

# Conformational Studies by Dynamic NMR. 65.<sup>1</sup> Interconversion of Stereolabile Meso and Racemic Diastereoisomers of Hindered 1,4-Diaclynaphthalenes

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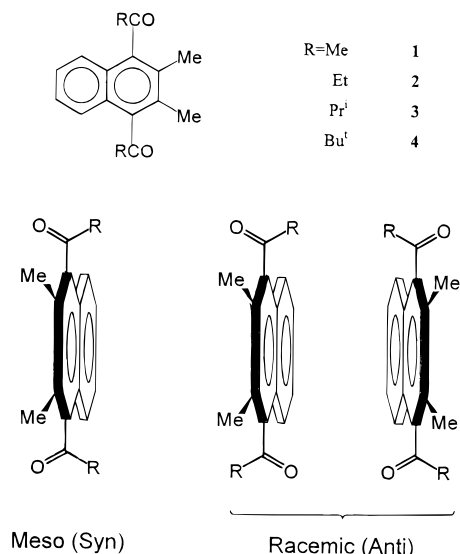
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1,4-Diaclynaphthalenes, bearing methyl groups in positions 2 and 3, display, at appropriate temperatures, NMR spectra due to meso and racemic stereolabile diastereoisomers, brought about by the restricted rotation of the two RCO substituents. As indicated by the diastereotopicity of appropriate prochiral substituents, these acyl groups are not coplanar to the naphthalene ring, and their C=O moieties can adopt either a syn or an anti arrangement. The meso (syn) and racemic (anti) structures were assigned, in solution, by taking into account the changes of their relative proportions in solvents of different polarity and, in the solid state, by X-ray diffraction. The free energies of activation for the interconversion were determined by computer line-shape simulation of the variable-temperature NMR spectra, and their values were found to increase substantially with the increasing bulkiness of the carbonyl-bonded alkyl groups (from 10.2 to 22.1 kcal mol<sup>-1</sup> for R = Me and R = *t*-Bu, respectively).

## Introduction

Hindered alkyl aryl ketones adopt nonplanar conformations<sup>3–6</sup> that can give rise to stereolabile enantiomers if the substituents are in such a position as to deprive the molecules of planes or center of symmetry.<sup>7</sup> 1-acyl-2-methylnaphthalenes<sup>8</sup> provided examples of such a situation. Naphthalenes bearing two equal acyl substituents in positions 1 and 4, as well as two methyl groups in positions 2 and 3, possess two identical chirality axes, and as a consequence, two stereolabile meso and racemic diastereoisomers (or conformers) are expected to be observed at temperatures where the Ar–CO rotation rate is rendered sufficiently slow. When the two carbonyl moieties are in a syn relationship, in fact, a molecular plane of symmetry is still maintained and a meso conformer is expected to occur, whereas a racemic conformer would result when the two carbonyl moieties are in an anti relationship (Chart 1). This situation is opposite to that encountered in the isomeric 1,5-diacyl-2,6-dimethylnaphthalenes,<sup>8</sup> where the anti relationship generates a meso and the syn a racemic conformer.

Chart 1



(1) Part 64: Casarini, D.; Lunazzi, L.; Mazzanti, A.; Foresti, E. *J. Org. Chem.* **1998**, *63*, 4746.

(2) In partial fulfillment of the Ph. D. requirements in Chemical Sciences, University of Bologna.

(3) (a) Abraham, R. J.; Angiolini, S.; Edgar, M.; Sancassan, F. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1973. (b) Abraham, R. J.; Angiolini, S.; Edgar, M.; Sancassan, F. *J. Chem. Soc., Perkin Trans. 2* **1997**, 41 and references quoted therein.

(4) Casarini, D.; Lunazzi, L.; Verbeeck, R. *Tetrahedron* **1996**, *52*, 2471.

(5) Casarini, D.; Lunazzi, L. *J. Org. Chem.* **1996**, *61*, 6240.

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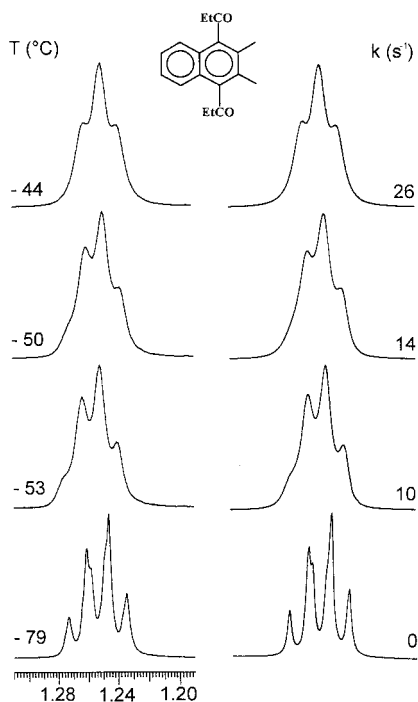
(7) Gasparrini, F.; Lunazzi, L.; Misiti, D.; Villani, C. *Acc. Chem. Res.* **1995**, *28*, 163.

(8) (a) Casarini, D.; Lunazzi, L.; Sgarabotto, P. *J. Crystallogr. Spectrosc. Res.* **1991**, *21*, 445. (b) Casarini, D.; Lunazzi, L.; Pasquali, F.; Gasparrini, F.; Villani, C. *J. Am. Chem. Soc.* **1992**, *114*, 6521.

Investigation of derivatives **1–4** of Chart 1 was thus undertaken in order to verify this prediction and to determine the values of the barriers involved in the interconversion process.

## Results and Discussion

The <sup>1</sup>H NMR spectra of **1–3** display signals that broaden on lowering the temperature and eventually split into two groups of lines with unequal relative intensity, due to the presence of two different species. The corresponding shift separations, being quite small, are difficult



**Figure 1.** Temperature dependence (left) of the  $^1\text{H}$  methyl triplets of the ethyl group of **2** ( $\text{R} = \text{Et}$ ) at 600 MHz in  $\text{CHF}_2\text{Cl}$ . On the right is reported the computer simulation obtained with the rate constants ( $k$ ,  $\text{s}^{-1}$ ) indicated.

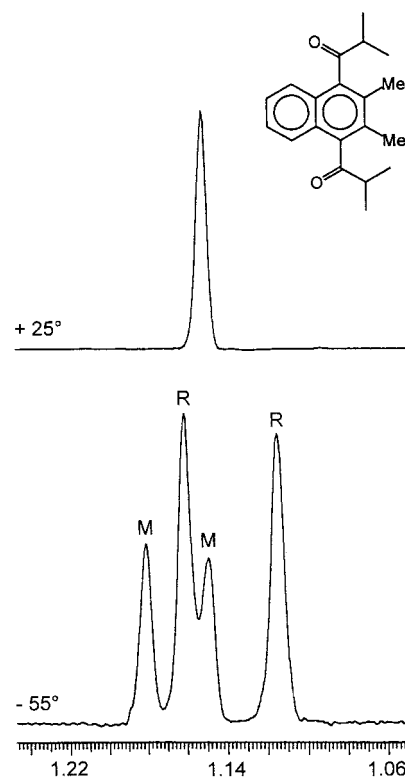
to be detected: for instance, in the case of **2** ( $\text{R} = \text{Et}$ ), a 600 MHz spectrometer was needed to clearly resolve the two methyl triplets due to the ethyl groups (Figure 1).

Compounds **2** ( $\text{R} = \text{Et}$ ) and **3** ( $\text{R} = i\text{-Pr}$ ) display, in addition, anisochronous signals for the diastereotopic methylene hydrogens (below  $-80^\circ\text{C}$ ) and for the diastereotopic isopropyl methyl groups (below  $-50^\circ\text{C}$ ), respectively, as shown, for the latter case, in Figure 2. This observation clearly indicates that the RCO substituents are not coplanar with the naphthalene ring in both the meso and the racemic forms. This is because the local plane bisecting the  $\text{CH}_2$  or the  $\text{Me}_2\text{CH}$  moieties is not coincident with the molecular plane of symmetry in the meso form or, of course, in the racemic form, as the latter does not possess any plane of symmetry.<sup>9</sup>

In derivative **4** ( $\text{R} = t\text{-Bu}$ ) even at ambient temperature it is possible to identify two sets of lines that broaden and coalesce only above  $100^\circ\text{C}$ ; in this case, therefore, the two species should be considered diastereoisomers (albeit quite labile) rather than conformers, although in such borderline cases the problem of the nomenclature is quite subjective.

Line-shape simulation of the spectra of **1–4** as function of temperature provided the rate constants, hence the free energies of activation ( $\Delta G^\ddagger$ ), for the interconversion of the more into the less stable form (Table 1).

Molecular mechanics calculations<sup>10</sup> suggested that in all the cases investigated here the racemic should be slightly more stable than the meso form, as shown in Figure 3 for compound **4** ( $\text{R} = t\text{-Bu}$ ). The latter derivative, however, displayed spectra where the relative proportion of the two stereolabile diastereoisomers ap-



**Figure 2.**  $^1\text{H}$  spectrum (300 MHz in  $\text{CD}_2\text{Cl}_2$ ) of the isopropyl methyl group of **3** ( $\text{R} = i\text{-Pr}$ ) at  $25^\circ\text{C}$  (top), decoupled at the frequency of the corresponding CH multiplet. Underneath is reported the decoupled spectrum obtained at  $-55^\circ\text{C}$ , showing two pairs of lines (36:64 intensity ratio) for the meso (M) and racemic (R) conformers, respectively. The restricted Ar-CO rotation generates two nonplanar conformers, each displaying diastereotopic isopropyl methyl groups.

**Table 1.** Interconversion Barriers ( $\Delta G^\ddagger$ ,  $\text{kcal mol}^{-1}$ ),<sup>a</sup> Conformer Ratio, and Shift Difference ( $\Delta\nu$  in Hz, 300 MHz) of the Monitored Groups of **1–4** at the Detection Temperature ( $^\circ\text{C}$ )

compd	$\Delta G^\ddagger$	solvent	racemic/ meso	monitored group	$\Delta\nu$ ( $T$ , $^\circ\text{C}$ )
<b>1</b> , $\text{R} = \text{Me}$	10.2	$\text{CHF}_2\text{Cl}$	60/40	$\text{CH}_3\text{-CO}$	6.1 ( $-120$ )
<b>2</b> , $\text{R} = \text{Et}$	11.5	$\text{CHF}_2\text{Cl}$	62/38	$\text{CH}_3\text{-CH}_2$	8.9 <sup>b</sup> ( $-80$ )
<b>3</b> , $\text{R} = \text{Pr}^i$	13.4	$\text{CD}_2\text{Cl}_2$	64/36	$(\text{CH}_3)_2\text{CH}$	9.4 ( $-55$ )
<b>4</b> , $\text{R} = \text{Bu}^t$	22.1	DMSO	46/54	$(\text{CH}_3)_3\text{C}$	2.8 (22)

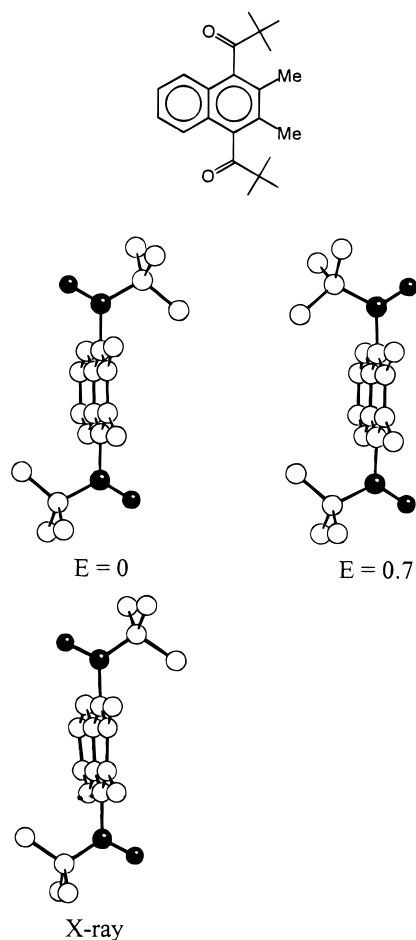
<sup>a</sup> These values correspond to the interconversion of the more into the less stable species. <sup>b</sup> At 600 MHz.

peared to be reversed in solvents of different polarity (Table 2). Of the two  $^1\text{H}$  lines observed for each pair of equivalent methyl groups in positions 2 and 3, the one at higher field is *more* intense in highly polar solvents but *less* intense in solvents with a low polarity.

It is, of course, a prerequisite to exclude unambiguously that the inversion of the intensity ratio is not the consequence of an interchange between the two very similar shifts, due to the use of different solvents. Thus, a crystal of **4** was dissolved in  $\text{CD}_2\text{Cl}_2$  at  $-50^\circ\text{C}$  and the spectrum recorded at  $-20^\circ\text{C}$ , having always kept the sample cooled below this temperature. Since in the solid state only one of two possible diastereoisomers is usually present, the naphthyl-bonded methyl groups displayed, now, a *single* signal (2.27 ppm), corresponding to only one of the two possible diastereoisomers. The  $\Delta G^\ddagger$  value measured for their interconversion (22.1  $\text{kcal mol}^{-1}$ , as in Table 1) predicts in fact that the half-life time of the

(9) (a) Mislow, K.; Raban, M. *Top. Stereochem.* **1967**, *1*, 1. (b) Jennings, W. B. *Chem. Rev.* **1975**, *75*, 307.

(10) MMX force field as implemented in the program PC Model, Serena Software, Bloomington, IN.



**Figure 3.** Top: Molecular mechanics (MMX) structures for the racemic (left) and meso (right) diastereoisomers of **4** ( $R = t\text{-Bu}$ ). The computed relative energies ( $E$ ) are given in kcal mol<sup>-1</sup>. Bottom: experimental (X-ray) structure of the diastereoisomer of **4** obtained by ambient temperature crystallization (see text).

**Table 2.** Ambient-Temperature Ratio of the Racemic and Meso Diastereoisomers of **4** ( $R = t\text{-Bu}$ ) in Solvents of Low and High Dielectric Constant ( $\epsilon$ )

solvent	polarity ( $\epsilon$ )	racemic/meso
CS <sub>2</sub>	low (2.3)	57/43
CDCl <sub>3</sub>	low (4.8)	57/43
CD <sub>2</sub> Cl <sub>2</sub>	low (8.9)	62/38
acetone- <i>d</i> <sub>6</sub>	high (25.0)	40/60
CD <sub>3</sub> OD	high (32.6)	43/57
DMSO- <i>d</i> <sub>6</sub>	high (46.5)	46/54

diastereoisomers of **4** at  $-20\text{ }^\circ\text{C}$  should be extremely long (approximately 16 days).

When the sample was allowed to reach ambient temperature inside the spectrometer, the line of the second diastereoisomer began to appear at *higher* field (2.26 ppm), eventually reaching the proportion (38%) expected for the equilibrium in CD<sub>2</sub>Cl<sub>2</sub>.<sup>11</sup>

The same experiment was repeated using CD<sub>3</sub>OD, where again a single line (2.31 ppm) for the same methyl groups was observed at  $-20\text{ }^\circ\text{C}$ . In this case, the second line, which also began to appear at higher field (2.295 ppm)<sup>11</sup> on warming the sample, became the more intense

one (57%) when the ambient temperature equilibrium was attained (see Table 2).

Changing the solvent polarity does not modify, therefore, the relative shifts of these lines, so that the reversal in the intensity ratio must be a consequence of a reversed stability of the meso and racemic diastereoisomers. Likewise, in **3**, the ratio of the signals at the equilibrium ( $-55\text{ }^\circ\text{C}$ ) is reversed in CD<sub>3</sub>OD with respect to CD<sub>2</sub>Cl<sub>2</sub>.

The dipole moment of the racemic (anti) form is expected to be much smaller than that of the meso (syn) form: for instance, the MM-computed values for **4** are 1.1 and 4.9 D, respectively, and the corresponding values for **3** are 1.0 and 4.7 D. It is thus conceivable to assign (Table 2) the meso structure to the conformers that are more stable in polar solvents and the racemic to those that are more stable in solvents of low polarity (accordingly, in the not too polar CHF<sub>2</sub>Cl the racemic forms of **1** and **2** should yield the more intense signals in the spectra taken below  $-90\text{ }^\circ\text{C}$ ).

It also has to be mentioned that in the experiment where the crystals of **4** were dissolved at low temperature, the spectrum of the same single form (racemic) was observed either when **4** had been previously crystallized from highly polar (CH<sub>3</sub>OH) or from less polar (CH<sub>2</sub>Cl<sub>2</sub>) solutions. As a consequence, only the racemic diastereoisomer of **4** could be isolated with this method, whereas the meso was not obtained as a solid, even when employing solutions where its form was predominant. Apparently, the growth of these crystals at room temperature is controlled by the molecular shape rather than by the relative stability.

To isolate also the meso diastereoisomer, a preparative thick-layer chromatography at  $-20\text{ }^\circ\text{C}$  (CH<sub>2</sub>Cl<sub>2</sub> as eluent) had to be used. Under these conditions, it was found that the more retained compound was, as conceivable, the polar meso diastereoisomer. In fact, when dissolved and kept in CD<sub>2</sub>Cl<sub>2</sub> at  $-20\text{ }^\circ\text{C}$ , the latter displayed an NMR spectrum where the *single* signal of the aryl-bonded methyl groups appeared, now, at a field (2.26 ppm) *higher* than that of its less retained (racemic) partner. When this solution was subsequently allowed to reach ambient temperature, the spectrum of the second (racemic) diastereoisomer appeared at *lower* field (2.27 ppm),<sup>11</sup> eventually attaining the expected proportion (62%, as in Table 2) at the equilibrium. When left at ambient temperature, the crystalline meso diastereoisomer of **4** transformed completely into the racemic diastereoisomer (as checked by the mentioned technique of taking spectra of solutions constantly kept below  $-20\text{ }^\circ\text{C}$ ), the interconversion process requiring a few weeks to be completed in the solid state. Whereas in solution both the meso and racemic forms of **4** are present at the equilibrium, in the crystalline state the equilibrium is completely shifted toward the racemic diastereoisomer.

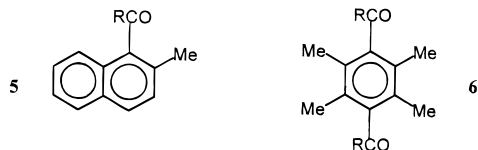
To unambiguously confirm the structure of the more stable crystalline form of **4**, a X-ray diffraction determination was performed. As shown in Figure 3, the structure is indeed racemic, with the two CO-*t*-Bu substituents (anti to each other) twisted by  $90.5^\circ$  with respect to the naphthalene plane. The 2-fold symmetry axis of the molecule coincides with the crystallographic *z*-axis of the *Ab*a2 space group (see Experimental Section).

The barriers ( $\Delta G^\ddagger$ ) that interconvert the meso and racemic stereolabile diastereoisomers (conformers) increase, as expected, with the increasing bulkiness of the carbonyl-bonded alkyl groups (Table 1). These values are

(11) Since the two lines are extremely close to each other, it is only the observation of the growth of the second diastereoisomer that guarantees the correctness of the shift assignment.

constantly 2 kcal mol<sup>-1</sup> higher than those reported for the corresponding 1-acyl-2-methylnaphthalene derivatives, **5**.<sup>8b</sup>

This is a manifestation of the so-called buttressing effect:<sup>12</sup> two vicinal methyl groups hinder the Ar-CO rotation more than a single methyl, owing to their mutual repulsion.



This interpretation is confirmed by the fact that the barriers in **1–4** are essentially equal to those measured for the corresponding 1,4-diacetyldurenes **6**, which are known to experience a buttressing effect.<sup>5</sup>

Contrary to the case of the more symmetric acyldurene **6**, in derivatives **1–4** two possible pathways are available to the Ar-COR rotation, i.e., the passage of the R group either upon H-8 or upon Me-2. MM calculations seem to favor the passage of the R group upon H-8,<sup>13</sup> whereas PM-3 computations indicate as more facile the passage upon Me-2.<sup>14</sup> However, the computed activation energy differences between the two situations are indeed too small<sup>13,14</sup> to allow a reliable conclusion to be reached.

### Conclusions

Meso and racemic conformers, due to the presence of stereolabile chirality axes, have been directly observed for the title compounds, the corresponding interconversion barriers increasing with the dimension of the carbonyl-bonded alkyl groups. Structural assignment has been achieved by monitoring the dependence of the conformer ratio at the equilibrium upon the solvent polarity. In the case of the bulky *tert*-butyl derivative **4**, both stereoisomers have been isolated at low temperature, and on the basis of a X-ray structure determination, it has been possible to transfer the solid-state assignment to solution NMR signals in nonequilibrium conditions.

### Experimental Section

**Materials.** 1,4-Dibromo-2,3-dimethylnaphthalene was prepared according to literature:<sup>15</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.65 (s, 6H, Me), 7.54 (m, 2H, Ar), 8.28 (m, 2H, Ar). Derivatives **1–3** were prepared using the same procedure. As an example, the synthesis of **1** is reported in detail:

**1-(4-Bromo-2,3-dimethyl-1-naphthyl)-1-ethanol.** To a solution of 1,4-dibromo-2,3-dimethylnaphthalene (3.12 g, 10 mmol) in dry THF (100 mL) kept at -40 °C under nitrogen was added a solution of 1.6 M *n*-BuLi (6.3 mL, 10 mmol) dropwise. After a few minutes, the mixture was treated with an excess of acetaldehyde, the temperature was raised to 20 °C, and after 30 min, the reaction was quenched with a saturated aqueous solution of NH<sub>4</sub>Cl. The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent removed in vacuo. The crude

product was purified on silica gel (eluent: petroleum ether/Et<sub>2</sub>O 1:1) to yield 2.18 g (78%): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.67 (d, 3H, Me), 2.12 (bs, 1H, OH), 2.45 (s, 3H, Me), 2.60 (s, 3H, Me), 5.75 (q, 1H, CH), 7.45 (m, 2H, Ar), 8.34 (m, 1H, Ar), 8.55 (m, 1H, Ar).

**1-[4-(1-Hydroxyethyl)-2,3-dimethyl-1-naphthyl]-1-ethanol.** To a solution of 1-(4-bromo-2,3-dimethyl-1-naphthyl)-1-ethanol (1.39 g, 5 mmol) in dry THF (50 mL) kept at -40 °C under nitrogen was added a solution of 1.6 M *n*-BuLi (6.3 mL, 10 mmol) dropwise. After some minutes, the mixture was treated with an excess of acetaldehyde, the temperature was raised to 20 °C, and after 30 min, the reaction was quenched with a saturated aqueous solution of NH<sub>4</sub>Cl. The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent removed in vacuo. The crude product was purified on silica gel (eluent: petroleum ether/Et<sub>2</sub>O 1:1) to yield 0.8 g (65%): <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 1.65 (d, 6H, Me), 2.50 (s, 6H, Me), 5.87 (m, 2H, CH), 7.23 (m, 2H, Ar), 8.60 (m, 2H, Ar).

**1,4-Diacetyl-2,3-dimethylnaphthalene (1).** A solution of 1-[4-(1-hydroxyethyl)-2,3-dimethyl-1-naphthyl]-1-ethanol (0.73 g, 3 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was added to a stirred solution of pyridinium chlorochromate (1.50 g, 7 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (15 mL) with constant stirring at room temperature. After 15 min, the solid was filtered off and the solvent removed. TLC chromatography (eluent: Et<sub>2</sub>O/petroleum ether 2:1) gave 0.35 g (48%) of **1**: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.24 (s, 6H, CH<sub>3</sub>), 2.54 (s, 6H, CH<sub>3</sub>), 7.35–7.60 (m, 4H, Ar); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 16.75 (Me), 33.06 (Me), 124.18 (CH), 126.37 (CH), 127.17 (quat), 129.32 (quat), 139.71 (quat), 208.05 (quat). Anal. Calcd for C<sub>16</sub>H<sub>16</sub>O<sub>2</sub>: C, 79.97; H, 6.71. Found: C, 79.93; H, 6.77.

**1,4-Dipropionyl-2,3-dimethylnaphthalene (2):** <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.25 (t, 6H, CH<sub>3</sub>), 2.25 (s, 6H, CH<sub>3</sub>), 2.85 (q, 4H, CH<sub>2</sub>), 7.38–7.43 (m, 4H, Ar); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 7.59 (Me), 16.93 (Me), 38.86 (CH<sub>2</sub>), 124.29 (CH), 126.30 (CH), 127.64 (quat), 129.62 (quat), 139.72 (quat), 211.05 (quat). Anal. Calcd for C<sub>18</sub>H<sub>20</sub>O<sub>2</sub>: C, 80.56; H, 7.51. Found: C, 80.59; H, 7.55.

**1,4-Diisobutyryl-2,3-dimethylnaphthalene (3):** <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>) δ 1.22 (d, 12H, Me), 2.28 (s, 6H, Me), 3.10 (sept, 2H, CH), 7.40–7.50 (m, 4H, Ar); <sup>13</sup>C NMR (CD<sub>2</sub>Cl<sub>2</sub>) δ 18.28 (Me), 18.53 (Me), 44.01 (CH), 125.63 (CH), 128.99 (quat), 131.60 (quat), 140.04 (quat), 214.36 (quat). Anal. Calcd for C<sub>20</sub>H<sub>24</sub>O<sub>2</sub>: C, 81.04; H, 8.16. Found: C, 81.07; H, 8.12.

**1,4-Bis(2,2-dimethylpropanoyl)-2,3-dimethylnaphthalene (4).** To a solution of 1,4-dibromo-2,3-dimethylnaphthalene (3.12 g, 10 mmol) in dry THF (100 mL) kept at -40 °C under nitrogen was added a solution of 1.6 M *n*-BuLi (6.3 mL, 10 mmol) dropwise. After a few minutes, the mixture was treated with 2,2-dimethylpropanoyl chloride (0.92 g, 10 mmol) in THF (5 mL). The temperature was raised to room temperature and, after 30 min, lowered again to -78 °C. A second portion of 1.6 M *n*-BuLi (6.3 mL, 10 mmol) was subsequently added, and the mixture was treated with pivaloyl chloride (0.92 g, 10 mmol) in THF (5 mL). After 30 min, the system was allowed to reach ambient temperature and the reaction quenched with a saturated aqueous solution of NH<sub>4</sub>Cl. The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent removed in vacuo. The crude product was purified on silica gel (eluent: petroleum ether/Et<sub>2</sub>O 10:1) to yield 1.7 g (64%) of **4**: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.26 (s, 18H, CH<sub>3</sub>), 2.27 (s, 6H, CH<sub>3</sub> minor isomer), 2.28 (s, 6H, CH<sub>3</sub>, major isomer), 7.37–7.50 (m, 4H, Ar); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 18.36 (CH<sub>3</sub>, minor isomer), 18.59 (CH<sub>3</sub>, major isomer), 27.87 (CH<sub>3</sub>, minor isomer), 28.03 (CH<sub>3</sub>, major isomer), 45.58 (quat), 125.30 (CH, minor isomer), 125.63 (CH major isomer), 127.81 (quat, minor isomer), 127.94 (quat, major isomer), 129.66 (quat), 138.46 (quat, minor isomer), 138.78 (quat, major isomer), 217.53 (quat, minor isomer), 218.72 (quat, major isomer). Anal. Calcd for C<sub>22</sub>H<sub>28</sub>O<sub>2</sub>: C, 81.44; H, 8.70. Found: C, 81.49; H, 8.66.

**NMR Measurements.** The variable-temperature <sup>1</sup>H NMR spectra were recorded at 300 MHz; those of **2** were also obtained at 600 MHz, for which we thank the Highfield NMR Laboratory of the University of Florence, Italy, and Mr. M. Lucci for assistance. The computer simulation of the line

(12) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; J. Wiley and Sons: New York, 1994; pp 704 and 1144.

(13) For instance, in the case of **1** (R = Me), the computed<sup>10</sup> barriers are 13.2 and 14.5 kcal mol<sup>-1</sup> for the passage of the methyl group upon H-8 and Me-2, respectively.

(14) For instance, in the case of **1** (R = Me), the computed barriers are 9.1 and 8.6 kcal mol<sup>-1</sup> for the passage of the methyl group upon H-8 and Me-2, respectively. (PM3 program, as implemented in the package MOPAC7. See also: Stewart, J. P. P. *J. Comput. Chem.* **1989**, *10*, 221.)

shape was performed by a computer program<sup>16</sup> based on DNMR6 routines (QCPE), and the best fit was visually judged by superimposing the plotted and experimental traces. The free energies of activation were calculated assuming a coefficient transmission of 1/2 because both the carbonyl groups have the same probability to exchange;<sup>6</sup> the use of a unitary coefficient would have given  $\Delta G^\ddagger$  values 0.3–0.4 kcal mol<sup>-1</sup> higher than those reported in Table 1. Within the errors, the  $\Delta G^\ddagger$  values were found to be independent of the temperature, thus suggesting negligible  $\Delta S^\ddagger$  values, as is often observed in conformational processes. The samples for measurements below -90 °C were prepared by connecting the NMR tubes, containing the desired compound as well as a small amount of CD<sub>2</sub>Cl<sub>2</sub> for locking purposes, to a vacuum line and condensing the gaseous CHF<sub>2</sub>Cl with liquid nitrogen. The tubes were then sealed in vacuo and introduced in the precooled probe of the spectrometer. The temperatures were calibrated by means of a precision thermocouple inserted into the probe of the spectrometers before or after the spectral determination.

**X-ray Diffraction.** Crystal data for **4**:  $M = 324.44$ , orthorhombic, space group  $ABa2$ ,  $a = 12.189(2)$  Å,  $b = 12.267(2)$  Å,  $c = 12.748(3)$  Å,  $U = 1906.1(8)$  Å<sup>3</sup>,  $Z = 4$ ,  $D_c = 1.13$  Mg/m<sup>3</sup>,  $F_{(000)} = 704$ ,  $T = 293$  K,  $\mu(\text{Mo-K}\alpha) = 0.070$  mm<sup>-1</sup>. Data were collected on a three-circle diffractometer fitted with a CCD-type area detector and using graphite-monochromated

Mo-K $\alpha$  X-radiation ( $\lambda = 0.71073$  Å) range  $2.85^\circ < \theta < 28.68^\circ$ . Of 2126 independent reflections  $R(\text{int}) = 0.0255$ , 1345 having  $I > 2\sigma(I)$  were considered observed. The structure was solved by direct methods and refined by full-matrix least-squares on  $F^2$ , using the SHELX program packages.<sup>17</sup> Weights were used in according to the equation  $w = 1/[\sigma^2(F_o^2) + (0.1196P)^2]$ , where  $P = (F_o^2 + 2F_c^2)/3$ . The hydrogen atoms were located by geometrical calculations and refined using a "riding" method. The final agreement indices were  $R = 0.0585$ ,  $wR = 0.1611$ , and the goodness of fit on  $F^2 = 0.942$ . Largest difference peak and hole was 0.385 and -0.218 e Å<sup>-3</sup>.

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**Supporting Information Available:** Listing of fractional atomic coordinates, thermal parameters, relevant atomic distances, and observed and calculated structure factors for derivative **4** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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