ^{1}H signals of both the *tert*-butyl moieties. The observed NOE values are indicated for each signal.

(b) LIS Measurements. Paramagnetic complexes, such as Eu(fod)$_3$, are known to interact with the oxygen atom of the sulfoxide moiety,[14] thus displacing downfield the signals of the nearby protons much more than those of the protons farther away from the binding site. In the *Z* conformer of 4, it is accordingly expected that the H-8 signal will be displaced more than that of the 2-methyl group, whereas the opposite would occur in the E-conformer.

(14) Eu(fod)$_3$ stays for europium 1,1,1,2,2,3,3,-heptafluoro-7,7-dimethyl-4,6-octanedionate. See: Cockerill, H. F.; Davies, G.L.O.; Harden, R. C.; Rackham, D. M. *Chem. Rev.* **1973**, *73*, 553 and references cited therein.

Table II. Averaged Interproton Distances (in Å) between the *tert*-Butyl Group and the H-8 or 2-Me Groups (MM Calculations) (Columns 2 and 3) for the *Z* and *E* Conformers of 4, Respectively, Distance Ratios (Columns 4 and 5), Corresponding Ratios (Elevated to −1/6) of the NOE Values between the *Less* and the *More* Abundant Conformer (Column 6)

protons involves	distances^a Z	distances^a E	distance ratios (Z/E)	distance ratios (E/Z)	(NOE ratios)$^{-1/6}$
H-8/Bu^t	4.54	4.68	0.97	1.03	1.04^b
2-Me/Bu^t	5.54	5.44	1.02	0.98	0.93^c

[a] The distances are the averaged values obtained as described in ref 13. [b] In various independent measurements this ratio never exceeded the range 1.01–1.04. [c] In various independent measurements this ratio never exceeded the range 0.93–0.97.

In 4, a larger effect was indeed observed for the H-8 signal of the more abundant than for the 2-Me signal of the less abundant conformer (see Experimental Section). By contrast, no LIS effect was detected for the 2-Me of the more and for the H-8 signals of the less abundant conformer, respectively. These results agree well with the assignment (*Z* being more stable) obtained from the NOE experiments. Since the ^{1}H shift and the relative intensities of the 2-Me and H-8 signals of 1–3 follow the same trend observed for 4, the same conformational assignment (i.e., *Z* being more stable) was also attributed to these derivatives. These assignments are corroborated by the MM calculations carried out on 1–3 (Table I).

Derivative 5 (R = Ph) displays an opposing trend in the low-temperature proton shifts with respect to 1–4, the H-8 signal being upfield and the 2-Me signal downfield in the more with respect to the less abundant conformer (see Experimental Section). This could be due either to a reversal of the shifts (owing to the ring current effects of the phenyl group) or to an actual reversal of the relative stability of the *E* and *Z* conformers. We dismissed the latter notion, however, because the ^{13}C spectrum of 5 at −80 °C exhibited the 2-methyl signal of the minor conformer *upfield* of that of the major conformer, as was observed[10] in 4 (Figure 4). If a reversal of the *E,Z* population had occurred, the ^{13}C signals too would had shown interchanged intensities. The phenyl ring currents are, in fact, expected to affect the ^{1}H much more than the ^{13}C shifts, thus accounting for their different behavior.

1-Naphthyl sulfoxides that lack a methyl group at position 2 of the naphthalene moiety fail to exhibit line-broadening effects at low temperatures, even in the case of the most hindered 1-naphthyl *tert*-butyl sulfoxide (7). This could be due either to a very low interconversion barrier between the two conformers or to the presence of only a single conformer at equilibrium. In the case of 7, the second hypothesis seems the most likely. MM

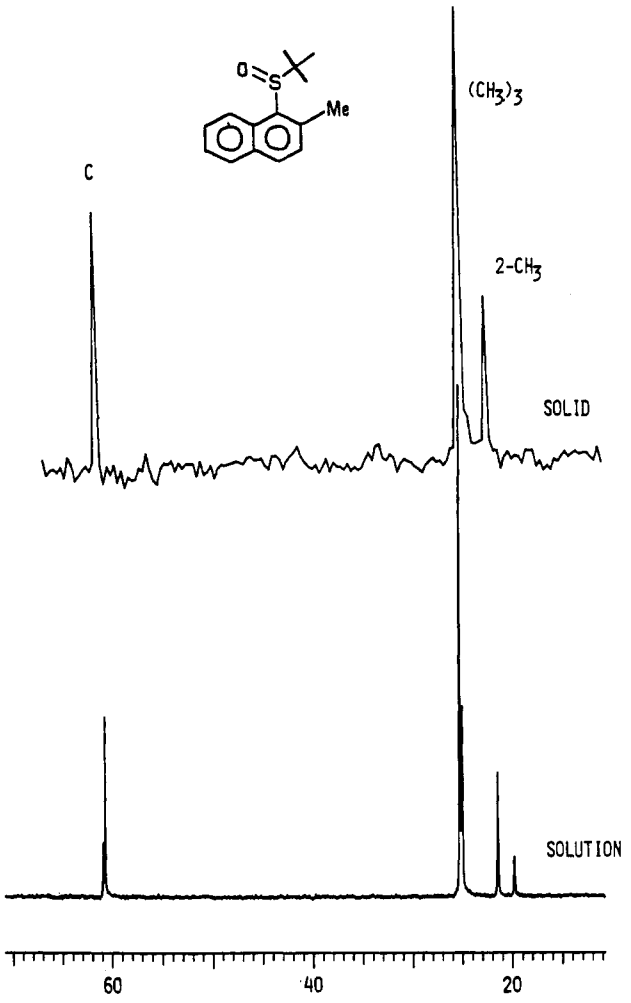


Figure 4. Upper trace: solid-state ^{13}C (CP MAS) NMR spectrum (line width 30 Hz) of the aliphatic region of sulfoxide **4** (75.5 MHz) showing the presence of a single atropisomer. Lower trace: ^{13}C spectrum in solution ($CDCl_3$) showing the signals of both the *E* and *Z* atropisomers.

calculations suggest an interconversion barrier for **7** of about 8 kcal mol^{-1}, which should be detectable by DNMR measurements, but an energy difference between the *E,Z* conformers of 1.6 kcal mol^{-1} was indicated. This corresponds to a 1:200 conformer ratio[15] at −120 °C, a temperature low enough to allow detection of lines broadened by a dynamic process with an 8 kcal mol^{-1} barrier, if the proportions of the exchanging species are comparable. Since such a broadening was not observed in **7** even at −120 °C (in dimethyl ether as solvent), it appears that only a single conformer is populated. Contrary to the case of the 2-methyl substituted sulfoxides **1–4**, calculations also indicate that in the unsubstituted derivative **7**, the *E* conformer would be the more stable one. This prediction found experimental support in the observation that, at any temperature, the H-8 shift of **7** is 8.25 ppm, which is in the range (8.25–8.35 ppm) observed for the *E* conformers of derivatives **1–4**. The H-8 shift expected for the *Z* conformer of **7** would be, on the other hand, in the range 9.05–9.45 ppm, as observed for the sulfoxides **1–4**. Furthermore, a LIS measurement carried out on **7** showed an extremely large downfield displacement for the H-2 signal, but a much smaller one for the H-8 signal. This behavior is that expected for a situation in which the *E* conformer is predominant and proves that in **7** the equilibrium lies largely toward the latter.

It is thus evident that elimination of the methyl group from position 2 of the naphthalene moiety reverses the relative stabilities of the two conformers.

Solid-State Structure and Conformation. Significant variations of the conformer ratio of **4** were observed upon changing the solvent. For instance the 3:1 *Z/E* ratio in $CDCl_3$ became 1.8:1 in C_2Cl_4. It was therefore important to unambiguously identify the actual solid-state conformation.

The high-resolution ^{13}C NMR (CP-MAS) spectrum of powdered **4** revealed the presence of only one of the two possible atropisomers. In Figure 4, the aliphatic ^{13}C NMR signals in the solid state are compared with those observed in solution. Whereas the solution spectrum displays two lines (separated by 1.6 ppm) for the 2-methyl group, only a single line (having the same shift as that of the more intense line of the solution spectrum) is detected in the solid. As a consequence, when the crystals of **4** are dissolved at low temperature (e.g., below −50 °C in CD_2Cl_2) and the ^1H spectrum recorded with the solution kept at −50 °C, only the spectrum of the more stable (*Z*) conformer is observed. If the solution is allowed to reach the equilibrium at higher temperatures and subsequently is cooled again at −50 °C, the signal of the minor (*E*) conformer (23% in these conditions) becomes visible also.

On the basis of these results, it is expected that a single-crystal X-ray diffraction determination of **4** would provide the structure of the more stable atropisomer and the subsequent analysis confirmed that it indeed has the *Z* structure (Figure 1). The only noticeable difference from the MM calculations is the position of the methyl groups of the *tert*-butyl moiety, which appear to be rotated by 60° in the computed with respect to the experimentally determined *Z* structure. The latter structure was found to correspond to a theoretical minimum, but with an energy 0.8 kcal mol^{-1} higher than that reported in Figure 1 (top left). It is possible that crystal packing is responsible for this minor deviation. The computed dihedral angle O,S,C-1,C-9 of the atropisomer *Z* (40.5°) is in reasonable agreement with the experimental one (28.7°). This agreement gives us confidence in the value computed for the same angle in the atropisomer *E* (147.3°) which cannot be experimentally determined.

Chiral Separation. In Scheme II the four possible situations generated by the presence of the stereogenic sulfur atom and by the restricted rotation about the Ar–S bond are illustrated. From the NMR measurements we know that the *E,Z* interconversion is too fast to allow isolation of the four species under normal conditions: only the pairs (*E,R*), (*Z,R*) can be separated from the pair (*E,S*), (*Z,S*) at ambient temperature.

(a) Enantiomeric Separation at Ambient Temperature. All the racemic sulfoxides **1-7** were resolved on a π-acid chiral stationary phase (CSP). This CSP (SS-DACH-DNB, see Experimental Section)[16a] shows a remarkable enantioselectivity toward a large number of alkyl aryl sulfoxides, the extent of the chiral recognition being essentially determined by the π-basic character of the aromatic moiety as well as by the size and the shape

(15) This result is obtained by assuming a negligible value of the entropy difference between the conformers.

(16) (a) Gasparrini, F.; Misiti, D.; Villani, C. *Chirality* **1992**, *4*, 447 and references cited therein. (b) Gargaro, G.; Gasparrini, F.; Misiti, D.; Palmieri, G., Pierini, M.; Villani, C. *Chromatographia* **1987**, *24*, 505.

Table III. Chromatographic Resolution Parameters at 25 °C of Sulfoxides 1-7 (Eluent: Hexane/Dioxane/Methanol (60/40/3) for a Column 250- × 4-mm i.d. Packed with (*S,S*)-DACH-DNB CSP (UV Detection at 300 nm)

compd	$(K'_1)^a$	α^b	$(R_S)^c$
1 (R = Me)	7.53	1.10	1.1
2 (R = Et)	7.13	1.21	1.3
3 (R = Pr^i)	6.76	1.21	1.2
4 (R = Bu^t)	3.17	1.74	1.5
5 (R = Ph)	4.67	1.09	0.9
6 (R = *p*-Tol)	5.65	1.10	1.0
7	2.08	1.50	1.4

[a] Capacity factor of the first eluted enantiomer. [b] Enantioselectivity factor, defined as the ratio of the capacity factors of the second and first eluted enantiomers. [c] Resolution factor, defined as $2(t'_2 - t'_1)(\omega_2 + \omega_1)$, where t'_1 are the corrected retention times of the enantiomers and ω_1 are the peak widths at the base.

of the alkyl substituent on the SO group.[16b] Asymmetric diaryl sulfoxides (e.g., 5 and 6) can be also resolved on the same CSP, although with lower values of enantioselectivity (α).

Chromatographic data pertinent to the chiral resolution of sulfoxides 1-7 are collected in Table III. As anticipated, the more hindered sulfoxides 4 and 7 show a higher degree of chiral recognition than the less bulky derivatives 1-3. The low α-values observed when R is an aromatic substituent (5 and 6) can be accounted for by considering two competing recognition mechanisms involving the aromatic moieties.

The elution order of the resolved enantiomers was established by making use of samples enriched in enantiomers of known configuration. Alkyl naphthyl derivatives 1-4 and 7 were enantiomerically enriched by a modified Sharpless asymmetric oxidation of the corresponding sulfides, a procedure that is known to yield sulfoxides mostly in the R configuration.[17] In all cases, the R enantiomers were those retained longer on the chiral column employed (CSP with SS configuration) as shown in Figure 5 for sulfoxide 7. This reaction, however, cannot be used to obtain enriched diaryl sulfoxides like 5 (R = phenyl), so we made use of the commercially available (−)-menthyl (*S*)-*p*-tolylsulfinate to produce (*via* Andersen reaction[18]) the enantiomerically enriched sulfoxide 6 (R = *p*-tolyl) which is very similar to 5 (R = phenyl). This reaction is known to proceed *via* inversion of configuration at the sulfur atom,[18,19] thus transforming the *S*-sulfinate into the sulfoxide enriched in the *S* enantiomers (the use of the same term *S* for the starting and the inverted final material is a consequence of the change in the substituent priority). The *S*-configuration of 6 was also confirmed by its CD spectrum, which has essentially the same shape, though in mirror-image, as those of 1-4 which have the *R* configuration. In the case of 6, an elution order opposite to that of 1-4 and 7 was observed, the *S*-enantiomer being the more retained. By comparing the CD spectra of the separated enantiomers of 6 with those of the enantiomers of 5, we could also assign the *S* configuration to the more retained enantiomer of the latter. It thus appears that in 1-naphthyl sulfoxides the elution order of the enantiomers is reversed when the sulfur-bonded alkyl group is replaced by an aryl substituent.

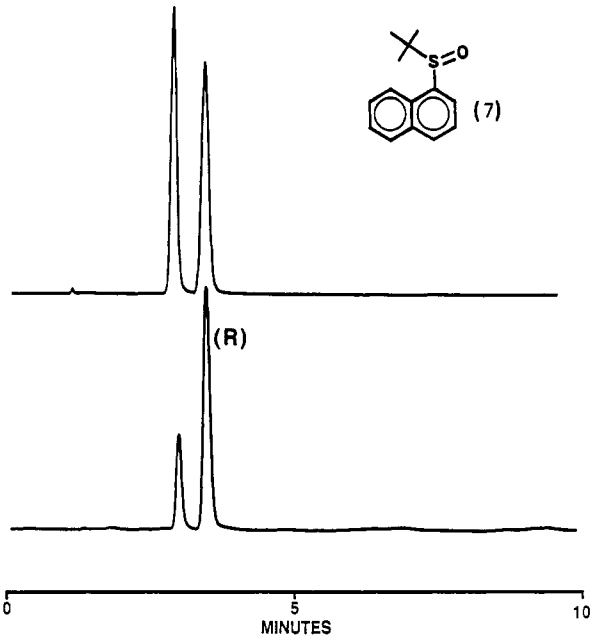


Figure 5. Chromatogram of racemic (top) and enantiomerically (*R*) enriched (bottom) sulfoxide 7, obtained by asymmetric oxidation of the corresponding sulfide. The CSP employed and the chromatographic conditions are given in Table III.

(b) Conformer and Enantiomer Separation at Low Temperatures. Chiral dynamic HPLC (Chir-DHPLC) either in the form of variable-temperature or variable-flow chromatography[20] offers an additional tool to investigate the exchange of stereolabile compounds, provided the rates of the dynamic process and of the chromatographic separation are compatible.

From the NMR determination of the interconversion barriers (Table I), we know that only sulfoxide 4 (R = Bu^t) has relatively long lived *E,Z* conformers. The corresponding ΔG^* value (18.4 kcal mol^{-1}) indicates in fact that a temperature of about −30 °C is required to attain a half-life close to 0.5 h, which would comfortably allow their physical separation. For 3, (R = Pr^i, ΔG^* = 13.4 kcal mol^{-1}), such a lifetime can only be reached at close to −90 °C, a temperature which is beyond the current technical capabilities. For the other less hindered 1-naphthyl sulfoxides, the required temperatures are even lower.

In Figure 6, the temperature-dependent chromatographic behavior of racemic 4 on the mentioned chiral column is shown for the range −35 to +100 °C (UV detection). Between −10 and −25 °C, the two equally intense peaks of the *R,S* enantiomers, observed above 25 °C, broaden and resharpen again on further cooling to −35 °C. At this temperature, as predicted, four peaks with 1:1:3:3 relative integrated intensities are detected, the 1:1 pair corresponding to the earliest eluted species. A chromatographic analysis at −35 °C of the enantiomerically pure 4 in the *S* configuration (obtained by preparative chiral chromatography) enabled us to establish the elution order. In the case of (*S*)-4, in fact, only two peaks (intensity ratio 1:3) were observed, their retention times (3.5 and 11 min) corresponding, respectively, to those of the first and third peak shown in Figure 6. By combining this result with the NMR assignment, the following elution sequence

(17) Pitchen, P.; Dumach, E.; Deshmukh, M. N.; Kagan, H. B. *J. Am. Chem. Soc.* **1984**, *106*, 8188.
(18) Andersen, K. K. *J. Org. Chem.* **1964**, *29*, 1953.
(19) (a) Mislow, K.; Green, M. M.; Laue, P.; Melillo, J.T.; Simmons, T.; Ternay, A. L., Jr.; *J. Am. Chem. Soc.* **1965**, *87*, 1958. (b) Axelrod, M.; Bickart, P.; Jacobus, J.; Green, M. M.; Mislow, K. *J. Am. Chem. Soc.* **1968**, *90*, 4835.
(20) (a) Mannschreck, A.; Zinner, H.; Pustet, N. *Chimia*, **1989**, *43*, 165 and references cited therein. (b) Stephan, B.; Zinner, H.; Kastner, F.; Mannschrek, A. *Chimia*, **1990**, *44*, 336.

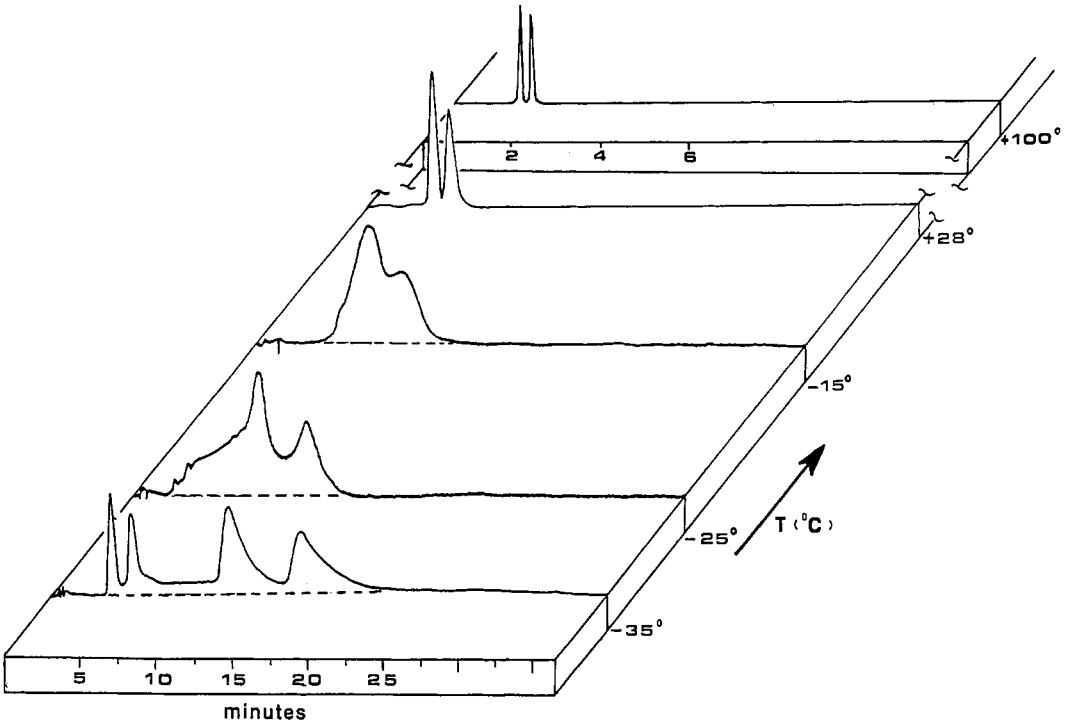


Figure 6. Dynamic HPLC of racemic 4 on a (*S,S*)-DACH-DNB chiral stationary phase (see Experimental Section). At −35 °C the capacity factors are 3.64, 5.15 (α = 1.42), 12.49, and 18.20 (α = 1.46) and the intensities (area of the integrated peaks) 12.6%, 12.1%, 38.5%, and 36.8% from left to right, respectively.

(in order of increasing retention time) could be established unambiguously: (*E,S*), (*E,R*), (*Z,S*), (*Z,R*).

The enantiomeric relationship between the resolved peaks was confirmed by circular dichroic detection achieved by connecting the chiral column to a CD spectrometer. When a sample of racemic 4 is resolved (either at ambient temperature or at −35 °C), the enantiomers yield equally intense peaks of opposite sign (Figure 7). The conformational relationship between the peaks of 4 was confirmed by means of a dynamic HPLC analysis carried out on a racemic version of the same CSP. Although this column does not separate the enantiomers it retains the same diastereoselectivity and is able to resolve the two atropisomers at low temperature.

It is worth mentioning that the diastereoselectivity factor at −35 °C is more than twice the enantioselectivity factor (see Figure 6), indicating that the direction of the SO bond with respect to the naphthalene moiety has a pronounced effect on the affinity for the stationary phase, the less stable (E) conformer being less retained.

Conclusions

Variable-temperature dynamic NMR and CD spectroscopies, combined with low-temperature HPLC techniques, have permitted the physical separation and the stereochemical assignment of atropisomers having interconversion barriers as low as 18–19 kcal mol^{-1}. In the case of 1-naphthyl *tert*-butyl sulfoxide 4, which was used to exemplify this procedure, we measured a *Z,E* interconversion barrier of 18.4 kcal mol^{-1}. The more stable *Z* atropisomer was retained (at −35 °C) longer than its *E* companion and the *R*- longer than the *S*-enantiomer, when a chiral stationary phase (DACH-DNB) of *SS* configuration was employed. The *E,Z* assignment was obtained by NMR techniques (NOE and LIS experiments), whereas the *R,S* absolute configurations were established by means of asymmetric syntheses of known stereochemistry. It was also observed that the retention order of the *R* and *S* enantiomers is reversed when the sulfur-bonded alkyl moieties are replaced by a phenyl group. The NMR spectra of the powder and X-ray diffraction data of a single crystal of 4 proved that only the more stable (*Z*) of the two possible atropisomers (predicted by Molecular Mechanics calculations and observed in solution) is present in the solid state.

Experimental Section

Materials. Racemic sulfoxides were prepared by the standard oxidation method of the corresponding sulfides, as described in detail for the case of sulfoxide 4.

2-Methyl-1-(2-methyl-2-propylsulfinyl)naphthalene (4). To a cooled (0 °C) solution (2.3 g, 10 mmol in 50 mL of chloroform) of the corresponding sulfide [2-methyl-1-(2-methyl-2-propylthio)naphthalene] were added 3.5 g of a suspension of 3-chloroperbenzoic acid (10 mmol) in water (1:1 ratio). After being stirred for 1 h at 0 °C the mixture was washed (saturated $NaHCO_3$), dried (sodium sulfate), and concentrated to give 2.2 g (90% yield) of crystallized (ether/hexane) compound.

IR 1039 cm^{-1} (ν_{SO}); ^{1}H NMR ($CDCl_3$) δ 1.25 (s, 9H, Me_3C, minor) and 1.30 (major), 2.62 (s, 3H, CH_3Ar, major) and 2.95 (minor) 7.25–7.80 (m, 5H, Ar), 8.35 (m, 1H, H-8, minor) and 9.45 (major); ^{13}C NMR ($CDCl_3$) δ 19.81 (CH_3Ar, minor) and 21.47 (major), 24.99 (Me_3C, minor) and 25.26 (major), 60.73 (CMe_3, major) and 60.96 (minor), 126.26 (CH, Ar, major), 126.62 (CH, Ar, major), 126.81 (CH, Ar, major), 128.67 (CH, Ar, major), 129.05 (CH, Ar, major), 131.63 (C, Ar, major), 132.30 (CH, Ar, major), 133.68 (C, Ar, major), 133.98 (C, Ar, major), 139.45 (C, Ar, major) and 141.40 (C, Ar, minor); the signals of the remaining three aromatic quaternary carbons, due to the minor conformer, were not detected; four of the expected six CH aromatic signals, due to the minor conformer, were also observed at δ 124.08, 125.94, 128.8, 131.26. Anal. Calcd for $C_{15}H_{18}OS$: C, 73.14; H, 7.37; S, 12.99. Found: C, 73.20; H, 7.33; S 12.93.

2-Methyl-1-(2-methyl-2-propylthio)naphthalene. To a solution of 1-bromo-2-methylnaphthalene (2.21 g, 10 mmol) in

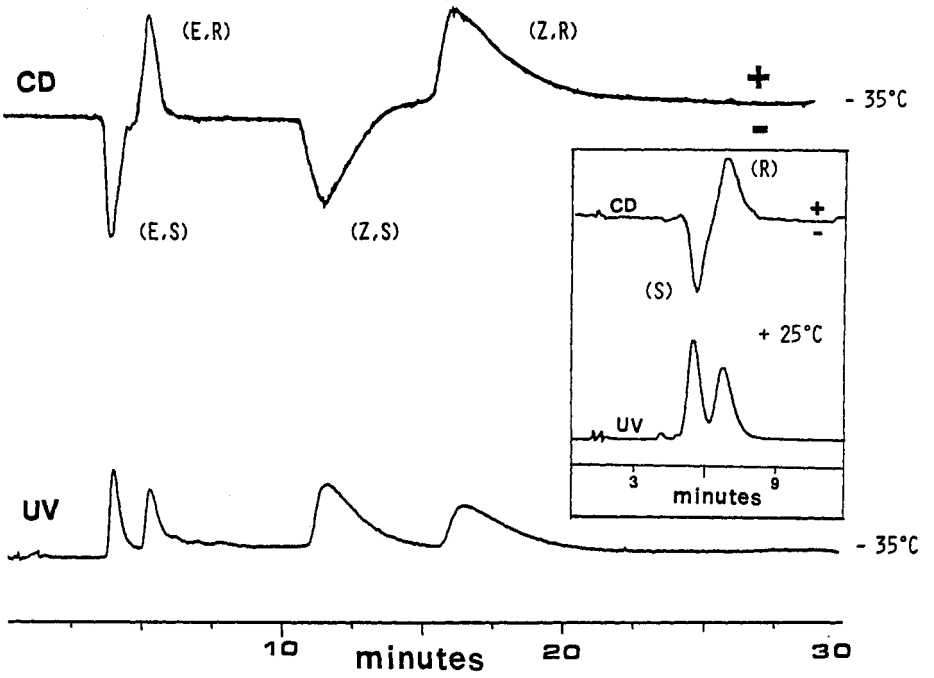


Figure 7. Chromatogram of racemic **4** at −35 °C (obtained by simultaneous UV and CD detection at 300 nm) showing the resolution of the two enantiomers and their associated atropisomers: *ES*, *ER*, *ZS*, and *ZR*. The inset shows the same separation carried out at 25 °C where only the two enantiomers can be resolved.

n-butanol (25 mL) were added sodium 2-methyl-2-propanethiolate (1.12 g, 10 mmol) and palladium tetrakis(triphenylphosphine) (0.12 g, 0.1 mmol) under argon atmosphere[21]. The solution was refluxed for 6 h, and after the solvent was removed at reduced pressure, the residue was purified by preparative HPLC on silica (hexane) to yield 1.3 g (56% yield) of the solid compound.

Derivatives **1-3** and **5-7** were identified as follows:

1-(Methylsulfinyl)-2-methylnaphthalene (1): IR 1058 cm^{-1} (ν_{SO}); ^1H NMR (CD_2Cl_2) δ 2.80 (s, 3H, CH_3Ar), 3.00 (s, 3H, CH_3SO), 7.30 (d, 1H, Ar), 7.52 (m, 2H, Ar), 7.85 (m, 2H, Ar), 9.10 (m, 1H, H-8), at −90 °C δ 2.66 (s, 3H, CH_3Ar, major) and 3.00 (minor), 8.25 (m, 1H, H-8, minor) and 9.30 (major); ^{13}C NMR (CD_2Cl_2) δ 19.78 (CH_3Ar), 39.68 (CH_3SO), 124.06 (CH, Ar), 126.70 (CH, Ar), 127.87 (CH, Ar), 129.79 (CH, Ar), 130.21 (CH, Ar), 131.50 (C, Ar), 132.41 (CH, Ar), 134.10 (C, Ar), 136.49 (C, Ar) 137.40 (C, Ar). Anal. Calcd for $C_{12}H_{12}OS$: C, 70.55; H, 5.92; S, 15.69. Found: C, 70.44; H, 5.91; S, 15.72.

1-(Ethylsulfinyl)-2-methylnaphthalene (2): IR 1056 cm^{-1} (ν_{SO}). ^1H NMR (CD_2Cl_2) δ 1.20 (s, 3H, CH_3CH_2), 2.70 (s, 3H, CH_3Ar), 3.12 (m, 1H, CH_2), 3.40 (m, 1H, CH_2), 7.28 (d, 1H, Ar), 7.52 (m, 2H, Ar), 7.85 (m, 2H, Ar), 9.05 (m, 1H, H-8), at −70 °C δ 2.62 (s, 3H, CH_3Ar, major) and 2.92 (minor), 8.30 (m, 1H, H-8, minor) and 9.25 (major); ^{13}C NMR (CD_2Cl_2) δ 8.56 (CH_3CH_2), 20.04 (CH_3Ar), 47.30 (CH_2), 124.32 (CH, Ar), 126.58 (CH, Ar), 127.68 (CH, Ar), 129.64 (CH, Ar) 130.05 (CH, Ar), 131.95 (C, Ar), 132.37 (CH, Ar), 133.99 (C, Ar), 133.99 (C, Ar), 134.89 (C, Ar), 138.40 (C, Ar). Anal. Calcd for $C_{13}H_{14}OS$: C, 71.63; H, 6.47; S, 14.66. Found: C, 71.64; H, 6.46; S, 14.69.

2-Methyl-1-(prop-2-ylsulfinyl)-naphthalene (3): IR 1031 cm^{-1} (ν_{SO}); ^1H NMR ($CDCl_3$) δ 0.9 (d, 3H, CH_3CH), 1.6 (d, 3H, CH_3CH) 2.70 (s, 3H, CH_3Ar), 3.25 (m, 1H, CH), 7.22 (d, 1H, Ar), 7.5 (m. 2H, Ar), 7.8 (m, 2H, Ar), 9.0 (br.s, 1H, H-8); at −55 °C δ 2.62 (s, 3H, CH_3Ar, major) and 2.90 (minor), 8.33 (m, 1H, H-8, minor), and 9.06 (major); ^{13}C NMR ($CDCl_3$) δ 16.82 (CH_3CH), 17.40 (CH_3CH), 20.55 (CH_3Ar), 52.20 (CHSO), 124.49 (CH, Ar), 126.30 (CH, Ar), 127.51 (CH, Ar), 128.90 (C, Ar), 129.36 (CH, Ar) 131.88 (C, Ar), 132.32 (CH, Ar), 133.61 (C, Ar), 133.75 (C, Ar), 139.12 (C,Ar). Anal. Calcd for $C_{14}H_{16}OS$: C, 72.39; H, 6.95; S, 13.78. Found: C, 72.40; H, 6.95; S, 13.69.

2-Methyl-1-(phenylsulfinyl)naphthalene (5): IR 1037 cm^{-1} (ν_{SO}); ^1H NMR (CD_2Cl_2) δ 2.80 (s, 3H, CH_3Ar), 7.40 (m, 8H, Ar), 7.75 (m, 2H, Ar), 8.60 (m, 1H, H-8); at −85 °C 2.48 (s, 3H, CH_3Ar, minor) and 2.96 (major), 8.50 (m, 1H, H-8, major) and 8.75 (minor); ^{13}C NMR (CD_2Cl_2) δ 20.27 (CH_3Ar), 124.76 (CH, Ar), 125.10 (2CH, Ar), 126.70 (CH, Ar) 128.05 (CH, Ar), 129.50 (CH, Ar) 129.71 (2CH, Ar), 130.18 (CH, Ar), 130.39 (CH, Ar), 133.28 (CH, Ar), 134.05 (C, Ar), 135.70 (C, Ar), 140.21 (C, Ar), 145.01 (C, Ar); at −85 °C 17.90 (CH_3Ar, minor) and 20.47 (major). Anal. Calcd for $C_{17}H_{14}OS$: C, 76.67; H, 5.30; S, 12.02. Found: C, 76.80; H, 5.33; S, 11.94.

2-Methyl-1-[(4-methylphenyl)sulfinyl]naphthalene (6): IR 1042 cm^{-1} (ν_{SO}); ^1H NMR ($CDCl_3$) δ 2.32 (s, 3H, CH_3Ph), 2.78 (s, 3H, CH_3Ar), 7.15–7.50 (m, 7H, Ar), 7.81 (m, 1H, Ar), 7.87 (d, 1H, Ar), 8.65 (m, 1H, H-8); ^{13}C NMR ($CDCl_3$) 20.25 (CH_3Ar), 21.52 (CH_3Ph), 124.69 (CH, Ar), 125.01 (2CH, Ar), 126.54 (CH, Ar), 128.06 (CH, Ar), 129.25 (CH, Ar), 129.95 (CH, Ar), 130.33 (2CH, Ar), 131.90 (C, Ar), 133.14 (CH, Ar), 133.77 (C, Ar), 136.30 (C, Ar), 139.94 (C, Ar), 140.56 (C, Ar), 141.98 (C, Ar). Anal. Calcd for $C_{18}H_{16}OS$: C, 77.12; H, 5.76; S, 11.41. Found: C, 77.13; H, 5.75; S, 11.43.

1-[(2-Methylprop-2-yl)sulfinyl]naphthalene (7): IR 1040 cm^{-1} (ν_{SO}); ^1H NMR ($CDCl_3$) δ 1.19 (s, 9H, Me_3C), 7.55 (m, 2H, Ar), 7.66 (dd, 1H, H-3), 7.85–7.90 (m, 1H, Ar), 7.96 (m, 1H, Ar) 8.10 (dd, 1H, H-2), 8.23 (m, 1H, H-8); ^{13}C NMR ($CDCl_3$) δ 123.86 (CH, Ar), 125.51 (CH, Ar), 126.11 (CH, Ar), 126.83 (CH, Ar), 127.20 (CH, Ar), 129.14 (CH, Ar), 131.97 (CH, Ar), 132.14 (C, Ar), 133.69 (C, Ar), 137.47 (C, Ar). Anal. Calcd for $C_{14}H_{16}OS$: C, 72.39; H, 6.95; S, 13.78. Found: C, 72.49; H, 6.93; S, 13.80,

Synthesis of Enantiomerically Enriched (*R*)-1-4, 7. Oxidation of alkyl aryl sulfides on a millimolar scale has been carried out according to a known procedure[17] using (*R*,*R*)-diethyl tartrate (DET) as a chiral auxiliary [$Ti(OPr^i)_4$: (*R*,*R*)-DET: H_2O in a 1:2:1 ratio]. Sulfoxides **1-4** and **7** were obtained with an ee = 60–75% in a 50–60% yield (73 h at −23 °C).

Synthesis of Enantiomerically Enriched (*S*)-6. To a solution of 2.0 g (9.05 mmol) of 1-bromo-2-methylnaphthalene in THF (25 mL), cooled at −78 °C under Argon atmosphere, was added a hexane solution (5.66 mL) of *n*-BuLi (1.6 M, 9.05 mmol). After 30 min the solution was transferred into a 25-mL THF solution (cooled at −78 °C) of (−)-menthyl-(−)-(*S*)-*p*-toluensulfinate (2.66 g, 9.05 mmol) and stirred for additional 20 min. The solution was allowed to reach room temperature (in about 30 min) and poured into a 50-mL saturated NH_4Cl solution. After extraction with $CHCl_3$, the organic layer was washed, dried (Na_2SO_4), and concentrated to give a yellow oil (2.2 g with an ee

(21) Migita, T.; Shimizu, T.; Asami, Y; Shiobara, F.; Kato, Y.; Kosugi, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1385.

= 85.9% determined by chiral HPLC on a (*S,S*)-DACH-DNB chiral stationary phase). Purification by preparative HPLC on silica ($CHCl_3$), followed by crystallization (Et_2O), provided 1.7 g of (*S*)-6 with an ee = 99.9%.

NMR Spectroscopy. The variable-temperature spectra were recorded at 200 MHz and the calibration carried out by means of the shift dependence of methanol (low temperatures) or ethylene glycol (high temperatures). The spectral simulations were performed with a two sites computer program[22] based on the Bloch equations, and the best fit was judged by superimposing the plotted traces with the experimental spectra. The differential NOE experiments were carried out in nitrogen saturated solutions ($CDCl_3$ or acetone-d_6) at 200 MHz. The two *tert*-butyl signals of 4 were presaturated for times equal to about $3T_1$–$5T_1$ before acquiring the spectra with the decoupler turned off. The irradiation was carried out by setting the decoupler at the frequencies of both the lines to be saturated and cycling it over these lines (about 50 cycles). A program which accumulates the difference between two FIDs (the one of the preirradiated spectrum and the one where irradiation was kept away from any signal) was employed. Usually 1000–2000 scans were accumulated, with the probe temperature kept constant at 23 °C, and the resulting FID transformed with a line broadening of 3 Hz. A control spectrum, with half the number of scans, was subsequently acquired in the same conditions. The use of different irradiation powers and of different solvents and concentrations yielded slightly different absolute NOE values in independent experiments: however, the NOE ratios (elevated to −1/6) were always found the same, within less than ±2%. The LIS experiments were obtained by adding five increasing amounts of $Eu(fod)_3$[14] to $CDCl_3$ solutions of 4 or 7, the molar ratios covering the range 1–50 × 10^{-3}. The linear dependence of the displaced shifts *vs* the molar ratios had correlation coefficients equal to or better than 0.9987. In the case of 4 the slope of the lines are 7.1 ppm for the H-8 signal of the more abundant conformer (*Z*) and 2.0 ppm for the 2-Me signal of the less abundant conformer (*E*); in 7 (which is essentially in the *E* conformation) the slopes are 17.3 ppm for the H-2 signal and 2.1 ppm for the H-8 signal. The samples for the solid state ^{13}C CP-MAS spectra (75.5 MHz) of 4 were fitted in Zr_2O rotors spun at 3.8 KHz and the spectra acquired (about 2000 scans) with a standard cross polarization sequence using a contact time of 5 ms and a recycling time of 3 s.

X-ray Diffraction. The crystal system of 4 is monoclinic with space group $P2_1/c$, a = 13.140(4) Å, b = 7.023(3) Å, c = 15.138(4) Å, β = 102.28(6)°, V = 1365.0 Å^3, Z = 4, D_c = 1.13 g cm^{-3}. Mo Kα radiation λ = 0.7107 Å, (MoKα) = 1.77 cm^{-1}, $F(000)$ = 496.0. Intensity data were collected by a CAD4 diffractometer using $\omega/2\vartheta$ scan range $2.5° \leq \vartheta \leq 25°$. The unit cell parameters were determined by a least-squares refinement on diffraction angles for 25 automatically centered reflections $8° < \theta < 14°$. Of 2329 independent reflections, 204 having $I < 2.5\,\sigma(I)$ were considered unobserved. The structure of 4 was solved by direct methods and refined anisotropically by full-matrix least-squares analysis using the SHELX program packages. The hydrogen atoms were found in the Fourier difference syntheses, but not refined. The final agreement index was R = 0.059, S = 0.93. Maximum Δ/σ = 0.030. Final difference map excursion 0.29 to −0.38 e Å^{-3}. A listing of fractional atomic coordinates, thermal parameters, relevant atomic distances, and observed and calculated structure factors for derivative 4 have been deposited at the Cambridge Crystallografic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

Chromatographic Measurements. The HPLC apparatus, cooling devices for low-temperature chromatography, and on-line CD detection have been described in ref 4b. Variable-temperature HPLC analysis of sulfoxide 4 on the chiral and racemic column (150- × 2-mm i.d.) were carried out using a ternary mixture of hexane/2-propanol/methanol (ratio 80/20/0.5) as mobile phase, delivered at 0.7 mL/min.

Acknowledgment. This work was carried out with the financial support of the National Research Council (CNR) and Ministry of the University and Scientific Research (MURST), Rome.

(22) Bonini, B. F.; Grossi, L.; Lunazzi, L.; Macciantelli, D. *J. Org. Chem.* 1986, *51*, 517.