JOC Article

Conformational Studies by Dynamic NMR. 97.[1] Structure, Conformation, Stereodynamics and Enantioseparation of Aryl Substituted Norbornanes

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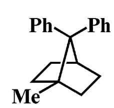
The structure of a 1,7,7-triaryl norbornane (compound **3**) has been determined by X-ray diffraction and was found essentially equal to that predicted by molecular mechanics calculations. Restricted rotation of the aryl groups also has been observed by dynamic NMR spectroscopy in this compound and in a number of analogously substituted norbornanes. The aryl−norbornane bond rotation barriers were measured by line shape analysis of the ^{13}C NMR spectra obtained at temperatures lower than −100 °C and were found to cover the range 6.0 to 7.9 kcal mol^{-1}. An exception was the rotation involving the *o*-anisyl group in compound **5**, which occurs near ambient temperature since the corresponding barrier is much higher (14.4 kcal mol^{-1}). In one case (compound **4**) configurational enantiomers could be separated by chiral HPLC and the corresponding CD spectra recorded.

Introduction

The importance of studies concerning the arene−arene interactions [2] recently has been pointed out again by Martinez and co-workers who, for this purpose, investigated a number of 7,7-diaryl-substituted norbornanes.[3,4] In particular they were able to measure the rotation barriers about the aryl−carbon bond when the aryl is a phenyl group bearing a fluorine substituent in the ortho position.[3] Subsequently we could also determine the much lower barriers occurring in the analogous 9,9-diaryl biciclononanes.[5] We have now extended our studies to the case of 7,7-diaryl-substituted norbornanes that do not necessarily bear an ortho substituent in the aryl group. In particular we investigated norbornanes **1**−**5** by means of low-temperature NMR spectroscopy, Molecular Mechanics calculations, and X-ray diffraction.



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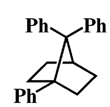

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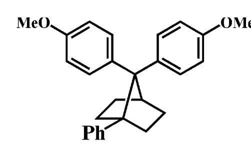

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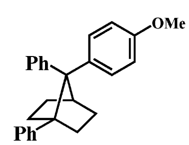

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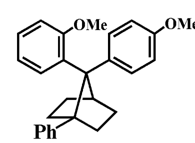

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Results and Discussion

Theoretical MM calculations (MMX force field[6]) carried out for compound **1** indicate that the ground-state conformation has the two phenyl rings in an apical cofacial[3] relationship (as shown in Figure 1), which does not display the propeller-like shape exhibited by the diaryl methane derivatives.[7]

The tridimensional energy surface computed as a function of the two phenyl-C7 bond angles (Figure 1)

(1) (a) Part 96: Grilli, S.; Lunazzi, L.; Mazzanti, A.; Pinamonti, M. *Tetrahedron Symposium in Print*. Submitted for publication. (b) Part 95: Anderson, J. E.; de Meijere, A.; Kozhushkov, S. I.; Lunazzi, L.; Mazzanti, A. *J. Org. Chem*. **2003**, *68*, 8494. (c) Part 94: Coluccini, C.; Grilli, S.; Lunazzi, L.; Mazzanti, A. *J. Org. Chem*., **2003**, *68*, 7266.

(2) (a) Cozzi, F.; Cinquini, M.; Annunziata, R.; Siegel, J. S. *J. Am. Chem. Soc.* **1993**, *115*, 5330. (b) Cozzi, F.; Ponzini, F.; Cinquini, M.; Annunziata, R.; Cinquini, M.; Siegel, J. S. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1019. (c) Jennings, W. B.; Farrell, B. M.; Malone, J. F. *Acc. Chem. Res.* **2001**, *34*, 885. (d) Carver, F. J.; Hunter, C. A.; Livingstone, D. J.; McCabe, J. F.; Seward, E. M. *Chem. Eur. J.* **2002**, *8*, 2847. (e) Cozzi, F.; Annunziata, R.; Benaglia, M.; Cinquini, M.; Raimondi, L.; Baldridge, K. K.; Siegel, J. S. *Org. Biomol. Chem*. **2003**, 157. (f) Meyer, E. A.; Castellano, R. K.; Diederich, F. *Angew. Chem., Int. Ed*. **2003**, *42*, 1210.

(3) Martinez, A. G.; Barcina, J. O.; Cerezo, A. de F.; Rivas, R. G. *J. Am. Chem. Soc.* **1998**, *120*, 673.

(4) (a) Martinez, A. G.; Barcina, J. O.; Albert, A.; Cano, F. H.; Subramanian, L. R. *Tetrahedron Lett.* **1993**, *34*, 6753. (b) Martinez, A. G.; Barcina, J. O.; Cerezo, A. de F. *Chem. Eur. J.* **2001**, *7*, 1171.

(5) Casarini, D.; Rosini, C.; Grilli, S.; Lunazzi, L.; Mazzanti, A. *J. Org. Chem*. **2003**, *68*, 1815.

(6) MMX force field as implemented in the computer package PC Model v 6, Serena Software, Bloomington, IN.

(7) (a) Barnes, J. C.; Paton, J. D.; Damewood, J. R.; Mislow, K. *J. Org. Chem*. **1981**, *46*, 4975. (b) Feigel, M. *J. Mol. Struct. (THEOCHEM)* **1996**, *36*, 83. (c) Grilli, S.; Lunazzi, L.; Mazzanti, A. *J. Org. Chem*. **2001**, *66*, 5853.

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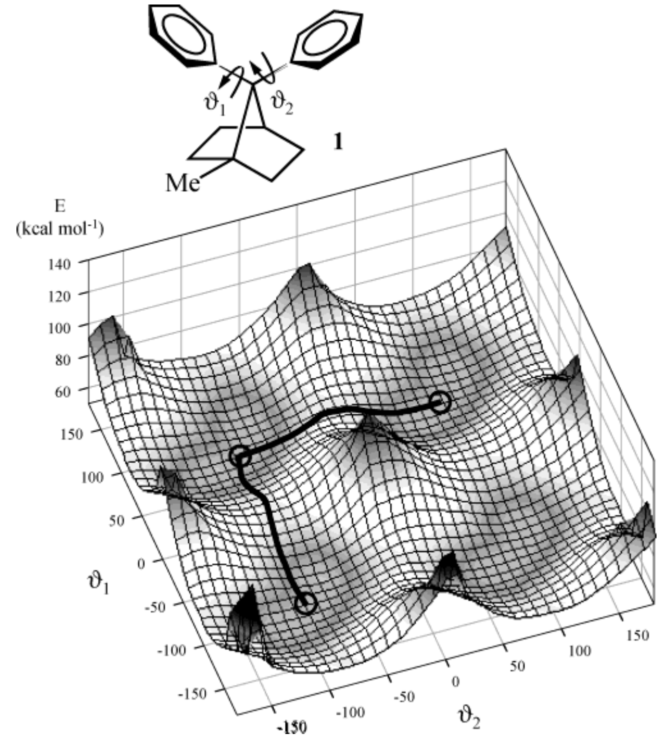


FIGURE 1. Computed[6] energy surface for **1** as a function of the phenyl-C7 rotation angles ϑ_1 and ϑ_2. The lines describe the pathway between the topomers visited by the rotation of each phenyl group.

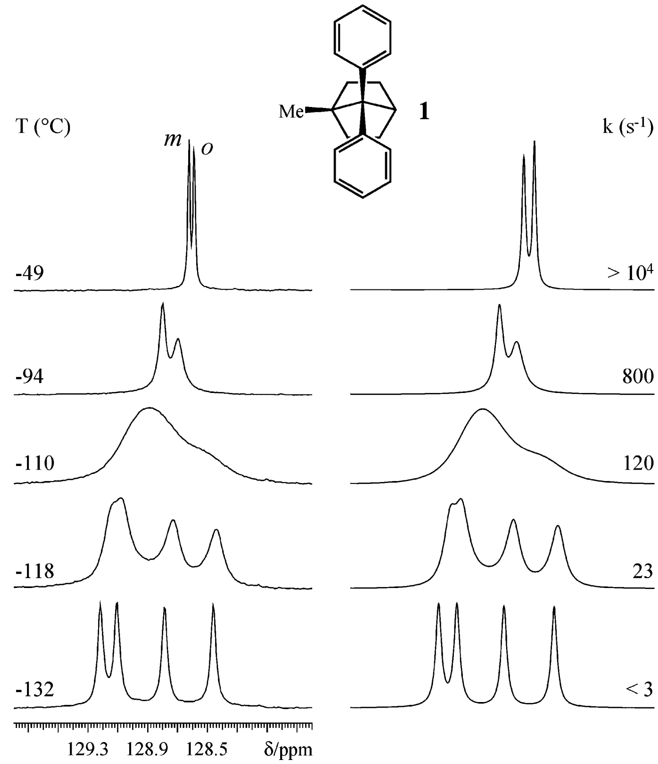


FIGURE 2. Left: ^{13}C NMR signals (100.6 MHz) of the ortho (*o*) and meta (*m*) carbons of the phenyl groups of **1** as a function of temperature in $CHF_2Cl/CHFCl_2$. The 1st and 3rd lines of the spectrum at −132 °C (129.25 and 128.8 ppm) are due to the diastereotopic meta carbons, the 2nd and the 4th (129.1 and 128.45 ppm) to the diastereotopic ortho carbons. Right: Computer simulation obtained with the rate constants indicated.

suggests that the two phenyl rings rotate independently of each other (in other words they do not undergo a correlated cogwheel pathway[8]): the barrier for this process is computed to be about 10 kcal mol^{-1}. Even allowing for the approximations involved in such computations, the value for this barrier should be high enough as to be amenable to an experimental verification by means of dynamic NMR spectroscopy.

In Figure 2 (left) the ^{13}C signals of the ortho and meta carbons (unambiguously assigned[9] by the HMBC sequence[10]) are reported as a function of temperature. The two sharp single lines, observed from ambient temperature until −49 °C, broaden on further cooling and each splits into a pair of equally intense lines at −132 °C. This is a consequence of the restricted rotation about the Ph−C7 bond that renders diastereotopic the ortho and meta positions, so that four lines are observed for the corresponding carbons. Computer line shape simulation (Figure 2, right) yields the values of the rate constants, hence the free energy of activation ($\Delta G^{\ddagger} = 7.9 \pm 0.15$ kcal mol^{-1}), for the rotation of the phenyl group (Table 1). As is often observed in conformational processes, this value turns out to be independent of temperature, within the experimental uncertainty.[11] The difference (about 2 kcal mol^{-1}) between the experimental and computed barrier is quite acceptable, given the complexity of the molecule investigated.

TABLE 1. Experimental Rotation Barriers ($\Delta G^{\ddagger}$, ±0.15 kcal mol^{-1}) for Compounds 1−5

bond rotation	1	2	3	4	5
phenyl-C7	7.9	6.0		6.1_5	
p-anisyl-C7			6.0	6.1	6.7
phenyl-C1				6.0_5	7.5
o-anisyl-C7					14.4

When the methyl group of **1** is replaced by a phenyl group (as in derivative **2**), two rotational processes are expected to occur, in principle, for the two types of phenyl substituents. However, MM calculations[6] indicate that the barrier for the rotation of the phenyl in position 1 is almost equal to that for the two phenyl groups in position 7 (depending on the approach involved in the computing

(8) (a) Mislow, K. *Acc. Chem. Res.* **1976**, *9*, 26, (b) Mislow, K. *Chemtracts Org. Chem*. **1989**, *2*, 151. (c) Biali, S. E.; Nugiel, D. A.; Rappoport, Z. *J. Am. Chem. Soc.* **1989**, *111*, 846. (d) Glaser, R. In *Acyclic Organonitrogen Stereochemistry*; Lambert, J. B., Takeuchi, Y., Eds.; VCH: New York, 1992; Chapter 4, p 123. (e) Grilli, S.; Lunazzi, L.; Mazzanti, A.; Mazzanti, G. *J. Org. Chem.* **2001**, *66*, 748 and references quoted therein.

(9) At ambient temperature the orthocarbon line is at lower field with respect to the meta, but moves at higher field on cooling, the crossing point occurring at about 0 °C where the two lines are coincident.

(10) Claridge, T. D. W. *High-Resolution NMR Techniques in Organic Chemistry*; Pergamon: Oxford, UK, 1999; Chapter 6.

(11) Hoogosian, S.; Bushweller, C. H.; Anderson, W. G.; Kigsley, G. *J. Phys. Chem.* **1976**, *80*, 643. Lunazzi, L.; Cerioni, G.; Ingold, K. U. *J. Am. Chem. Soc.* **1976**, *98*, 7484. Bernardi, F.; Lunazzi, L.; Zanirato, P.; Cerioni, G. *Tetrahedron* **1977**, *33*, 1337. Lunazzi, L.; Magagnoli, C.; Guerra, M.; Macciantelli, D. *Tetrahedron Lett.* **1979,** 3031. Anderson, J. E.; Tocher, D. A.; Casarini, D.; Lunazzi, L. *J. Org. Chem.* **1991**, *56*, 1731. Cremonini, M. A.; Lunazzi, L.; Placucci, G.; Okazaki, R.; Yamamoto, G. *J. Am. Chem. Soc.* **1992**, *114*, 6521. Borghi, R.; Lunazzi, L.; Placucci, G.; Cerioni, G.; Foresti, E.; Plumitallo, A. *J. Org. Chem.* **1997**, *62*, 4923.

procedure, the values cover the range 6.3 ± 0.4 kcal mol^{-1}). Such a near identity of the two barriers can be accounted for by considering that the motion of the phenyl bonded to C1 is essentially correlated to that of each phenyl bonded to C7. The rotation of the phenyl bonded to C1 simultaneously drives the rotation of the other two phenyl rings, according to a type of cogwheel pathway where the three rings move in unison, thus sharing a common transition state.[8] The barrier for this process is predicted to be significantly lower than the corresponding barrier previously computed for **1**, as often occurs when correlated motions are involved.[1c] The calculations also establish that in the ground state of **2** the phenyl in position 1 adopts a disposition having the ring essentially orthogonal to the plane of symmetry of the molecule (the plane of this phenyl is actually computed to deviate by 25° from a perfect orthogonal arrangement, but a low barrier libration process[12] establishes again a dynamic C_s symmetry in the NMR time scale). For this reason the corresponding rotation is NMR invisible since the ortho and the meta positions remain indistinguishable, as in the conditions of fast rotation, even when this motion is frozen: consequently a single line for the corresponding pairs of carbons is observed at any accessible temperature.

The barrier involving the rotation of the two phenyl groups bonded to C7 could be experimentally determined, yielding a value (6.0 ± 0.15 kcal mol^{-1}) definitely lower than that (7.9 kcal mol^{-1}) measured in **1**, in agreement with the above theoretical predictions. This supports the existence of the mentioned cogwheel pathway and also agrees with the predicted arrangement of the phenyl in position 1, which implies a lower hindrance to the rotation of the other two phenyl groups with respect to the case of a methyl bonded to C1. Although this result provides an indirect support to the computed conformation of **2**, direct evidence, such as that provided by the X-ray structure, would be desirable.

In the case of **2** we were unable to grow single crystals suitable for X-ray diffraction, but they could be obtained for the analogous compound **3**, which only differs from **2** by the presence of methoxy groups in the para positions. As shown in Figure 3, the experimental and computed structures are quite similar: in particular X-ray diffraction (see the Supporting Information) confirms that the plane of the phenyl group bonded to C1 is essentially orthogonal to the plane identified by C1,C7,C4 in the norbornane ring.

We also verified that in the case of **3** the barrier for the rotation of the phenyl in position 1 is NMR invisible and that the barrier for the observable rotation of the *p*-anisyl moieties ($\Delta G^{\ddagger} = 6.0 \pm 0.15$ kcal mol^{-1}) is equal, within the experimental errors, to that measured in the case of **2** for the corresponding unsubstituted phenyl groups. In other words, the presence of a methoxy group does not appreciably affect the rotation barrier.

To obtain an experimental determination of the dynamic process involving the phenyl group bonded to C1 it is thus necessary to desymmetrize the molecule by rendering the two substituents in position 7 different. Compounds **4** and **5** fulfill, in principle, this requirement.

(12) The computed[6] barrier for such a low amplitude libration process was found as small as 1.4 kcal mol^{-1}.

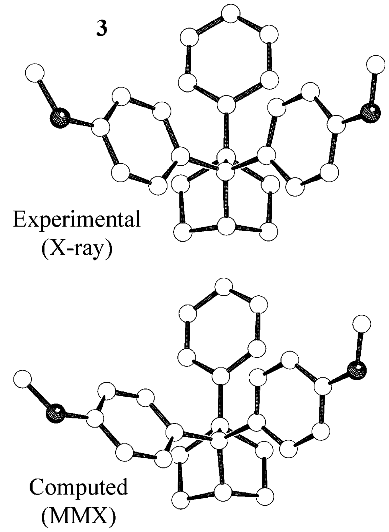


FIGURE 3. X-ray (top) and MM computed[6] structure (bottom) of compound **3**.

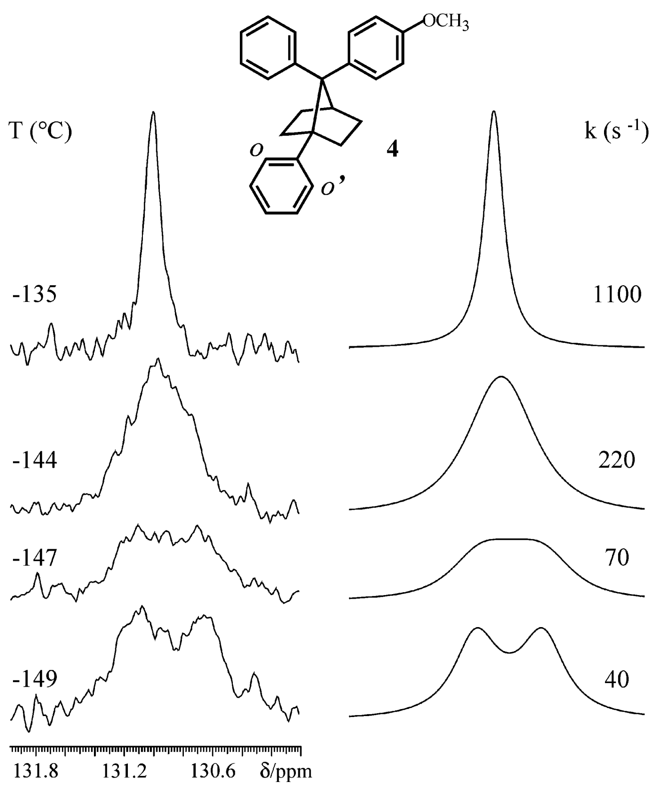
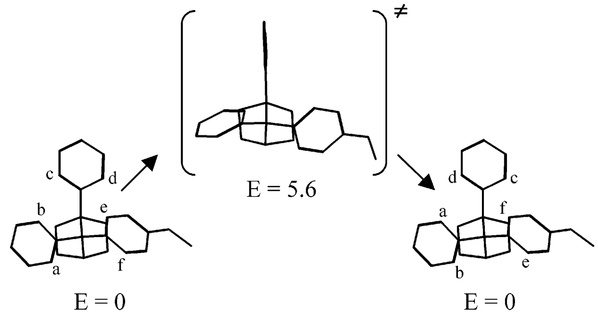


FIGURE 4. Temperature dependence of the ^{13}C NMR signals (100.6 MHz) in $CHF_2Cl/CHFCl_2$ of the ortho carbons (indicated as *o* and *o′*) of the phenyl in position 1 of compound **4** (left). On the right is displayed the computer simulation obtained with the rate constants indicated.

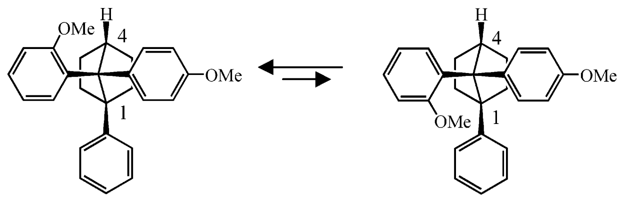
The low-temperature ^{13}C spectra of **4** (Figure 4) actually show that the ortho carbon signal of the phenyl in position 1 (identified via HSQC and HMBC sequences[10]) splits below −147 °C, indicating that the two ortho positions are now diastereotopic: the corresponding rotation barrier was found to be $6.0_5 \pm 0.15$ kcal mol^{-1}. As in the case of **2** and **3**, the ortho signals of the two aryl substituents in position 7 also split at low temperature in compound **4**, and barriers of 6.1_5 and 6.1 kcal

SCHEME 1[a]



[a] The computed relative energies are in kcal mol^{-1}.

SCHEME 2



5-E **5**-Z

mol^{-1} were determined for the rotation of the phenyl and of the *p*-anisyl groups, respectively. These three values are equal within the experimental uncertainty (see Table 1), in agreement with the proposed correlated process (cogwheel pathway[8]) that entails, as mentioned, a common transition state and, consequently, a unique $\Delta G^{\ddagger}$ value.[13]

As in the case of **1**, the MM computations carried out on **4** indicate that the rotation of each aryl group drives the rotation of the other two. This process leads to the corresponding topomer (where the positions a, c, e are exchanged, respectively, with the positions b, d, f) through a unique transition state, shared by the three rotating aryl groups, as shown in Scheme 1. The computed barrier for this topomerization process (5.6 kcal mol^{-1}) matches satisfactorily the corresponding experimental value (about 6.1 kcal mol^{-1}) reported in Table 1.

In the case of **5**, the restricted rotation about the *o*-anisyl to C7 bond is expected to generate two conformers, having the corresponding methoxy group on the same or on the opposite side with respect to the phenyl bonded to C1 (*Z*- and *E*-conformers, respectively, as in Scheme 2).

The ^1H NMR spectrum of **5**, in both $CDCl_3$ and toluene-d_8, showed that the methoxy line of the *o*-anisyl substituent, which was quite broad at ambient temperature, sharpened on warming as well as on cooling (see the Supporting Information): such behavior is typical for an exchange process between two very biased species.[14−16] Whereas above ambient temperature the relative intensity of the integrated OMe signal of the *o*-anisyl substituent corresponds exactly to three hydrogens, at a temperature (e.g. −20 °C) where the exchange process is blocked, its relative intensity is slightly lower. This is because the observed *o*-anisyl OMe signal corresponds, in these conditions, solely to the major of the two conformers, and lacks the contribution of the minor one. On this basis we carefully searched for the minor signal, which was eventually found 0.75 ppm upfield with respect to its major partner in $CDCl_3$,[17] its proportion being about 5 ± 1% at −20 °C (the minor signals of some other aliphatic hydrogens also displayed the same proportion).

The maximum incremental line-width broadening ($\Delta\omega$) measured at 600 MHz for the exchanging ortho OMe line of **5** was 38 Hz in $CDCl_3$ (at +29 °C) and 27 Hz in toluene-d_8 (at +25 °C). The appropriate formula ($k = 2\pi\Delta\omega$)[15] provided the rate constants (k = 240 and 170 s^{-1}, respectively) for the interconversion of the major into the minor conformer: the barriers ($\Delta G^{\ddagger}$) obtained from these rates turned out to have the same value (14.4 kcal mol^{-1}) in both solvents (Table 1).[18]

To decide whether the less-hindered *E*-conformer is actually more stable than the *Z*-conformer, a NOE experiment (DPFGSE-NOE sequence[19]) was carried out in toluene-d_8 at −20 °C, i.e., a temperature where the rotation rate is slow in the NMR time scale, thus minimizing the saturation transfer effects.[20] Irradiation of the CH triplet signal in position 4 of the norbornane

(13) As pointed out by one of the reviewers, even more important for assessing a correlated rotation is the near identity of the rate constants at the very same temperature (in such a way that the errors on the measure of temperature do not interfere with the result). In the spectra of **4** we could simulate the line shape, resulting from the three simultaneous rotation processes at a common temperature, in three cases (due to the different chemical shifts separation, the effects of the three motions were not simultaneously measurable in the whole temperature range). The rate constants for the three processes were found exactly equal to each other at −149 and −147 °C (40 and 70 s^{-1}, respectively): at −141 °C their differences were also very similar and, in any case, smaller than the uncertainty (about ±15%) on the rate obtained from the simulation (the three values were, in fact, 160, 180, and 190 s^{-1}, for the phenyl-C7, *p*-anisyl-C7, and phenyl-C1 rotation, respectively). These observations thus support the existence of a correlated motion.

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(15) Sandström, J. *Dynamic NMR Spectroscopy*; Academic Press: New York, 1982; p 84.

(16) Anet, F. A. L.; Yavari, I.; Ferguson, I. J.; Katritzky, A. R.; Moreno-Mañas, M.; Robinson, M. I. T. *Chem. Commun.* **1976**, 399. Cerioni, G.; Piras, P.; Marongiu, G.; Macciantelli, D.; Lunazzi, L. *J. Chem. Soc., Perkin Trans. 2* **1981**, 1449. Lunazzi, L.; Placucci, G.; Chatgilialoglu, C.; Macciantelli, D. *J. Chem. Soc., Perkin Trans. 2* **1984**, 819. Casarini, D.; Lunazzi, L.; Macciantelli, D. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1839. Lunazzi, L.; Placucci, G.; Macciantelli, D. *Tetrahedron* **1991**, *47*, 6427. Lunazzi, L.; Mazzanti, A.; Casarini, D.; De Lucchi, O.; Fabris, F. *J. Org. Chem.* **2000**, *65*, 883. Grilli, S.; Lunazzi, L.; Mazzanti, A. *J. Org. Chem.* **2000**, *65*, 3563.

(17) Such a large upfield shift is due to the fact that the OMe hydrogens of the *o*-anisyl in the minor Z-conformer lie almost exactly above the π-electron system of the *p*-anisyl ring, a feature that is well-known to move the corresponding signal upfield (see for instance: Jackman, L. M.; Sternhell, S. *Applications of NMR Spectroscopy to Organic Chemistry*, 2nd ed.; Pergamon Press: Oxford, UK, 1969; p 97. Abraham, R. J.; Fisher, J.; Loftus, P. *Introduction to NMR Spectroscopy*; J. Wiley and Sons: Chichester, UK, 1988; p 20. Wüthrich, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 3340).

(18) At the temperature (+29 °C) where the maximum broadening of the major OMe signal occurs in $CDCl_3$, the proportion of the minor conformer should be about 8%, according to the Boltzmann equation. By making use of this value and of the measured chemical shifts separation (i.e. 450 Hz, corresponding to 0.75 ppm at 600 MHz), a computer line shape simulation did reproduce the experimental broadening (38 Hz) when the same rate constant (240 s^{-1}), previously derived from the approximate formula, was employed. This provides an independent check of the 14.4 kcal mol^{-1} value for the interconversion barrier.

(19) Stonehouse, J.; Adell, P.; Keeler, J.; Shaka, A. J. *J. Am. Chem. Soc.* **1994**, *116*, 6037. Stott, K.; Stonehouse, J.; Keeler, J.; Hwang, T. L.; Shaka, A. J. *J. Am. Chem. Soc.* **1995**, *117*, 4199. Stott, K.; Keeler, J.; Van, Q. N.; Shaka, A. J. *J. Magn. Reson.* **1997**, *125*, 302. Van, Q. N.; Smith, E. M.; Shaka, A. J. *J. Magn. Reson.* **1999**, *141*, 191.

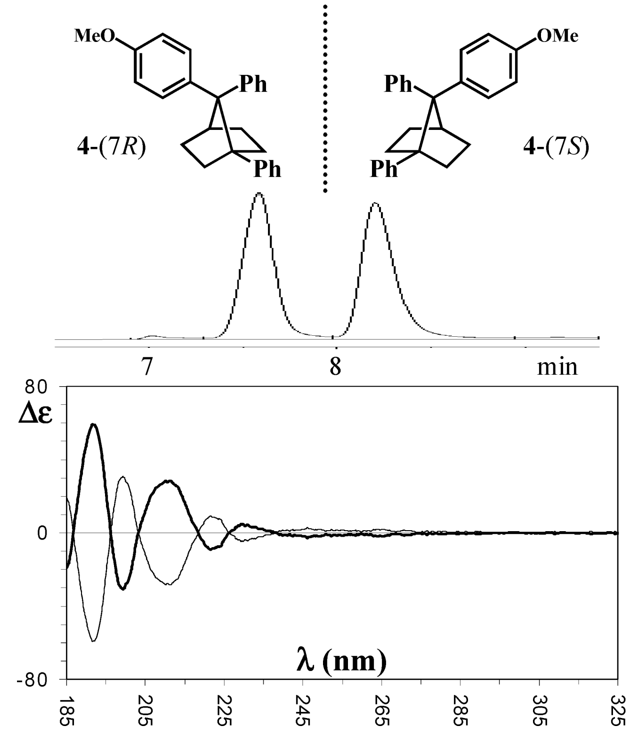


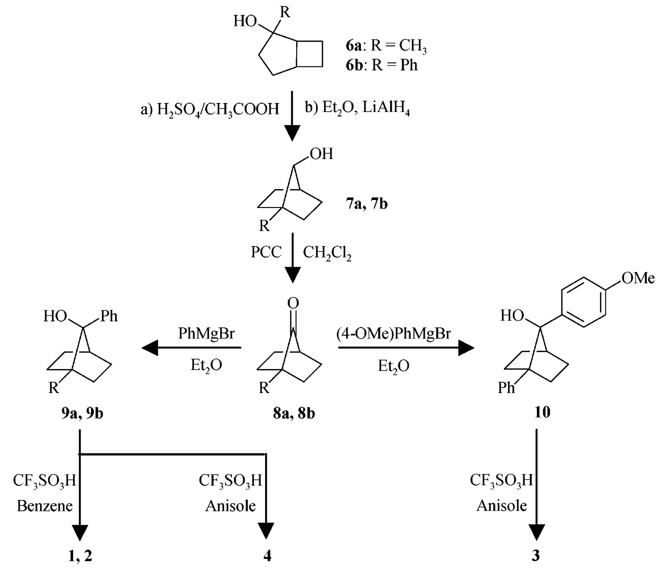
FIGURE 5. Enantioselective HPLC chromatogram (top) and CD spectra (bottom) of the enantiomers of **4**, the bold trace being that of the first eluted enantiomer. The terms *R* and *S* refer to the configuration of carbon in position 7 of the norbonane ring.

ring of the major conformer results in an enhancement of the corresponding major OMe line of the *o*-anisyl substituent and, likewise, irradiation of the latter line enhances the triplet of CH in position 4 (see the Supporting Information). Since the computed[6] average distance between the CH in position 4 and the OMe hydrogens of the *o*-anisyl group is 6.8 Å in the *Z*- and 3.9 Å in the *E*-conformer, the observed NOE effect clearly establishes that compound **5** essentially adopts the *E* conformation.

Restricted rotation was also observed for the aryl groups bonded to C1 and C7, which displayed anisochronous ^{13}C lines at −145 °C (see the Supporting Information) for the corresponding ortho and meta carbons (assigned by COSY and HSQC sequences[10]). Computer line shape analysis provided $\Delta G^{\ddagger}$ values of 7.5 and 6.7 kcal mol^{-1} for the phenyl-C1 and for the *p*-anisyl-C7 bond rotation, respectively (Table 1). Contrary to the case of **4**, the barriers for the three rotating aryl groups of **5** have different values. This indicates that the presence of the bulky *o*-anisyl substituent has disrupted the correlated rotation process occurring in **4** and has made each aryl group of **5** rotate independently of the other. For this reason we found three different activation energies (see Table 1) that correspond to the three possible transition states.[21]

As mentioned, compound **4** does not possess any element of symmetry (C_1 point group): the ^1H NMR single line of the methoxyl group thus splits, in a chiral environment,[22] into a pair of equally intense peaks (separated by 1.0 Hz at 600 MHz, as shown in the Supporting Information) corresponding to the signals expected for the two possible enantiomers. In fact, although compound **4** apparently has three asymmetric carbons (i.e. carbons in positions 1, 4, and 7 of the norbornane moiety), only a pair of enantiomers can exist: a change in the chirality of C7 implies, in fact, a simultaneous change of the configuration of the other two stereogenic centers (C1 and C4) that cannot therefore display a configuration independent of that of carbon in position 7.[23]

SCHEME 3



By making use of an appropriate enantioselective column (see the Experimental Section) two well-resolved peaks were actually detected in the HPLC chromatogram of **4**, as shown in Figure 5, where the corresponding oppositely phased CD spectra are also reported.

Experimental Section

Material. Compounds **1**−**4** were obtained according to the general procedure reported in Scheme 3.

All reactions were carried out under a nitrogen atmosphere, diethyl ether was dried over Na/benzophenone and CH_2Cl_2 over P_2O_5, benzene and anisole were dried by stirring overnight with activated molecular sieves (4Å, 4−8 mesh) under nitrogen atmosphere.

Compounds **6a**, **7a**, and **8a** were prepared according to the procedure described in the literature,[24] but in the last step only 3 equiv of PCC (pyridinium chlorochromate) was used.

2-Phenylbicyclo[3.2.0]heptan-2-ol (6b). 6b was obtained as previously reported[24] starting from bicyclo[3.2.0]heptan-2-one and PhMgBr. Pale yellow oil, yield 98%. ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ 1.39−1.72 (m, 3 H), 1.86−2.53 (m, 5 H

(20) Neuhaus, D.; Williamson, M. P. *The Nuclear Overhauser Effect in Structural and Conformational Analysis*; VCH: New York, 1989; Chapter 5.

(21) The barriers for the phenyl-C1 and for the *p*-anisyl-C7 bond rotation in **5** are higher than the corresponding barriers measured in **4** (Table 1). This further supports the existence of a correlated motion in **4** and its absence in **5**. Correlated processes are known, in fact, to reduce the barriers that make the rotation pathways more facile.[1c,8]

(22) Use was made of a 75:1 molar excess of enantiopure TFA, i.e., *R*-*l*-1-(9-anthryl)-2,2,2,-trifluoroethanol (see: Pirkle, W. H. *J. Am. Chem. Soc.* **1966**, *88*, 1837) in a CD_2Cl_2 solution at about −17 °C.

(23) If C7 has the *R* configuration, C1 and C4 have, forcibly, the *S* and *R* configuration, respectively. Likewise, if C7 has the *S* configuration, C1 and C4 must be *R* and *S*, respectively.

(24) Kirmse, W.; Steru, J. *Synthesis* **1983**, 994.

+ OH), 2.73−3.00 (m, 2 H), 7.16−7.38 (m, 5 H, Ph). ^{13}C NMR (50.3 MHz, $CDCl_3$, 25 °C): δ 18.2 (CH_2), 24.5 (CH_2), 30.2 (CH_2), 38.0 (CH), 39.0 (CH_2), 46.4 (CH), 83.0 (C_q), 125.2 (CH), 126.7 (CH), 128.0 (CH), 148.0 (C_q).

1-Phenylbicyclo[2.2.1]heptan-7-ol (7b). To a concentrated sulfuric acid solution in acetic acid (0.5 N, 42 mL) was added **6b** (5.88 g, 31.3 mmol). The mixture was stirred for 5 h at 80 °C, neutralized with $NaHCO_3$, and partitioned between water (400 mL) and Et_2O (150 mL). After being stirred for 10 min, the organic layer was separated, dried (sodium sulfate), filtered on silica gel, and concentrated. The residue was dissolved in dry Et_2O (70 mL) and slowly added to a solution of $LiAlH_4$ (2.04 g, 53.8 mmol) in dry Et_2O (30 mL) at 0 °C. The reaction was stirred for 2 h at ambient temperature, quenched (saturated ammonium chloride solution), and filtered on Celite. The mixture was then extracted with Et_2O and dried (Na_2SO_4) and the solvent was removed at reduced pressure affording a brown oil (5.09 g). The crude was purified by silica gel chromatography (petroleum ether/Et_2O 7:3) to yield 3.44 g (18.3 mmol) of **7b** as a yellow solid (60%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.31−1.38 (m, 1 H), 1.49−1.83 (m, 5 H + OH), 2.10−2.17 (m, 2 H), 2.19−2.22 (m, 1 H), 4.23 (br s, 1 H), 7.08−7.15 (m, 1 H), 7.30−7.37 (m, 4 H). ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 25.9 (CH_2), 28.0 (CH_2), 31.5 (CH_2), 36.8 (CH_2), 41.3 (CH), 53.2 (C_q), 81.7 (CH), 126.1 (CH), 127.0 (CH), 128.4 (CH), 143.3 (C_q).

1-Phenylbicyclo[2.2.1]heptan-7-one (8b). To a solution of **7b** (3.44 g, 18.3 mmol) in dry CH_2Cl_2 (60 mL) were added molecular sieves (4Å, activated powder, 10 g) and PCC (5.9 g, 27.4 mmol). After being stirred at ambient temperature for 1 h, the mixture was diluted with dry Et_2O (100 mL) and stirred for an additional 1 h. The brown suspension was filtered on Celite and subsequently on silica gel to give an orange organic solution that was concentrated under reduced pressure. The byproduct contained in the crude (1-phenyl-2-oxabicyclo[2.2.2]-octan-3-one) was eliminated by precipitation from Et_2O. Product **8b** was obtained as a pale yellow oil (1.85 g, 9.95 mmol) and used for the next steps without further purification. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.69−1.76 (m, 2 H), 2.00−2.21 (m, 7 H), 7.23−7.36 (m, 5 H). ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 23.8 (CH_2), 31.8 (CH_2), 40.4 (CH), 47.8 (C_q), 126.4 (CH), 127.6 (CH), 128.1 (CH), 138.8 (C_q), 214.9 (C_q).

The alcohols **9a**, **9b**, and **10** were synthesized according to the following general procedure. Four millimoles of the ketone (**8a**, **8b**) dissolved in dry Et_2O (5 mL) was slowly added at ambient temperature to a solution of the appropriate Grignard reagent (6 mmol of phenyl- or 4-methoxyphenylmagnesium bromide). The mixture was refluxed for about 1 h then quenched with saturated ammonium chloride solution, extracted with Et_2O, dried (Na_2SO_4), and concentrated at reduced pressure. The residue was purified by silica gel chromatography (petroleum ether/Et_2O 5:1, **9a**, or petroleum ether/Et_2O 10:1, **9b**). The crude alcohol **10** was directly used in the following step.

1-Methyl-7-phenylbicyclo[2.2.1]heptan-7-ol (9a). Solid (45%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 1.26−1.41 (m, 4 H, CH_2), 1.58−1.78 (m, 4 H, CH_2), 1.65 (s, 3 H, CH_3), 2.98 (br t, J = 4.0 Hz, 1 H, CH), 7.01−7.07 (m, 2 H, Ph), 7.13−7.20 (m, 4 H, Ph), 7.42−7.46 (m, 4 H, Ph). ^{13}C NMR (75.45 MHz, $CDCl_3$, 25 °C): δ 20.1 (CH_3), 27.6 (CH_2), 38.0 (CH_2), 46.2 (CH), 48.5 (C_q), 62.5 (C_q), 125.1 (CH), 127.8 (CH), 127.9 (CH), 146.0 (C_q).

1,7-Diphenylbicyclo[2.2.1]heptan-7-ol (9b). Sticky solid (50%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.36−1.43 (m, 1 H, CH_2), 1.51−1.66 (m, 2 H, CH_2), 1.75−1.85 (m, 2 H, CH_2), 1.88 (s, 1 H, OH), 2.01−2.10 (m, 1 H, CH_2), 2.30−2.38 (m, 1 H, CH_2), 2.45−2.53 (m, 1 H, CH_2), 2.65 (bt, J = 4.4 Hz, 1 H, CH), 7.12−7.17 (m, 5 H, Ph), 7.26−7.30 (m, 1 H, Ph), 7.32−7.37 (m, 2 H, Ph), 7.62−7.65 (m, 2 H, Ph). ^{13}C NMR (75.45 MHz, $CDCl_3$, 25 °C): δ 25.8 (CH_2), 28.1 (CH_2), 31.5 (CH_2), 40.6 (CH_2), 46.6 (CH), 52.6 (C_q), 88.4 (C_q), 126.1 (CH), 127.3 (CH), 127.4 (CH), 127.5 (CH), 128.2 (CH), 142.2 (C_q), 143.9 (C_q).

1-Phenyl-7-(4-methoxyphenyl)bicyclo[2.2.1]heptan-7-ol (10). Sticky solid (75%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.34−1.42 (m, 1 H, CH_2), 1.49−1.66 (m, 2 H, CH_2), 1.74−1.84 (m, 2 H, CH_2), 1.99−2.07 (m, 1 H, CH_2), 2.27−2.36 (m, 1 H, CH_2), 2.44−2.51 (m, 1 H, CH_2), 2.61 (br t, J = 4.4 Hz, 1 H, CH), 3.71 (s, 3 H, OCH_3), 6.65−6.68 (m, 2 H, anisole), 7.02−7.06 (m, 2 H, anisole), 7.24−7.29 (m, 1 H, Ph), 7.32−7.37 (m, 2 H, Ph), 7.62−7.65 (m, 2 H, Ph). ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 25.8 (CH_2), 28.2 (CH_2), 31.5 (CH_2), 40.6 (CH_2), 46.7 (CH), 52.6 (C_q), 55.1 (OCH_3), 88.0 (C_q), 113.4 (CH), 126.1 (CH), 127.5 (CH), 128.1 (CH), 128.5 (CH), 134.5 (C_q), 144.0 (C_q), 158.6 (C_q).

Compounds **1**, **2**, **3**, and **4** were prepared from the corresponding alcohols in accordance with a general procedure.[25] A solution of **9a**, **9b**, or **10** (1 mmol) in 5 mL of benzene (**1** and **2**) or anisole (**3** and **4**) was slowly added under nitrogen into a flask containing trifluoromethanesulfonic acid (1.5 mmol) in 5 mL of the same solvent. After being stirred for 1.5 h, the mixture was poured into water (20 mL) and the aqueous solution was neutralized with solid $NaHCO_3$ and extracted with CH_2Cl_2 (20 mL). The organic layer was dried (Na_2SO_4) and the solvent removed at reduced pressure. A further purification of the products was obtained by silica gel chromatography (**1**, petroleum ether, **3**, petroleum ether/Et_2O 10:1, **4**, cyclohexane/toluene 20:1), or by recrystallization (ethanol, **2**).

1-Methyl-7,7-diphenylbicyclo[2.2.1]heptane (1). Solid (53%); mp 73−73.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 1.26−1.41 (m, 4 H, CH_2), 1.58−1.78 (m, 4 H, CH_2), 1.65 (s, 3 H, CH_3), 2.98 (br t, J = 4.0 Hz, 1 H, CH), 7.01−7.07 (m, 2 H, Ph), 7.13−7.20 (m, 4 H, Ph), 7.42−7.46 (m, 4 H, Ph). ^{13}C NMR (75.45 MHz, $CDCl_3$, 25 °C): δ 20.1 (CH_3), 27.6 (CH_2), 38.0 (CH_2), 46.2 (CH), 48.5 (C_q), 62.5 (C_q), 125.1 (CH, para), 127.8 (CH, meta), 127.9 (CH, ortho), 146.0 (C_q). Anal. Calcd for $C_{20}H_{22}$: C (91.55); H (8.45). Found: C (91.53); H (8.42).

1,7,7-Triphenylbicyclo[2.2.1]heptane (2). Solid (65%); mp 133.5−134 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.46−1.51 (m, 2 H, CH_2), 1.67−1.72 (m, 2 H, CH_2), 2.04−2.09 (m, 2 H, CH_2), 2.39−2.44 (m, 2 H, CH_2), 3.33 (t, J = 4.3 Hz, 1 H, CH), 7.01−7.04 (m, 2 H, Ph), 7.09−7.12 (m, 4 H, Ph), 7.27−7.30 (m, 3 H Ph), 7.32−7.35 (m, 2 H, Ph), 7.48−7.50 (m, 2 H, Ph). ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 28.1 (CH_2), 36.8 (CH_2), 46.3 (CH), 55.0 (C_q), 64.6 (C_q), 125.3 (CH, para), 126.2 (CH, para), 127.4 (CH, meta), 127.5 (CH, meta), 128.9 (CH, ortho), 130.1 (CH, ortho), 142.8 (C_q), 145.4 (C_q). Anal. Calcd for $C_{25}H_{24}$: C (92.54); H (7.46). Found: C (91.53); H (7.45).

7,7-Bis(4-methoxyphenyl)-1-phenylbicyclo[2.2.1]heptane (3). Solid (50%); mp 162−163 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.43−1.51 (m, 2 H, CH_2), 1.65−1.72 (m, 2 H, CH_2), 2.00−2.09 (m, 2 H, CH_2), 2.35−2.43 (m, 2 H, CH_2), 3.24 (bt, J = 4.3 Hz, 1 H, CH), 3.70 (s, 6 H, OCH_3), 6.63−6.67 (m, 4 H, anisole), 7.15−7.19 (m, 4 H, anisole), 7.25−7.30 (m, 1 H, Ph), 7.31−7.36 (m, 2 H, Ph), 7.47−7.50 (m, 2 H, Ph). ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 28.2 (CH_2), 36.8 (CH_2), 46.6 (CH), 55.0 (OCH_3), 55.1 (C_q), 63.3 (C_q), 112.8 (CH, ortho, anisole), 126.1 (CH, para, Ph), 127.4 (CH, meta, Ph), 129.8 (CH, meta, anisole), 130.0 (CH, ortho, Ph), 138.0 (C_q), 143.0 (C_q), 156.9 (C_q). Anal. Calcd for $C_{27}H_{28}O_2$: C (84.34), H (7.34). Found: C (84.36); H (7.36).

7-(4-Methoxyphenyl)-1,7-diphenylbicyclo[2.2.1]heptane (4). Solid (90%); mp 134−135 °C. ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ 1.45−1.51 (m, 2 H, CH_2), 1.66−1.72 (m, 2 H, CH_2), 1.98−2.04 (m, 1 H, CH_2), 2.08−2.14 (m, 1 H, CH_2), 2.35−2.46 (m, 2 H, CH_2), 3.29 (bt, J = 4.3 Hz, 1 H, CH), 3.71 (s, 3 H, OCH_3), 6.65−6.67 (m, 2 H, anisole), 7.00−7.04 (m, 1 H, Ph), 7.08−7.12 (m, 2 H, Ph), 7.18−7.21 (m, 2 H, anisole), 7.25−7.30 (m, 3 H, Ph), 7.32−7.35 (m, 2 H, Ph), 7.48−7.50 (m, 2 H, Ph). ^{13}C NMR (150.8 MHz, $CDCl_3$, 25 °C): δ 28.1 (CH_2), 28.2 (CH_2), 36.4 (CH_2), 37.2 (CH_2), 46.4 (CH), 55.0 (OCH_3), 55.1 (C_q),

(25) Martinez, A. G.; Barcina, J. O.; Cerezo, A. F.; Schlüter, A.-D.; Frahn, J. *Adv. Mater.* **1999**, *11*, 27.

64.0 (C_q), 112.8 (CH, ortho, anisole), 125.1 (CH, para, Ph), 126.2 (CH, para, Ph), 127.4 (CH, meta, Ph), 127.5 (CH, meta, Ph), 128.7 (CH, ortho, Ph), 130.0 (CH, meta, anisole), 130.1 (CH, ortho, Ph), 137.5 (C_q), 142.9 (C_q), 146.0 (C_q), 157.0 (C_q). Anal. Calcd for $C_{26}H_{26}O$: C (88.09); H (7.39). Found: C (88.11); H (7.36).

7-(2-Methoxyphenyl)-7-(4-methoxyphenyl)-1-phenylbicyclo[2.2.1]heptane (5). To a solution of mesityllithium (1.24 mmol) in dry THF (3 mL) cooled to −78 °C was added ketone **8b** (210.mg, 1.13 mmol). The mixture was warmed to ambient temperature, further stirred for 1 h, quenched with a saturated NH_4Cl solution, extracted with Et_2O, dried (Na_2SO_4), and concentrated at reduced pressure. Purification by silica gel chromatography (petroleum ether/Et_2O 9:1) provided the alcohol 7-mesityl-1-phenylbicyclo[2.2.1]heptan-7-ol as a white solid (170 mg, 0.56 mmol, 49%). Under the same conditions reported above,[25] the reaction with trifluoromethanesulfonic acid (0.78 mmol) in anisole (3 mL) supplied a mixture of **3** and **5** that were separated by preparative TLC (petroleum ether/Et_2O 10:1) to yield 46 mg (0.12 mmol, 23%) and 50 mg (0.13 mmol, 25%), respectively. Mp of **5** 177.5−178.0 °C (ethanol). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ 1.32−1.58 (m, 4 H, CH_2), 1.71−1.81 (m, 1 H, CH_2), 1.97 (br s, 1 H, CH_2), 2.41 (br s, 1 H, CH_2), 2.81 (br s, 1 H, CH_2), 3.40 (br s, 3 H, OCH_3), 3.71−3.78 (m, 1 H, CH), 3.75 (s, 3 H, OCH_3), 6.62−6.69 (m, 4 H, Ar), 7.00−7.07 (m, 1 H, Ar), 7.17−7.32 (m, 5 H, Ar), 7.39−7.43 (m, 2 H, Ar), 7.52−7.57 (m, 1 H, Ar). ^{13}C NMR (75.45 MHz, $CDCl_3$, 25 °C): δ 28.2 (CH_2), 29.3 (CH_2), 33.5 (br s, CH_2), 40.8 (br s, CH_2), 45.2 (br s, CH), 55.0 (OCH_3), 55.3 (br s, OCH_3), 55.6 (C_q), 63.1 (C_q), 111.5 (CH), 112.4 (CH), 119.6 (CH), 125.7 (CH), 126.8 (CH), 127.3 (CH), 128.1 (CH), 129.8 (CH), 132.0 (CH), 143.8 (C_q), 157.0 (C_q), 157.5 (C_q), Anal. Calcd for $C_{27}H_{28}O_2$: C (84.34); H (7.34). Found: C (84.31); H (7.33).

NMR Spectra. The samples for the low-temperature measurements were prepared by connecting to a vacuum line the NMR tubes containing the compound and some deuterated solvent for locking purposes and condensing therein the gaseous solvents (CHF_2Cl and $CHFCl_2$) by means of liquid nitrogen. The tubes were subsequently sealed in vacuo and introduced into the precooled probe of the spectrometer. The temperatures were calibrated by substituting the sample with a precision Cu/Ni thermocouple before the measurements. Complete fitting of the dynamic NMR line shape was carried out by using a PC version of the DNMR-6 program.[26]

HPLC separation of the enantiomers of **4** was performed at +25 °C on a Chiralcel OD-H column (5 μm), 250 mm × 4.6 mm ID, UV 254 nm, flow rate 0.5 mL/min (*n*-hexane/^{i}PrOH 99.5:0.5). The necessary amount of the two separated enantiomers was obtained by collecting several elutions.

CD spectra of the enantiomers of **4** were recorded at +25 °C on a Jasco J-600 dicrograph in a 0.01 cm cell in the range 185−325 nm.

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Supporting Information Available: MMX data for **1**−**5**; crystallographic data and ORTEP drawing of **3**; temperature dependence of the OMe ^1H signals of **5**; NOE spectra of **5**; ^1H spectrum of **4** in chiral medium; temperature dependence of ^{13}C aromatic signals of **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) QCPE program no. 633, Indiana University, Bloomington, IN.