Conformational Studies by Dynamic NMR. 74.[1] Stereomutations of the Conformational Enantiomers in Peri-Substituted 1-Acylnaphthalenes

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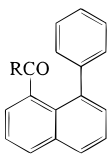
Naphthalenes bearing an acyl and a phenyl group in a peri relationship give rise to a pair of enantiomers in the temperature range where the rotations of the acyl group are slow. Such enantiomers were observed by means of low temperature NMR spectra in chiral environments. The barrier to rotation for the acyl substituents, that causes the interconversion of the enantiomers, was demonstrated to be lower than that for the phenyl group. In an appropriately synthesized derivative it was possible to measure the two barriers that were found equal to 10.4 and 15.9 kcal mol^{-1}, respectively. The barriers for the acyl group rotation increase regularly (from 9.5 to 13.2 kcal mol^{-1}) with the increasing dimension of the RCO groups (R = Me, Et, Pr^i, Bu^t). When a bromine atom replaces the phenyl group, the enantiomerization barrier for the corresponding acyl derivatives increases significantly.

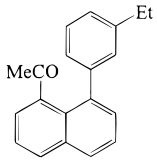
Introduction

Naphthalenes bearing two aromatic substituents lacking a local C_2 symmetry axis in the peri positions 1 and 8 give rise to stereolabile diastereoisomers, owing to the restricted naphthyl−aryl bond rotation.[3−6] This is a consequence of the planes of the aryl moieties being orthogonal to that of naphthalene.[3−7] The values of the corresponding barriers depend on the steric and electronic effects of the substituents and cover a range of 14−25 kcal mol^{-1}.[3−6] Likewise, the presence of two acyl groups in the peri relationship originates analogous stereolabile diastereoisomers since the same type of orthogonal conformation is adopted; the corresponding rotation barriers about the naphthyl-CO bond are, however, lower and cover a range of 6.7−14.6 kcal mol^{-1}.[8,9]

In a naphthalene having one acyl and one aryl substituent in a peri relationship, there are two possible stereogenic axes that might create either a pair of stereolabile enantiomers or diastereoisomers, depending on the symmetry of the aryl substituent. On the basis of the previously mentioned values, the rotation barrier about the naphthyl−CO and that about the naphthyl−aryl bonds are expected to be different, so that the restriction of the two motions will be detectable in different temperature ranges. With the purpose of studying the dynamic processes in this type of derivatives, the following 1,8-disubstituted naphthalene compounds **1**−**5** have been prepared and investigated by dynamic NMR spectroscopy:



1, R = Me; **2**, R = Et; **3**, R = Pr^i; **4**, R = Bu^t



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Results and Discussion

Molecular mechanic calculations (MMX force field)[10] indicate that 1-acetyl-8-phenylnaphthalene (**1**) has the planes of the acetyl and phenyl substituents parallel to each other and orthogonal to the plane of the naphthalene ring. As a consequence, **1** is expected to exist as a pair of stereolabile enantiomers that can be labeled as R_a and S_a (Scheme 1) or, alternatively, as M and P.

An experimental verification of this prediction can be achieved by rendering slow in the NMR time scale the rotation rates of both the MeCO and phenyl groups, since in these conditions the ortho and meta carbons of the phenyl ring would become diastereotopic. The ^{13}C spectrum of **1** in CD_2Cl_2 shows how the signals of these carbons broaden on cooling and eventually split, at −100 °C, into pairs of equally intense peaks, all the other signals remaining sharp (Figure 1). Computer line shape simulation yielded an activation energy for the corresponding dynamic process of 9.5 kcal mol^{-1} (Table 1).

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(3) Cosmo, R.; Sternhell, S. *Aust. J. Chem*. **1987**, *40*, 1107.

(4) (a) Cozzi, F.; Cinquini, M.; Annunziata, R.; Dwyer, T.; Siegel, J. S. *J. Am. Chem. Soc.* **1992**, *114*, 5729. (b) Cozzi, F.; Cinquini, M.; Annunziata, R.; Siegel, J. S. *J. Am. Chem. Soc.* **1993**, *115*, 5330. (c) Cozzi, F.; Ponzini, F.; Cinquini, M.; Annunziata, R.; Cinquini, M.; Siegel, J. S. *Angew. Chem., Int.Ed. Eng.* **1995**, *34*, 1019.

(5) Nagawa, Y.; Honda, K.; Nakanishi, H. *Magn. Reson. Chem*. **1996**, *34*, 78.

(6) (a) Zoltewicz, J. A.; Maier, N. M.; Fabian, W. M. F. *Tetrahedron* **1996**, *52*, 8703. (b) Zoltewicz, J. A.; Maier, N. M.; Fabian, W. M. F. *J. Org. Chem*. **1996**, *61*, 7018.

(7) (a) Clough, R. L.; Roberts, J. D. *J. Am. Chem. Soc.* **1976**, *98*, 1018. (b) Clough, R. L.; Kung, W. J.; Marsh, R. E.; Roberts, J. D. *J. Org. Chem*. **1976**, *41*, 3603.

(8) Staab, H. A.; Chi, C.-S.; Dabrowski, J. *Tetrahedron* **1982**, *38*, 3499.

(9) Casarini, D.; Lunazzi, L.; Foresti, E.; Macciantelli, D. *J. Org. Chem*. **1994**, *59*, 4637.

(10) Computer package PCMODEL, Serena Software, Bloomington, IN.

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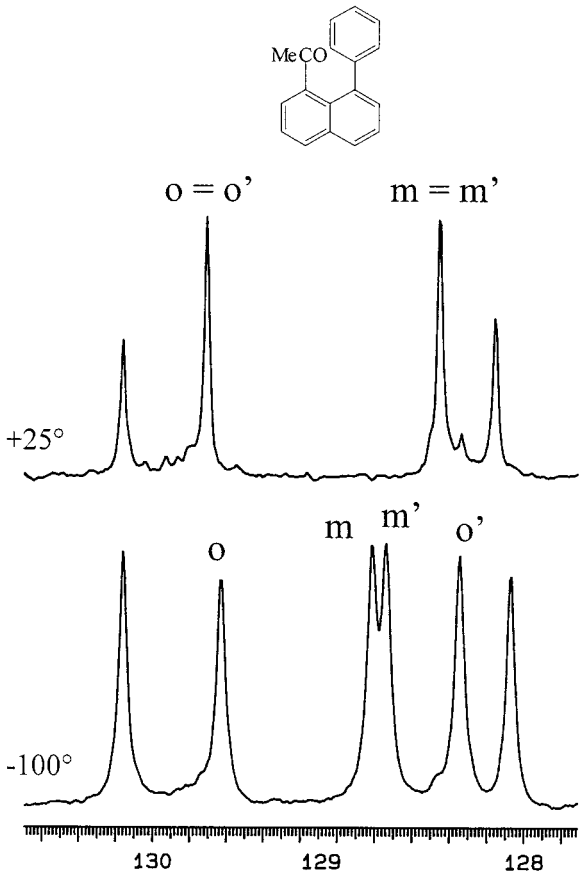
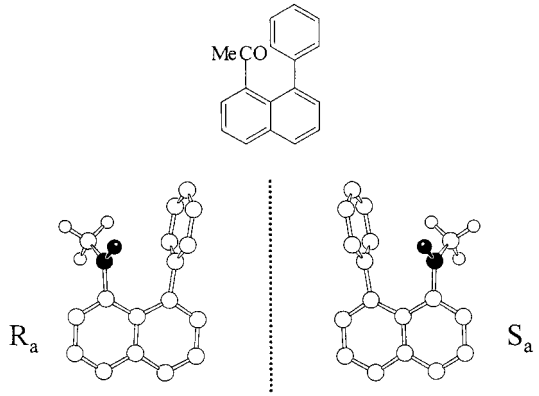


Figure 1. Portion of the ^{13}C spectral region of **1** (75.5 MHz in CD_2Cl_2) displaying a few aromatic signals at +25 °C (top) and at −100 °C (bottom). The single lines for the pair of ortho,ortho′ (o,o′) and meta,meta′ (m,m′) carbons are split at low temperature, owing to the restricted rotation of both the acetyl and phenyl groups.

Scheme 1. MM Computed Representation of the R_a and S_a Stereolabile Enantiomers of 1



Such a value corresponds to the *lower* of the two rotation barriers about the naphthyl−CO and naphthyl−Ph bonds. This experiment, however, does not allow one to decide which of the two motions is responsible for the measured activation energy.

To solve this dilemma, the spectrum of **1** was obtained in the presence of a chiral auxiliary agent. When a molar excess (Table 1) of an enantiomerically pure Pirkle's alcohol [1-(9-anthryl)-2,2,2-trifluoroethanol] is added to a solution of **1**, the ^1H signal of the methyl group broadens on cooling and splits into two lines below −70 °C (Figure 2). The two conformational enantiomers,

Table 1. Barriers ($\Delta G^{\neq}$) for the Enantiomerization, Due to the RCO Group Rotation, in 1−8

compd	$\Delta G^{\neq}$ (kcal mol^{-1})	frequency (MHz)	solvent
1	9.5	^{13}C (75.5)	CD_2Cl_2
	9.9	^1H (300)	CD_2Cl_2 + CSA (70:1)[a]
	10.1	^{13}C (75.5)	CD_3OD
2	10.4	^{13}C (75.5)	CD_2Cl_2
	10.4	^1H (300)	CD_2Cl_2
3	11.3	^{13}C (75.5)	CD_2Cl_2
	11.3	^1H (300)	CD_2Cl_2
4	13.2	^{13}C (75.5)	CD_2Cl_2
	14.3	^1H (400)	CD_2Cl_2 + CSA (270:1)[a]
5	10.4	^1H (300)	CD_2Cl_2
	[15.9][b]	^1H (300)	toluene-d_8 + Yb(fod)$_3$ [c]
6	13.5	^1H (400)	CD_2Cl_2
7	13.9	^{13}C (75.5)	$CDCl_3$
	14.0	^1H (300)	$CDCl_3$
8	18.0	^1H (400)	toluene-d_8 + CSA (315:1)[a]

[a] The CSA (chiral auxiliary agent) is (*R*)-(−)-1-(9-anthryl)-2,2,2-trifluoroethanol. The values in parentheses represent the molar excess of CSA with respect to the compound. [b] Barrier for the rotation of the *m*-ethylphenyl group (see text). [c] Yb(fod)$_3$ (see ref 16) has been added in trace amounts.

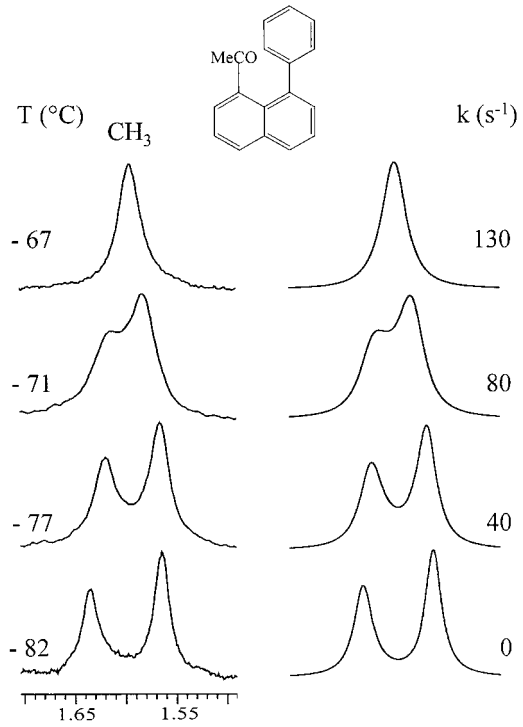


Figure 2. Left: experimental ^1H signal (300 MHz in CD_2Cl_2) of the Me group of **1** in the presence of a 70:1 molar excess of a chiral auxiliary agent (see text) as function of temperature. Right: computer simulation obtained with the rate constants (k in s^{-1}) indicated.

generated by the restricted rotation about the stereogenic naphthyl−CO axis, become, in fact, distinguishable in a chiral environment. This result is independent of the motion of the phenyl ring (topomerisation), so that the barrier measured by monitoring the methyl signal corresponds to that of the enantiomerization process brought about by the naphthyl−CO rotation. The rate constants used to simulate the experimental spectra (Figure 2) yield a $\Delta G^{\neq}$ of 9.9 kcal mol^{-1}, a value quite close to the one measured in the achiral solvent. The difference (0.4 kcal mol^{-1}) between the barriers measured in the achiral and chiral environments slightly exceed the experimental errors (±0.15 kcal mol^{-1}), and this might be attributed

to a different temperature dependence of the free energies of activation, due to not negligible $\Delta S^{\neq}$ values. However, in all these measurements we never found evidence of an appreciable temperature dependence, in agreement with what was reported in the majority of the conformational processes, so that the larger $\Delta G^{\neq}$ is likely to be a consequence of the increased polarity of the solution containing the Pirkle's alcohol.[11] To check this point the variable temperature ^{13}C spectrum of **1** was reinvestigated in CD_3OD in order to mimic, somewhat, the polarity due to the Pirkle's alcohol. In this solvent the $\Delta G^{\neq}$ value was found actually equal (10.1 kcal mol^{-1}), within the errors, to the one measured in the chiral medium. This result thus proves that the MeCO rotation has a barrier equal to or lower than that of the phenyl group The proportion of the two methyl signals displayed in Figure 2 is not 50:50, as might have been expected, but is about 59:41 at −82 °C and changes on rising the temperature (near the coalescence it becomes 55:45). This means that of the two diastereomeric solvates, due to the interaction of the *R*(−)-alcohol with one of the two enantiomers of **1**, one is more favored than the other. By using the alcohol with the opposite configuration *S* (+), the same unequal intensity ratio was again observed.

When the methyl groups of **1** (R = Me) is replaced by the *tert*-butyl group to yield derivative **4** (R = Bu^t) the *o*-and *m*-phenyl carbons display anisochronous ^{13}C signals at higher temperatures (−50 °C, rather than −100 °C). Accordingly, the free energy of activation for the observed dynamic process was found larger ($\Delta G^{\neq}$ = 13.2 kcal mol^{-1}) than in **1**, owing to the hindrance of the bulky *tert*-butyl group. The ^1H spectrum of **4**, obtained in the presence of the mentioned Pirkle's alcohol, displays two ^1H *tert*-butyl methyl signals at low temperature ($\Delta\nu$ = 0.019 ppm at −60 °C). As in the case of **1** the enantiomers yield two diastereomeric solvates displaying signals with a different proportion (58:42 at −60 °C). On warming, these lines coalesce yielding a $\Delta G^{\neq}$ of 14.3 kcal mol^{-1} for the related enantiomerization process. As observed for **1**, the presence the polar alcohol again makes this barrier slightly higher, but its value remains nonetheless close to that measured in the achiral solution (Table 1). This finding further confirms that the barrier for the acyl group rotation (corresponding to the enantiomerization process) is equal to or lower than that for the phenyl group rotation (topomerisation). Even when the former barrier has increased, still it does not overtake the value of the latter.

In derivative **2**, the methylene hydrogens of the ethyl group provide a probe for the direct determination of the enantiomerization barrier due to EtCO rotation, which can be thus measured in exactly the same conditions as those derived by monitoring the ortho and meta ^{13}C signals of the phenyl ring. Independently of the rotation of the phenyl group, the signal of the CH_2 hydrogens becomes anisochronous when the rotation about the naphthyl−CO bond is rendered slow at low temperature. The single CH_2 line, obtained by decoupling at the frequency of the methyl triplet, splits in fact into an AB-type spectrum (J = −19 Hz) when, at −85 °C, the two geminal hydrogens become diastereotopic, the corresponding shift separation being 0.14 ppm. Line shape simulation yielded rate constants corresponding to a $\Delta G^{\neq}$ of 10.4 kcal mol^{-1}, a value identical to that simultaneously determined from the appropriate phenyl carbon signals of **2**. Likewise in **3**, the same value was obtained for the barrier measured either monitoring the anisochronous Me signals of the isopropyl or the appropriate carbon signals of the phenyl group (11.3 kcal mol^{-1}).

Molecular mechanics calculations indicate that the rotation of the MeCO group in **1** may have two possible transition states, since either the methyl group or the oxygen atom can be directed toward the phenyl ring The corresponding calculated barriers are, respectively, 21.1 and 12.3 kcal mol^{-1} so that it is the lowest one that must correspond to the actual enantiomerization process. It is gratifying to observe that such a computed barrier is also the one closer to the experimental measurement (9.5 kcal mol^{-1}).

The enantiomerization barriers for **1**−**4**, measured in the same solvent (i.e., in CD_2Cl_2), increase regularly from 9.5 to 13.2 kcal mol^{-1} (Table 1) reflecting the increasing steric requirements of the Me, Et, Pr^i, and Bu^t substituents. The effect, however, is smaller than observed in other molecules with the same substituents,[12] and this seems to support the theoretical prediction that the transition state is the one having the oxygen atom directed toward the phenyl group in position 8. The alkyl moieties, in fact, cross over position 2, where their passage is not hindered to a large extent, due to the small dimensions of the hydrogen atom bonded to this carbon.

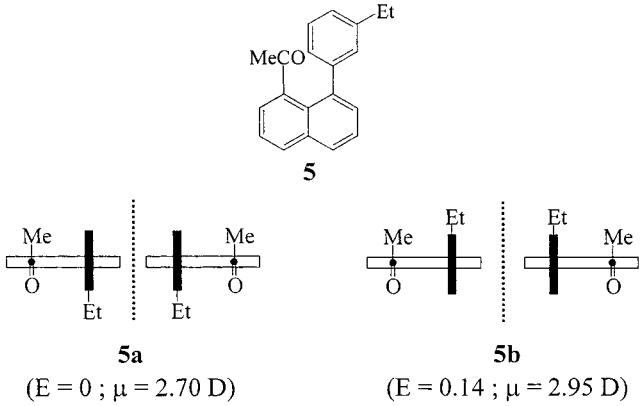
Although we have demonstrated that the phenyl rotation has a $\Delta G^{\neq}$ value equal to or higher than for the RCO rotation, its value has not yet been experimentally determined. The value calculated for the phenyl-naphthyl rotation (27.9 kcal mol^{-1}) is predicted to be higher than for the MeCO rotation, and suggests that the corresponding rate should be sufficiently slow as to become detectable even at ambient temperature. On the basis of these calculations we envisaged that introduction of an ethyl group in the meta position of the phenyl ring of **1** would cause the resulting derivative **5** to display, in addition to a pair of stereolabile diastereoisomers, two sufficiently stable enantiomers (atropisomers) which should be detectable at ambient temperature even in the presence of a fast MeCO rotation. In fact, the high barrier predicted for the rotation of the aryl group (here the *m*-ethylphenyl substituent) would deprive derivative **5** of any element of symmetry (Scheme 2).

Both the ^1H and ^{13}C NMR spectra are expected to indicate, in principle, the presence of two unequally populated conformational diastereoisomers by displaying two sets of signals of different intensity at low temperature. On the other hand the existence of the enantiomers at ambient temperature would be inferred by the ^1H spectrum displaying anisochronous methylene signals. Compound **5** does not have any element of symmetry if the aryl group, orthogonal to the naphthalene ring, is essentially locked at ambient temperature, even in the presence of a fast rotation of the MeCO group. However the ^1H spectrum of **5** does not reveal the predicted diastereotopicity of the methylene hydrogens in a number of solvents ($CDCl_3$, CD_3NO_2, pyridine-d_5, CD_2Cl_2), owing

(11) Casarini, D.; Davalli, S.; Lunazzi, L.; Macciantelli, D. *J. Org. Chem*. **1989**, *54*, 4616.

(12) (a) Casarini, D.; Lunazzi, L.; Verbeek, R. *Tetrahedron* **1996**, *52*, 2471. (b) Casarini, D.; Lunazzi, L. *J. Org. Chem*. **1996**, *61*, 175. (c) Jennings, W. B.; Kochanewycz, M. J. K.; Lunazzi, L. *J. Chem. Soc., Perkin Trans. 2* **1997**, 2271. (d) Casarini, D.; Lunazzi, L.; Mazzanti, A.; Foresti, E. *J. Org. Chem*. **1998**, *63*, 4991.

Scheme 2. Schematic Representation of the Four Observed Conformational Stereoisomers (Diastereoisomers and Enantiomers) of 5[a]



[a] The MM computed energies (E) are in kcal mol^{-1}; the computed dipole moments (μ) are in debye.

to accidental shift degeneracy at any temperature between −40° to +30 °C. Only the spectrum in toluene-d_8 does show that each quartet line is further split (0.005 ppm at +25 °C and 0.01 ppm at −20 °C).[13] The anisochronicity observed at ambient temperature, even if very small, proves that the barrier for the naphthyl−aryl rotation must be higher than that for the naphthyl−CO rotation.

At about −90 °C in toluene-d_8 all the ^{1}H aliphatic signals of **5** display two groups of lines having unequal intensity. For instance, the methyl line of the acetyl moiety splits into two, with the line upfield (1.64 ppm) more intense than its downfield (1.79 ppm) partner (ratio 65:35), an indication that, as conceivable, the two conformational diastereoisomers have a different stability. The interconversion of these two diastereoisomers has a $\Delta G^{\neq}$ value (10.4 kcal mol^{-1}, Table 1) that is similar to that determined for the enantiomerization process of the unsubstituted derivative **1**, since in both cases it is the result of the same naphthyl−CO rotation process (the slightly larger value reflects the hindrance of the *m*-ethylphenyl with respect to the unsubstituted phenyl group).

Molecular mechanics calculations predict that the diastereoisomer with the ethyl substituent syn to the oxygen atom (**5a** in Scheme 2**)** is 0.14 kcal mol^{-1} more stable than that having these two moieties in an anti relationship (**5b** in Scheme 2). Such an energy difference for the isolated molecule entails a 60:40 ratio at −90 °C,[14] a value quite close to that (65:35) experimentally determined in an inert solvent like toluene. These calculations also predict that the less stable conformer **5b** has a dipole moment (2.95 D) larger than that (2.70 D) of the more stable conformer **5a**. The NMR spectrum of **5** was thus taken in CD_2Cl_2 at −90 °C, where the dielectric constant ($\epsilon = 16$) is quite higher than that of toluene at the same temperature ($\epsilon = 2.7$). In CD_2Cl_2 the conformer ratio is reversed in that the highfield MeCO signal appeared less intense than its low field partner (ratio 43:57), a result that agrees with the previous assignment based on the energy values: the more polar conformer **5b** has in fact increased its proportion in a more polar solvent. A proof that such a variation depends indeed on the polarity of the solution and is not a consequence of a shift inversion in the different solvents employed, is offered by the spectrum obtained in a 1:1 mixture of CD_2Cl_2 and CF_2Br_2 at −90 °C. Here the observed ratio becomes 50:50, because the low dielectric constant of CF_2Br_2 ($\epsilon \approx 3$) has reduced the polarity of the CD_2Cl_2 solution, making the situation intermediate between that of the solutions in toluene-d_8 and in CD_2Cl_2.

An independent approach to support the structural identification of the diastereoisomers **5a** and **5b** was carried out by means of the Lanthanide Induced Shift (LIS) effect.[15] Addition of a given amount of Yb(fod)$_3$ [16] to a toluene-d_8 solution of **5** (kept at −95 °C) shifted downfield the ^{13}C methyl signal of the ethyl group markedly more in the case of the major (from 16.78 to 17.43 ppm) than in that of the minor conformer (from 17.72 to 18.15). As a consequence the separation of the two ^{13}C signals was reduced from 95 to 73 Hz (at 100.6 MHz) by the effect of Yb(fod)$_3$. Since in a derivative like **5** the paramagnetic Yb atom essentially interacts with the carbonyl group,[15,17] this effect requires that the distance of the ethyl group from the carbonyl moiety is shorter in the major than in the minor diastereoisomer. Consequently the major diastereoisomer must have the ethyl and carbonyl groups in a syn relationship, thus confirming its identification with structure **5a**. A similar result was observed in the proton spectrum where the downfield LIS displacement of the methyl triplet of the ethyl group was larger for the major than in the minor conformer. On the other hand the effect on the ^{1}H methyl signal of the MeCO moiety was found to be opposite, since in the minor diastereoisomer this line was displaced more than in the major one. The distances of the acetyl methyl group from the Yb atom are obviously the same in both cases, but the structure of **5a** (having the ethyl and the CO groups in a syn relationship) is more hindered, thus making the interaction of the Yb(fod)$_3$ with the carbonyl moiety less efficient[15,17] than in the case of **5b**. This accounts for the slightly larger LIS effect observed for the MeCO signal of the latter conformer and confirms, therefore, the structural assignment.[18]

As predicted, two conformational diastereoisomers were detected for **5 (**i.e. **5a** and **5b)** at low temperature, each of them being actually a racemic mixture of two conformational enantiomers (Scheme 2). This was ascertained by obtaining the ^{1}H spectrum of **5** at −100 °C in the presence of a 40:1 molar excess of the same R(−) Pirkle's alcohol mentioned above. Most of the lines

(13) Such a small shift difference (1.5 Hz at 300 MHz) makes the intensity of the outer lines of the AB portion of the ABX$_3$ spectrum too low to be observed, thus preventing the measurement of the geminal J_{AB} coupling constant.

(14) This results from the equation $\ln(N_1/N_2) = -\Delta G°/RT$, with $\Delta G°$ assumed to be independent of temperature.

(15) (a) von Ammon, R.; Fischer, R. D. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 675. (b) Cockerill, A. F.; Davies, G. L. O.; Harden, R. C.; Rackham, D. M. *Chem. Rev.* **1973**, *73*, 553. (c) Reuben, J. *Prog. NMR Spectrosc.* **1973**, *9*, 1. (d) Hofer, O. *Top. Stereochem.* **1976**, *9*, 111. (e) Peters, J. A. *Prog. NMR Spectrosc.* **1996**, *28*, 283.

(16) The term (fod) stays for 1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedioanate.[15b]

(17) Cipiciani, A.; Linda, P.; Macciantelli, D.; Lunazzi, L. *J. Chem. Soc., Perkin Trans. 2* **1979**, 1045.

(18) The LIS effect observed for the MeCO line indicates that in the more stable **5a** conformer the equilibrium with Yb(fod)$_3$ is shifted toward the C═O···Yb dimer less than in **5b**. Despite the consequent lower efficiency, the LIS effect experienced by the ethyl methyl signal is larger in **5a** than in **5b**, because in the diastereoisomer syn the C═O is closer to the Et group than in the diastereoisomer anti (the computed average distances between the carbonyl oxygen atom and the ethyl methyl hydrogens are 3.65 Å in **5a** and 5.52 Å in **5b**).

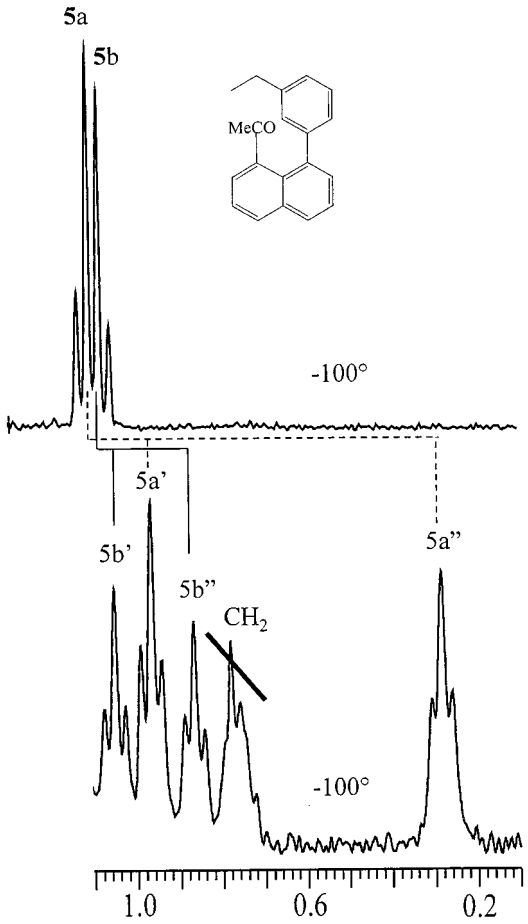


Figure 3. Top: spectrum of the methyl hydrogens of the ethyl moiety of **5** at −100 °C (300 MHz in CD_2Cl_2) showing two overlapping triplets (in a 57:43 ratio), due to the conformational diastereoisomers **5a** and **5b**. Bottom: the same spectrum at −100 °C in the presence of a 40:1 molar excess of a chiral auxiliary agent (see text), displaying four methyl triplets due to the conformational enantiomers **5a′**, **5a″, 5b′**, **5b″** (Scheme 2). In the same spectral region also appears, now, one of the four methylene quartets signals.

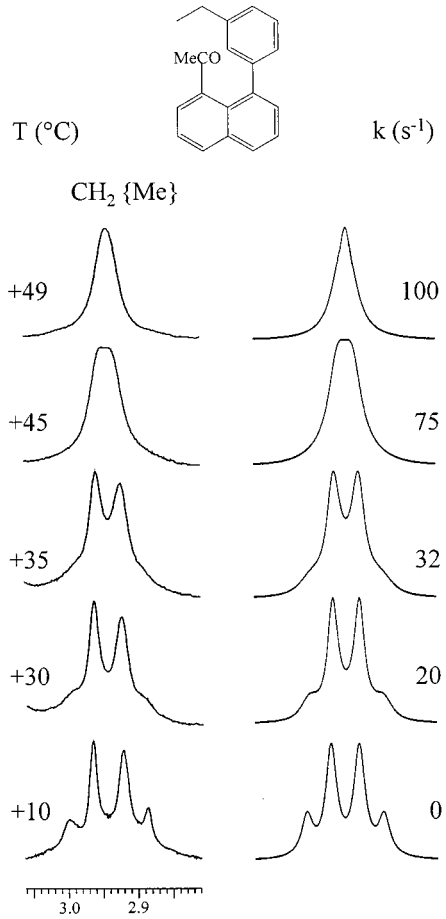
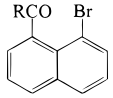


Figure 4. Left: temperature dependence of the methylene signal of **5** (decoupled at the frequency of the corresponding methyl triplet) in the presence of $Yb(fod)_3$ in toluene-d_8 at 400 MHz. Right: computer simulation obtained with the rate constants (k in s^{-1}) indicated.

displayed an additional splitting in this chiral environment: in particular both the overlapping methyl triplets of the ethyl moiety (indicated as **5a** and **5b** in Figure 3, top) were further split into two, yielding four triplets as a whole. Two of them (labeled **5a′** and **5a"**) correspond to the pair of enantiomers of conformer **5a** and have, accordingly, an intensity higher (ratio 57:43) than that of the other two (**5b′** and **5b"**), corresponding to the pair of enantiomers of **5b** (Figure 3, bottom).

The shift separation of the diastereotopic methylene hydrogens of **5**, previously observed at ambient temperature in toluene-d_8 (0.005 ppm), is indicative, as mentioned, of an aryl rotation barrier higher than that of MeCO, but is definitely too small to allow a meaningful measurement of the corresponding free energy of activation. Addition of even a small amount of $Yb(fod)_3$ allowed, however, to increase significantly this separation so that, when decoupled at the frequency of the methyl triplet, the methylene hydrogens of **5** displays an AB-type spectrum with a $J = -14$ Hz and a $\Delta\nu = 30$ Hz (at 400 MHz) as shown in Figure 4. In such a way an experimental $\Delta G^{\neq}$ value of 15.9 kcal mol^{-1} could be obtained for the enantiomerization process brought about by the aryl-naphthyl rotation (Table 1). Although quite lower than the computed value, this barrier is nonetheless higher, as theoretically predicted, than that for the exchange of the conformational diastereoisomers due to the MeCO rotation and is similar to other barriers reported for analogous situations.[3−6]

The large difference (5.5 kcal mol^{-1}) between the barrier for the MeCO and for the *m*-ethyl phenyl group rotation measured in **5** indicates that within the time required for the phenyl ring to complete a single rotation, the acetyl group makes a number of rotations exceeding 10^5. Thus, during the motion of the MeCO group, the phenyl stays essentially locked in the plane orthogonal to the naphthalene ring, so that it is perceived by the acetyl group as a flat substituent, with relatively small steric effects. Similar differences between the two rotation rates are logically expected to occur also for the other acyl substituents. This prediction can be checked by replacing, for instance, the phenyl ring of **2** with a spherical substituent, like a bromine atom, as in **6**.



R = Et, **6** ; R = Pr^i, **7**; R = Bu^t, **8**

Obviously bromine displays the same steric effects in any direction, contrary to the phenyl group whose effects,

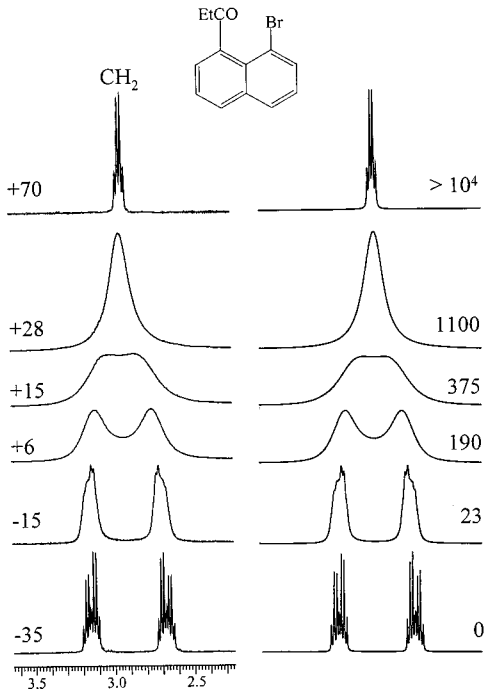


Figure 5. Left: temperature dependence of the methylene signal of **6** in CD_2Cl_2 at 400 MHz (except the trace at +70 °C, in CCl_4) showing how, on cooling, the quartet signal decoalesces into an AB-type spectrum, each line of which is also split into a quartet (ABX_3 spectrum). Right: computer simulation obtained with the rate constants (k in s^{-1}) indicated.

as mentioned, may vary significantly depending on its orientation with respect to the acyl moiety. For this reason, although the radius of bromine (1.86 ± 0.04 Å)[19] is much shorter than the average dimension (4.33 Å) of a rotating phenyl ring displaying a dynamic cylindrical symmetry (measured as distance between two *meta* hydrogen atoms), the effective radius of phenyl is actually smaller (1.62 Å)[19] than that of bromine. Accordingly, the steric hindrance experienced by the EtCO moiety in the resulting bromine derivative **6** should be larger than in **2.** As shown in Figure 5, the methylene hydrogens of **6** become indeed diastereotopic at a higher temperature, because the enantiomerization barrier, consequent to the EtCO rotation, has actually increased by about 3.1 kcal mol^{-1} with respect to **2**, reaching a value of 13.5 kcal mol^{-1} (Table 1).

Likewise the isopropyl derivative **7** and the *tert*-butyl derivative **8** yield barriers higher than those of the corresponding derivatives **3** and **4** (Table 1).[20] It is thus established that a spherical substitutent, like bromine, has a larger steric effect than the "flat" phenyl substituent and the average difference for the three pairs of examined molecules[21] is $\Delta\Delta G^{\neq} = 3.2 \pm 0.5$ kcal mol^{-1}. The very same $\Delta\Delta G^{\neq}$ difference between a bromine and a phenyl substituent had been also reported for another class of compounds.[19]

(19) Bott, G.; Field, L. D.; Sternhell, S. *J. Am. Chem. Soc.* **1980**, *102*, 5618.

(20) To observe two signals for the pair of enantiomers of **8**, the measurement had to be carried out in the presence of a chiral solvating agent (see Table 1), so that the comparison has to be made with the barrier of **4** obtained in the same conditions (i.e., 14.3 kcal mol^{-1}).

(21) The three differences are 3.1, 2.7 and 3.7 kcal mol^{-1}, respectively, for the ethyl derivatives **6** and **2**, for the isopropyl derivatives **7** and **3** and for the *tert*-butyl derivatives **8** and **4** (see Table 1).

Experimental Section

Materials. 8-Bromo-1-naphthoyl chloride was prepared as described in the literature.[22]

1-Bromo-3-ethylbenzene. To a solution of 1,3 dibromobenzene (50 mmol in 125 mL of dry THF) kept under N_2 at −78 °C was added dropwise a solution of *n*-BuLi (52 mmol, 1.6 M in hexane). After 10 min, the reaction was quenched with Et-I (75 mmol in 10 mL of dry THF), and the mixture was allowed to warm to room temperature. After addition of aqueous NH_4Cl, the product was extracted (Et_2O) and dried (Na_2SO_4), and Et_2O and THF were distilled off with an adiabatic still column (15 cm height). The crude was purified using the same column at reduced pressure (bp 80° at 13 mm): final yield 65%; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.25 (3H, t, J = 7.5 Hz), 2.65 (2H, q, J = 7.5 Hz), 7.10−7.22 (2H, m), 7.30−7.40 (2H, m); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 15.2 (CH_3), 24.4 (CH_2), 122.3 (quat), 126.4 (CH), 128.6 (CH), 129.7 (CH), 130.8 (CH), 146.4 (quat).

3-Ethylphenylboronic Acid.[23] To a solution of 1-bromo-3-ethylbenzene (15 mmol in 40 mL of dry THF) kept under N_2 at −78 ° was added dropwise a solution of *n*-BuLi (16 mmol, 1.6 M in hexane). After 10 min, the solution was added dropwise to a solution of B(O-*i*-Pr)$_3$ (30 mmol in 10 mL of dry THF) kept at −78 °C. The resulting solution was stirred for 10 min at −78 °C and then allowed to warm to room temperature. After addition of 50 mL of 1 M HCl, the product was extracted (Et_2O), dried (Na_2SO_4), and concentrated at reduced pressure. The crude was purified by crystallization (H_2O). The resulting filtrate was washed with pentane to remove traces of the starting product: final yield 84%; ^1H NMR (DMSO-d_6, 300 MHz), δ 1.18 (3H, t, J = 7.6 Hz), 2.60 (2H, q, J = 7.6 Hz), 7.20−7.26 (2H, m), 7.50−7.65 (2H, m), 7.93 (2H, broad s); ^{13}C NMR (DMSO-d_6, 75.5 MHz), δ 15.7 (CH_3), 28.2 (CH_2), 127.3 (CH), 129.4 (CH), 131.4 (CH), 133.5 (CH), 141.4 (quat).

1-(8-Bromo-1-naphthyl)-1-ethanone. To a suspension of CuI (5.5 mmol in 10 mL of dry THF) kept at −78 °C under N_2 was added dropwise a solution of MeLi (12 mmol, 1.5 M in Et_2O). The temperature was raised to −40 °C for 5 min and then lowered again to −78 °C. A solution of 8-bromo-1-naphthoyl chloride (5 mmol in 5 mL of dry THF) was subsequently added, and the resulting brown-yellow solution was stirred at −78 °C for about 1 h. The reaction was quenched at −78 °C with 10 mL of aqueous NH_4Cl. After ambient temperature was reached, the crude was extracted (Et_2O), dried (Na_2SO_4), and concentrated at reduced pressure. The resulting compound was purified on silica gel (eluent petroleum ether/Et_2O 3:1 v/v): final yield after purification 60%; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.72 (3H, s), 7.30−7.52 (3H, m), 7.80−7.91 (3H, m); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 33.9 (CH_3), 119.2 (quat), 125.5 (CH), 125.8 (CH), 126.8 (CH), 128.5 (quat), 128.6 (CH), 130.7 (CH), 132.7 (CH), 135.7 (quat), 141.3 (quat), 205.4 (CO). Anal. Calcd for $C_{12}H_9BrO$: C, 57.86; H, 3.64; Br, 32.08. Found: C, 57.92; H, 3.69; Br, 32.15.

1-(8-Bromo-1-naphthyl)-1-propanone (6). To a solution of lithium diisopropylamine (LDA), prepared by adding *n*-BuLi (1.4 mmol, 1.6M in hexane) to a solution of diisopropylamine (1.4 mmol in 4 mL of dry THF) kept at 0 °C was added dropwise at −78 °C a solution of 1-(8-bromo-1-naphthyl)-1-ethanone (1 mmol in 3 mL of dry THF). The solution was stirred at −78 °C for 1 h, and a solution of MeI (10 mmol in 2 mL of THF) was subsequently added. The system was allowed to warm to room temperature and quenched with aqueous NH_4Cl. The product was extracted (Et_2O), dried (Na_2SO_4), and concentrated at reduced pressure. The crude was purified on preparative TLC (eluent: petroleum ether/Et_2O 2:1 v/v): final yield after purification 65%; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.26 (3H, t, J = 6.9 Hz), 2.95 (2H, broad s), 7.32−7.37 (2H, m), 7.46−7.50 (1H, m), 7.81−7.90 (3H, m). ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 9.0 (CH_3), 40.3 (CH_2), 119.8 (quat), 126.3 (CH), 126.8 (CH), 127.5 (CH), 129.4 (quat), 129.5 (CH), 131.1 (CH), 133.4

(22) Bailey, R. J.; Card, P. J.; Shechter, H. *J. Am. Chem. Soc.* **1983**, *105*, 6103.

(CH), 136.5 (quat), 141.9 (quat), 208.8 (CO). Anal. Calcd for $C_{13}H_{11}BrO$: C, 59.34; H, 4.21; Br, 30.37. Found: C, 59.41; H, 4.15, Br, 30.28.

1-(8-Bromo-1-naphthyl)-2-methyl-1-propanone (7). To a solution of LDA, prepared by adding (at 0 °C) *n*-BuLi (0.7 mmol, 1.6 M in hexane) to diisopropylamine (0.7 mmol dissolved in 2 mL of dry THF) was added dropwise at −78 °C a solution of 1-(8-bromo-1-naphthyl)-1-propanone (0.5 mmol in 2 mL of THF). The system was then stirred at −78 °C for 1 h, and a solution of MeI (5 mmol in 1 mL of THF) was subsequently added. The system was allowed to warm to room temperature and quenched with aqueous NH_4Cl. The product was extracted (Et_2O), dried (Na_2SO_4), and concentrated at reduced pressure. The crude was purified on preparative TLC (eluent: petroleum ether/Et_2O 2:1 v/v): final yield after purification 52%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.23 (6H, b b s), 3.24 (1H, sept., J = 6.9 Hz), 7.30−7.38 (2H, m), 7.44−7.52 (1H, m), 7.80−7.91 (3H, m). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 19.9 (CH_3, b s), 44.2 (CH), 119.3 (quat), 125.4 (CH), 126.7 (CH), 127.4 (CH), 128.7 (CH), 129.0 (quat), 130.6 (CH), 132.5 (CH), 135.7 (quat), 139.6 (quat), 212.3 (CO). Anal. Calcd for $C_{14}H_{13}$-BrO: C, 60.67; H, 4.73; Br, 28.83. Found: C, 60.71; H, 4.66, Br, 28.75.

1-(8-Bromo-1-naphthyl)-2,2-dimethyl-1-propanone (8). To a suspension of CuCN (4.5 mmol in 10 mL of dry THF) kept at −78 °C under N_2 was added dropwise a solution of *t*-BuLi (9 mmol, 1.5 M in pentane). The temperature was raised to −40 °C for 5 min and then lowered again to −78 °C. A solution of 8-bromo-1-naphthoyl chloride (4 mmol in 5 mL of dry THF) was subsequently added, and the resulting brown-yellow solution was stirred at −78 °C for about 1 h. The reaction was quenched at −78 °C by adding 10 mL of aqueous NH_4Cl. The mixture was then allowed to warm to room temperature, and the crude was extracted (Et_2O), dried (Na_2SO_4), and concentrated at reduced pressure. The product was purified on silica gel (eluent: petroleum ether/Et_2O 1:1 v/v): final yield after purification 64%; ^{1}H NMR ($CDCl_3$, 200 MHz), δ 1.30 (9H, s), 7.22−7.31 (3H, m), 7.38−7.48 (1H, m), 7.72−7.85 (3H, m); ^{13}C NMR ($CDCl_3$, 50.3 MHz), δ 28.0 (CH_3,), 46.4 (quat), 118.9 (quat), 125.0 (CH), 125.8 (CH), 126.4 (CH), 128.7 (CH), 129.1 (quat), 129.8 (CH), 132.3 (CH), 135.2 (quat), 139.2 (quat), 216.0 (CO). Anal. Calcd for $C_{14}H_{13}BrO$: C, 60.67; H, 4.73; Br, 28.83. Found: C, 60.71; H, 4.66, Br, 28.75.

Compounds **1**−**4** were prepared according to the following general procedure.[24] To a solution of 1-(8-bromo-1-naphthyl)-1-ethanone (0.5 mmol in 3 mL of benzene) were added K_2CO_3 (1 mmol, 2 M solution in H_2O), phenylboronic acid (0.6 mmol in 1 mL of ethanol), and $Pd(PPh_3)_4$ (0.05 mmol) at room temperature. The mixture was gently refluxed for 2−4 h until the starting bromo ketone disappeared (TLC). The reflux was then stopped and the product extracted (Et_2O), dried (Na_2SO_4), and concentrated to reduced pressure. The crude was purified on preparative TLC (eluent: petroleum ether/Et_2O 4:1 v/v). Final yields were 60% for **1**, 45% for **2**, 50% for **3**, and 30% for **4**. Compound **5** was obtained with the same procedure, using 3-ethyl-phenylboronic acid instead of phenylboronic acid.

1-(8-Phenyl-1-naphthyl)-1-ethanone (1): ^{1}H NMR (CD_2-Cl_2, 300 MHz) δ 1.91 (3H, s), 7.34−7.63 (9H, m), 7.89−8.01 (2H, m). ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 31.0 (CH_3), 125.6 (CH), 125.6 (CH), 126.8 (CH), 127.4 (CH), 128.2 (CH), 128.9 (CH), 129.1 (quat), 129.3 (CH), 130.5 (CH), 130.9 (CH), 132.0 (CH), 135.7 (quat), 140.4 (quat), 142.0 (quat), 143.8 (quat), 204.1 (CO). Anal. Calcd for $C_{18}H_{14}O$: C, 87.77; H, 5.73. Found: C, 87.86; H, 5.67.

1-(8-Phenyl-1-naphthyl)-1-propanone (2): ^{1}H NMR (CD_2Cl_2, 300 MHz) δ 0.51 (3H, t, J = 7.1 Hz),2.39 (2H, q, J = 7.1 Hz), 7.30−7.60 (8H, m), 7.88−8.00 (3H, m). ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 8.1 (CH_3), 37.6 (CH_2), 125.7 (CH), 126.7 (CH), 127.3 (CH), 128.1 (CH), 128.9 (quat), 129.0 (CH), 129.3 (CH), 130.6 (CH), 131.1 (CH), 131.7 (CH), 134.9 (quat), 139.5 (quat) 140.8 (quat), 143.5 (quat), 207.7 (CO). Anal. Calcd for $C_{19}H_{16}O$: C, 87.66; H, 6.19. Found: C, 87.74; H, 6.23.

2-Methyl-1-(8-phenyl-1-naphthyl)-1-propanone (3): ^{1}H NMR (CD_2Cl_2, 300 MHz) δ 0.40 (6H, d, J = 6.8 Hz), 2.64 (1H, septet, J = 6.8 Hz), 7.32−7.40 (6H, m), 7.45−7.61 (3H, m),7.88−8.00 (3H, m); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 18.9 (CH_3), 42.7 (CH_2), 125.8 (CH), 126.7 (CH), 128.1 (quat), 128.3 (CH), 128.9 (CH), 129.1 (CH), 129.4 (CH), 131.28 (CH), 131.35 (CH), 131.8 (CH), 135.1 (quat), 139.4 (quat), 139.5 (quat), 142.0 (quat), 213.3 (CO). Anal. Calcd for $C_{20}H_{18}O$: C, 87.56; H, 6.61. Found: C, 87.53; H, 6.67.

2,2-Dimethyl-1-(8-phenyl-1-naphthyl)-1-propanone (4): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.72 (9H, s), 7.23(1H, dd, J = 7.0, 1.4 Hz), 7.30−7.55 (8H, m), 7.88 (1H, dd, J = 8.2, 1.3 Hz), 7.95 (1H, dd, J = 8.2, 1.3 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 27.3 (CH_3), 45.4 (quat), 124.4 (CH), 125.6 (CH), 125.9 (CH), 127.5 (CH), 127.9 (CH), 128.1 (quat), 128.2 (CH), 130.1 (CH), 130.7 (CH), 134.3 (quat), 139.6 (quat), 140.0 (quat), 140.6 (quat), 215.2 (CO). Note: the signal of a CH is extremely broad, its chemical shift can be calculated as 132.5 ppm by the spectrum at −40 °C. Anal. Calcd for $C_{21}H_{20}O$: C, 87.46; H, 6.99. Found: C, 87.50; H, 6.95.

1-[8-(3-Ethylphenyl)-1-naphthyl]-1-propanone (5): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.25 (3H, t, J = 7.7 Hz), 1.82 (3H, s) 2.66 (2H, q, J = 7.7 Hz), 7.15−7.37 (4H, m), 7.43−7.60 (4H, m), 7.85−7.96 (2H, m); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 15.2 (CH_3), 28.8 (CH_2), 30.5 (CH_3), 124.8 (CH), 126.0 (CH), 126.7 (CH), 127.0 (CH), 127.1 (CH), 128.1 (CH), 128.2 (quat), 128.7 (CH), 129.6 (CH), 130.0 (CH), 131.3 (CH), 134.8 (quat), 139.7 (quat), 141.2 (quat), 142.5 (quat), 144.2 (quat), 207.7 (CO). Anal. Calcd for $C_{20}H_{18}O$: C, 87.56; H, 6.61. Found: C, 87.54; H, 6.56.

NMR Measurements. The NMR spectra were obtained with either a 300 MHz or a 400 MHz spectrometer. All the ^{13}C signals were identified by DEPT sequence. The temperatures within the probes of the two instruments were calibrated by substituting the samples with a Ni/Cu thermocouple before the experiments. In the spectra obtained in the presence of chiral solvating agents, the shift separation ($\Delta\nu$) is temperature dependent. By means of an empirical equation this separation was related to the temperature in the range where the rotation rate is undoubtedly negligible. The $\Delta\nu$ values were subsequently extrapolated in the temperature range where a significant exchange rate occurred, allowing one to obtain reliable line shape simulations (use was made of PC version of the DNMR 6 Program[25]). To observe sufficiently separate ^{1}H NMR signals for the enantiomers, a very large molar excess (up to 300:1) of the chiral solvating agent (CSA) was needed. Thus in these experiments the concentration of the substrate had to be quite small (typically 10^{-3} M) in order to have, in any case, a concentration of CSA lower than the saturation point. Otherwise the DNMR spectra were acquired using a 10^{-2} M solution for ^{1}H and 10^{-1} for ^{13}C NMR, respectively.

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(23) Thompson, W. J.; Gaudino, J. *J. Org. Chem.* **1984**, *49*, 5237.
(24) Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513.
(25) QCPE program no. 633, Indiana University, Bloomington, IN.