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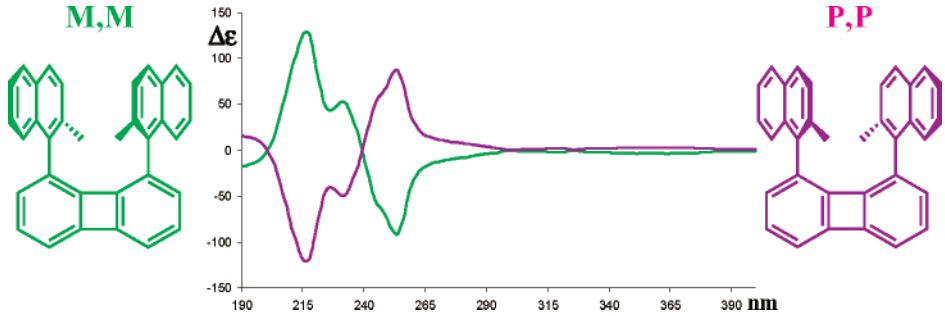
Arylbiphenylene Atropisomers: Structure, Conformation, Stereodynamics, and Absolute Configuration

Lodovico Lunazzi, Michele Mancinelli,[1] and Andrea Mazzanti*

Department of Organic Chemistry "A. Mangini", University of Bologna, Viale Risorgimento 4, Bologna 40136, Italy

mazzand@ms.fci.unibo.it

Received November 21, 2007



Anti and syn conformers, due to restricted sp^2-sp^2 bond rotation, were detected in hindered 1,8-diarylbiphenylenes, the aryl moieties being phenyl groups bearing *o*-alkyl substituents such as Me, Et, *i*-Pr, and *t*-Bu. By means of low-temperature NOE experiments, the corresponding structures were assigned and were found to be in agreement with the results of single-crystal X-ray diffraction. The interconversion barriers of these conformers were determined by line-shape simulation of the variable-temperature NMR spectra and the experimental values were reproduced satisfactorily by DFT calculations. In the case of the bulkiest aryl substituent investigated (i.e., 2-methylnaphthalene), the syn and anti atropisomers were stable enough as to be separated at ambient temperature. The two enantiomers (M,M and P,P) of the isomer anti were also isolated by enantioselective HPLC, and the theoretical interpretation of the corresponding CD spectrum allowed the absolute configuration to be assigned.

Introduction

Aryl substituents bonded to planar frameworks in sufficiently close positions adopt a parallel face-to-face arrangement, thus displaying through-space interactions that, as pointed out by Cozzi et al.,[2] play an important role in a variety of chemical properties such as molecular recognition,[3] stereocontrolled reactions,[4] protein and nucleic acid structures,[5] and crystal packing.[6] The stereodynamic processes occurring in many compounds of this type have been studied mainly by NMR spectroscopy.[7−12] Recently, we reported an unprecedented NMR detection[13] of the exchange processes between stereolabile conformers and enantiomers that occur in the case of biphenylenes bearing two *m*-tolyl or two *m*-xylyl substituents in positions 1,8. In the present work, we have extended the study to biphenylenes substituted by aryl groups with increasing steric requirements, with the aim of obtaining sufficiently long-living isomers (or enantiomers) that could be physically isolated. For this purpose, a number of aryl moieties bearing, in the ortho positions, alkyl groups of various sizes were attached to the positions 1,8 of biphenylene.

(1) In partial fulfilment of the requirements for the Ph.D. degree in Chemical Sciences, University of Bologna.

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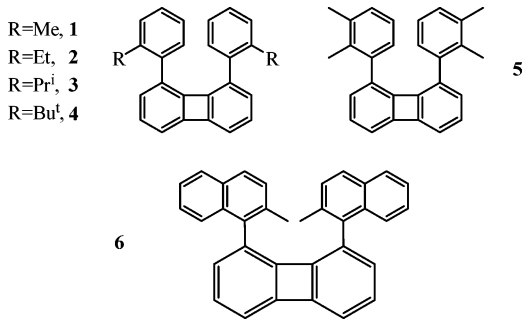
10.1021/jo702502n CCC: $40.75
Published on Web 02/16/2008

CHART 1



Results and Discussion

The compounds synthesized for this investigation are listed in Chart 1.

As pointed out by Clough and Roberts,[14] derivatives resembling compound **1** can exist as three possible conformers, depending on the relative positions of the two substituted aryl groups. In the case of **1,** DFT computations[15] actually predict the existence of three energy minima,[16] corresponding to the conformers displayed in Figure 1.

In the case of the less hindered *m*-tolyl biphenylene derivatives[13] mentioned above, the 90° torsion barrier interconverting the anti-in into the anti-out conformers, as well as that interconverting the two enantiomers of the syn conformer, are sufficiently high as to allow an experimental NMR detection of the corresponding exchange process. In the present case, on the contrary, these barriers are predicted to be significantly lower (1.7 kcal mol^{-1}, according to DFT computations), so that the 90° torsion processes are much faster and only the 180° rotation, which interconverts the rapidly exchanging anti conformers into the rapidly exchanging syn enantiomers, displays a barrier (DFT computed value of 10.5 kcal mol^{-1}) high enough to make the corresponding pathway accessible to a direct NMR detection.

Indeed, the ^{1}H methyl signal of **1** broadens on cooling and eventually splits, at −92 °C, into a pair of lines in a 60:40 proportion (Figure 2), one corresponding to the rapidly interconverting anti conformers and the other to the rapidly interconverting enantiomers of syn conformers: owing to the fast 90° torsion process mentioned above, both the anti and the syn conformers display a single methyl line (other exchange processes were not observed, even when cooling the sample to −175 °C). Line shape simulation of the methyl signals as function of temperature yielded the rate constants for the interconversion of the major into the minor conformer; from these values a free energy of activation ($\Delta G^{\ddagger}$)[17] equal to 10.3

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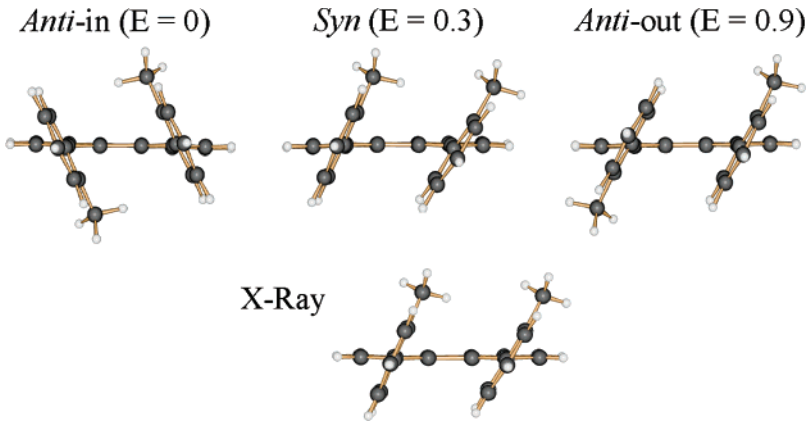

FIGURE 1. Top: DFT-computed structures of the conformers of **1** with the relative energies (*E*) in kcal mol^{-1} (for convenience only one of the two enantiomeric forms is displayed). Bottom: experimental structure obtained by single-crystal X-ray diffraction.

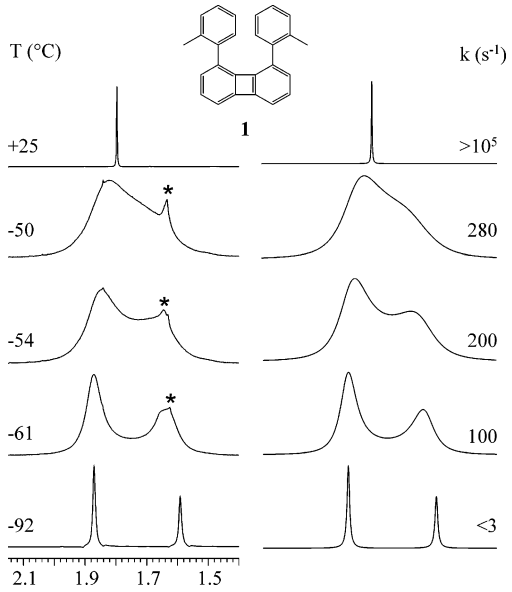

FIGURE 2. Left: experimental NMR ^{1}H signal (600 MHz in CD_2Cl_2) of the methyl group of **1** as function of temperature (the starred line is a trace of HDO present in the solvent). Right: line shape simulation obtained with the rate constants indicated.

TABLE 1. Experimental and DFT Computed Barriers (kcal mol^{-1}) for the Interconversion of the Major into the Minor Conformer in Compounds 1−6[a]

compd	1	2	3	4	5	6
experimental	10.3	11.4	13.9	17.0 [b]	13.0	34.5[c]
(% of anti)	(40)	(60)	(87)	(80)	(62)	(64)[c]
computed	10.5	11.9	13.7	16.8	13.3	34.7

[a] The proportion of the conformer anti in compounds **1**−**5**, measured at equilibrium in CD_2Cl_2 at appropriate low temperatures, is shown in parentheses. [b] See ref 26. [c] Determined in DMSO at +140 °C (see text).

± 0.15 kcal mol^{-1} was obtained, a result which agrees well with that predicted by DFT computations (Table 1).

Single-crystal X-ray diffraction shows that in the solid state the structure of compound **1** is essentially equal to that computed for the syn conformation (Figure 1): this might be due to the existence of a more stable crystal lattice when the molecule adopts a syn disposition,[18,19] but could also reflect the fact that, despite the higher computed energy, the syn might have a larger population in solution as a consequence of its higher entropy relative to the more symmetric anti form.[20] Actually, the DFT computations of chemical shifts[15] predict that the syn should have the ^{1}H methyl signal at a field lower (by 0.23 ppm) than the anti-in. As shown in Figure 2, the more intense methyl line is 0.28 ppm at lower field with respect to its less intense companion: this feature seems to support the hypothesis that the syn is actually the more populated conformer in solution. For this reason an unambiguous experimental assignment of the two conformers observed in solution had to be undertaken.

To solve this problem, a NOE experiment was carried out at a quite low temperature (−118 °C) in order to make negligible the saturation transfer effects:[21] at this temperature, in fact, the rate constant for the exchange is predicted to be as low as 0.01 s^{-1}. As shown in Figure 3, irradiation of the major methyl signal (trace b) yields significant enhancements only on two signals of the major conformer, i.e., those of H3,3′ in the tolyl rings

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(20) It has to be taken into account that the syn conformer exists as four degenerate forms (two identical pairs of enantiomers), whereas the anti-in exists solely as two degenerate forms, corresponding to a pair of enantiomers (the presence of the anti-out can be, in practice, neglected, since its higher relative energy of 0.9 kcal mol^{-1} would correspond to a proportion lower than 8% at −92 °C). Owing to the greater probability, the actual population of the *syn* conformer might be higher than expected solely on the basis of its computed energy. In fact, both of the anti forms belong to the C_2 point group and are therefore disfavored by RT ln 2 (i.e., 0.24 kcal mol^{-1} at −92 °C, see: Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds;* Wiley: New York, 1994; pp 97 and 601). Accordingly, when corrected for this factor the energy difference becomes 0.06 kcal mol$^{-1,}$ a value that corresponds to an anti/syn ratio of 54/46. When the proportions are so close to 50/50, the approximations involved in the computed energy do not allow one to obtain a reliable assignment for the situation in solution because, in these conditions, even a small solvent effect might cause a reversal of the assignment.

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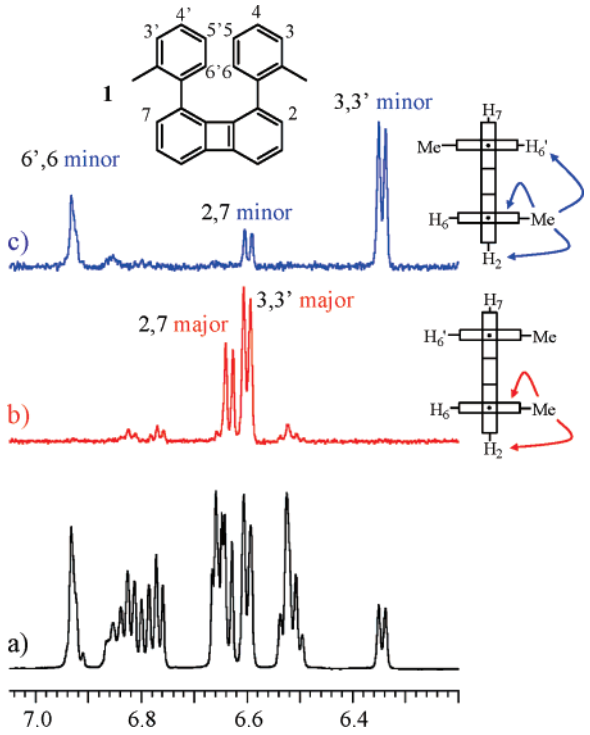

FIGURE 3. Trace a: aromatic region (600 MHz at −118 °C in CD_2Cl_2) displaying ^1H signals for the major and minor conformers of **1**. Trace b: NOE due to irradiation of the major methyl signal (1.87 ppm), showing significant enhancement for two aromatic signals of the major conformer (syn). Trace c: NOE due to irradiation of the minor methyl signal (1.59 ppm), showing significant enhancements for three aromatic signals of the minor conformer (anti).

and of H2,7 in the biphenylene ring. On the other hand, irradiation of the minor methyl signal (trace c) yields significant enhancement on three signals of the minor conformer: in addition to the H3,3′ signal in the tolyl rings and the H2,7 signal in the biphenylene ring, also the signal of the hydrogens in positions 6,6′ in the tolyl rings is significantly enhanced. The latter effect can only occur in the *anti* conformer because the methyl in position 2 of one tolyl ring is close to the H6′ in the second tolyl ring (and likewise the methyl in position 2′ is close to H6 in the second ring). Thus the minor conformer, displaying three large NOE enhancements, must have the anti structure whereas the major, displaying only two large NOE enhancements, must have the syn structure. There is no doubt, therefore, that the syn is the more populated conformer of **1** in solution, as it is in the crystalline state.

When the dimension of the ortho substituent is increased, as in derivative **2** (R = Et), the situation is reversed in that the more stable conformer in solution appears to be the less hindered anti form (about 60%). This was proved by an analogous low-temperature NOE experiment (Figure S-1 of the Supporting Information) where opposite effects, with respect to the case of **1**, were observed. In fact, simultaneous irradiation of the two major signals of the diastereotopic methylene hydrogens yields enhancement on three aromatic signals of the more intense spectrum, whereas only two aromatic signals of the less intense spectrum are enhanced when irradiating the two minor signals of the diastereotopic methylene hydrogens.[22]

The effect of steric hindrance in controlling the relative stability of the anti and syn conformers was also noticed in the case of derivative **5**. Here the introduction of an additional methyl group in the meta position of the aryl ring produces the so-called buttressing effect,[23] which generates a steric hindrance more similar to that of the ethyl groups in **2** than to that of the methyl groups in **1**, thus making higher the rotation barrier ($\Delta G^{\ddagger}$ = 13.0 kcal mol^{-1} as in Table 1). The increased steric hindrance also renders the anti conformer of **5** more stable than the syn (as proved by the low-temperature NOE experiments[24] in Figure S-2 of the Supporting Information), contrary to the case of the apparently similar compound **1**. This assignment is further confirmed by the observation that the DFT-computed shifts of the two methyl groups for the anti conformer of **5** correspond to the more intense pair of the experimental methyl lines, whereas the shifts computed for the *syn* conformer correspond to the less intense lines of the experimental spectrum.

In the even more hindered derivative **3** (R = isopropyl), the proportion of the minor syn conformer[25] is further reduced (13%) and the interconversion barrier, obtained by line shape simulation (Figure S-3 of the Supporting Information), is increased (13.9 kcal mol^{-1}, Table 1).

As conceivable, the barrier increases further in the *tert*-butyl derivative **4**,[26] although the proportion of the more stable conformer anti[25] does not increase accordingly in that, surprisingly, it is lower than in the case of **3**: solvent effects might be responsible for this feature.[27]

Contrary to the case of **1**, the single-crystal X-ray diffraction of **4** shows that the anti conformation is adopted in the solid

(22) When the rotation about the aryl-biphenylene bond is frozen, the methylene hydrogens are diastereotopic because the conformers adopt a non planar conformation. For the same reason are diastereotopic at low temperature the methyl groups of the isopropyl moieties of compound **3**. See: Mislow, K.; Raban, M. *Top. Stereochem.* **1967**, *1*, 1. Jennings, W. B. *Chem. Rev.* **1975**, *75*, 307. Eliel, E. L. *J. Chem. Ed.* **1980**, *57*, 52. Casarini, D.; Lunazzi, L.; Macciantelli, D. *J. Chem. Soc., Perkin Trans* **1992**, *2*, 1363.

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(24) Irradiation (Figure S-2 of the Supporting Information) of the major signal of the methyls in position 3,3′ of the xylyl rings (1.67 ppm) of **5**, yields enhancement for the major signal of the corresponding hydrogens in position 4,4′ (6.90 ppm) of the same xylyl rings and for the major signal of the hydrogens in positions 5′,5 (6.96 ppm) of the other ring, as expected for an anti conformer, where the latter distance is short enough to produce NOE effects. On the contrary irradiation of the minor signal (1.86 ppm) of the methyls in position 3,3′ of the xylyl rings, enhances solely the minor signal of the corresponding hydrogens in position 4,4′ of the same ring (6.74 ppm). Likewise irradiation of the major signals of the methyl in positions 2,2′ of the xylyl rings (1.37 ppm) enhances the corresponding signals of the hydrogens in positions 2,7 of the biphenylene moiety (6.59 ppm) and also that of the hydrogens in positions 6′,6 of the other xylyl ring (6.96 ppm). On the contrary, irradiation of the minor signal of the methyl groups (1.76 ppm) enhances solely the corresponding H2,7 minor signal of biphenylene (6.60 ppm), as expected for a syn conformer where the distance between the hydrogens of the methyl in position 2 of one ring and the hydrogen in position 6′ of the other ring is too large to yield a NOE effect.

(25) The conformational assignment in compounds **3** and **4** was obtained by means of the mentioned low temperature NOE experiments.

(26) For the NMR determination of the larger barrier of **4** it was necessary to use a solvent (tetrachloroethane-d_2) with a higher boiling point than the solvent (CD_2Cl_2) employed for measuring the barriers of compounds **1**−**3** and **5**.

(27) The lower proportion of the conformer anti observed in compound **4** with respect to **3** might be also interpreted as the consequence of a statistic effect, due to the possibility of having both the anti-in and anti-out situations in the case of **3**, whereas solely a single anti form occurs in **4**.

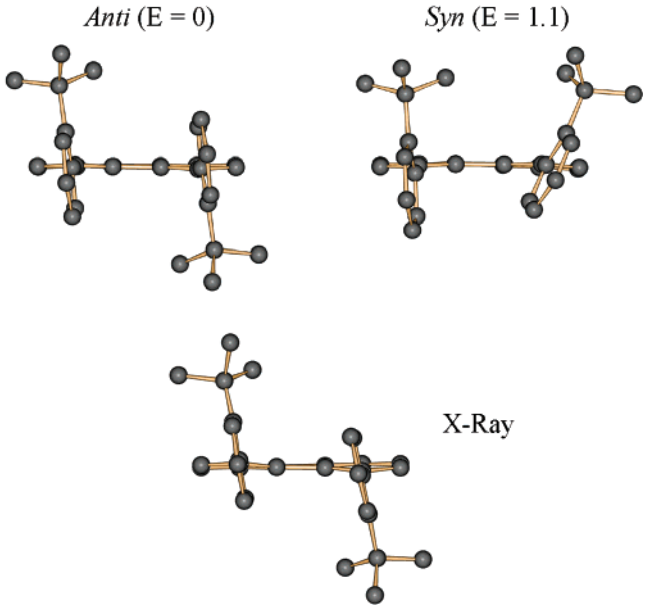

FIGURE 4. DFT-computed structures of the syn and anti conformers of **4** with the relative energies (*E*) in kcal mol^{-1} (top). Experimental structure obtained by single-crystal X-ray diffraction (the hydrogen atoms are omitted for convenience) (bottom).

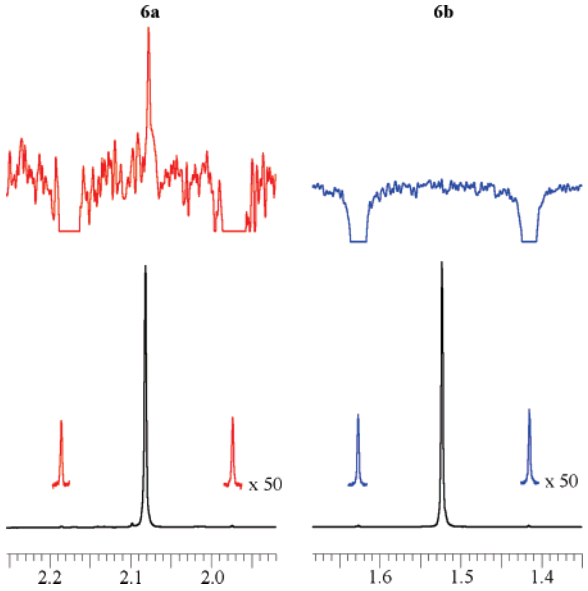

FIGURE 5. Left: methyl signal of **6a** (600 MHz in $CDCl_3$ at 0 °C) with the amplified ^{13}C satellites (red) in the inset of the lower trace. The NOE effect, obtained by irradiating the ^{13}C satellites, is displayed in the top trace (red). Right: methyl signal of **6b** (600 MHz in acetone-d_6 at 0 °C) with the amplified ^{13}C satellites (blue) in the inset of the lower trace. The absence of NOE effect, on irradiation of the ^{13}C satellites, is clearly evident in the top trace (blue).

state, a result which agrees with the computations predicting the anti to be more stable by 1.1 kcal mol^{-1} than the syn (Figure 4): also the DFT calculations of chemical shifts confirm such an assignment. According to computations the dihedral angle between the aryl rings and the biphenylene moiety (81°) is very close to 90°; thus, only one type of conformer anti occurs in **4**, because the anti-in and anti-out conformations of Figure 1 become essentially indistinguishable when the planes are nearly orthogonal: the same value for this dihedral angle was also found in the X-ray structure.[27]

The barrier measured for **4** (17.0 kcal mol^{-1}) indicates that even the presence of the large *tert*-butyl group in the ortho position of the benzene rings is not sufficient to allow a physical separation of the anti and syn forms at ambient temperature, in that the lifetime of the corresponding conformers is exceedingly short ($t_{1/2} \approx 0.3$ s at +25 °C).

Such a separation could be, however, achieved in the case of compound **6**, were two β-methylnaphthyl rings are bonded to the biphenylene moiety in the 1,8 positions: computations predict, in fact, a barrier as high as 34.7 kcal mol^{-1} (Table 1) for the corresponding naphthylbiphenylene rotation process. The two isomers, indicated as **6a** and **6b**, were isolated at ambient temperature by HPLC, and their structural assignment was carried out with an alternative NOE approach, which was found more appropriate for the present case.

Following the procedure reported[28] for the assignment of symmetric isomers, the ^{13}C satellites of the methyl signals of **6a** and of **6b** (both with $J_{CH} = 126.7$ Hz) were irradiated at a temperature of 0 °C.[29] As shown in Figure 5, simultaneous irradiation of the two satellite lines of the isomer having the lower field methyl signal at 2.08 ppm (**6a**) yields a NOE effect, indicating that this signal must be that of the isomer syn, where the hydrogens of the two methyl groups are sufficiently close to experience a reciprocal NOE enhancement. On the other hand, irradiation of the satellites of the compound having the higher field methyl signal at 1.52 ppm (**6b**) does not produce any NOE effect, indicating that this signal corresponds to the isomer anti,[30] where the hydrogens of the two methyl groups are too far apart to experience a reciprocal NOE enhancement. In this way, an unambiguous assignment could be achieved for the isomers **6a** (syn) and **6b** (anti).

The process leading to the interconversion of the configurationally stable isomers of **6** was followed by monitoring the time dependence of the NMR methyl signal of the pure syn isomer (**6a**) in DMSO at +140 °C. The intensity of the original methyl line of **6a** decreases, while that of the anti isomer **6b** begins to appear at higher field with an intensity which increases until an equilibrium, corresponding to a syn/anti ratio of 36:64 (Table 1), is reached (as in the case of compounds **2**−**5** the anti is more stable than the syn in equilibrium conditions). From the first-order kinetics equation for a process at the equilibrium, the appropriate rate constants were obtained (details in Figure S-4 of the Supporting Information), and the barrier for exchanging the more (anti, **6b**) into the less (syn, **6a**) stable isomer was derived ($\Delta G^{\ddagger} = 34.5$ kcal mol^{-1}). The result agrees well with the DFT computed value (34.7 kcal mol^{-1}) reported in Table 1.

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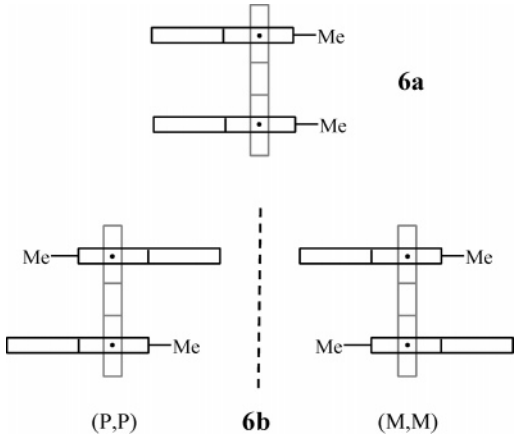
(29) The temperature of 0 °C was selected in order to obtain a better signal to noise ratio in the DPFGSE-NOE experiment. In order to avoid the interference of the HDO signal (present as an impurity in our $CDCl_3$) with the signals of **6b**, the spectrum of the latter was obtained in acetone-d_6 (the impurity of HDO in our acetone-d_6 lies in a position that does not interfere with the signals of **6b**).

(30) The isomer anti (**6b**) displays a methyl signal at a substantially higher field than the methyl signal of the isomer syn (**6a**) owing to the effect of the aromatic ring currents, since in the anti situation the methyl groups lie above the plane of the naphthalene rings, see: Jackman, L. M.; Sternhell, S. *Applications of NMR Spectroscopy in Organic Chemistry*, 2nd ed.; Pergamon Press: Oxford, 1969; p 95. Jennings, W. B.; Farrell, B. M.; Malone, J. F. *Acc. Chem. Res*. **2001**, *34*, 885. Wüthrich, K. *Angew. Chem., Int. Ed*. **2003**, *42*, 3340.

SCHEME 1. Schematic Representation of the Syn (Meso), 6a, and Anti (Racemic), 6b, Isomers of Compound 6



The syn isomer **6a** (C_s point group), having two equal stereogenic axes with opposite (M,P) handedness, corresponds to a meso form, whereas the anti isomer **6b** (C_2 point group) exists as a pair of enantiomers (M,M and P,P),[31,32] as illustrated in Scheme 1. The two enantiomers of **6b** were separated by enantioselective HPLC, and the corresponding CD spectra display the two opposite signed traces shown in Figure 6. The intense band at ~215 nm is due to the ^{1}B transition of naphthalene, and that at ~255 nm is that of the biphenylene moiety (these bands are also observed at the same wavelengths in the experimental UV spectrum as in Figure S-5 of the Supporting Information). In order to assign the absolute configuration (AC), the CD spectrum of one enantiomer is calculated by theoretical methods and its shape (and intensity) compared with that of the experimental spectrum. If they match, the AC assumed in the calculations should then be assigned to the enantiomer whose experimental spectrum has been recorded.

For this approach, use was made of the TDDFT method (implemented in the Gaussian 03 program[15]), since such a technique has been successfully employed several times[33] to predict CD spectra (the geometry had been already optimized at the B3LYP/6-31G(d) level). As shown in Figure 6, the CD

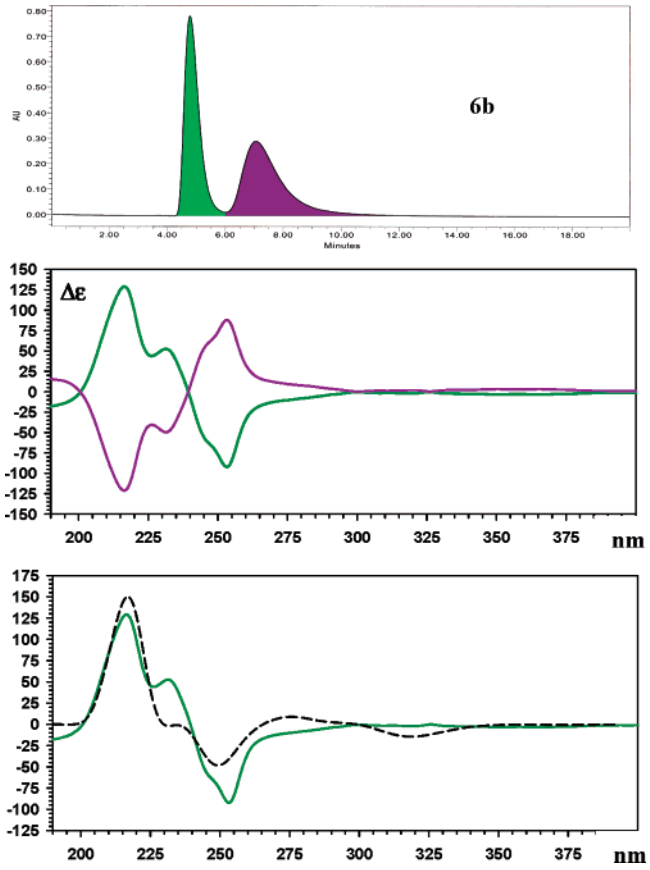


FIGURE 6. Enantioselective HPLC trace of the two enantiomers of the anti isomer **6b** (top). CD spectra of the two enantiomers (middle). Computed CD spectrum (blue-shifted by 7 nm, dashed trace) for the M,M configuration, compared with the experimental spectrum (green) of the first eluted enantiomer (bottom).

spectrum calculated by assuming the M,M configuration has a shape analogous to that of the spectrum of the first eluted enantiomer, with a significant positive Cotton effect at lower wavelengths (~220 nm), as well as a significant negative effect at higher wavelengths (~255 nm). Accordingly, the first eluted enantiomer has the M,M configuration and, as a consequence, the P,P configuration must be assigned to the second eluted enantiomer. (In the Supporting Information, the velocity rotational strengths are plotted in Figure S-6 and the transitions energies, oscillator strengths and rotational strengths of the absolute configuration M,M for the lowest 60 states are collected in Table S-1.)

Experimental Section

Materials. 2-Methylphenylboronic acid, 2-ethylphenylboronic acid, 2-isopropylphenylboronic acid, and 2,3-dimethylphenylboronic acid were commercially available. 1,8-Dibromobiphenylene,[34] 1,3-

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dibromo-2-iodobenzene,[35] and 2-methylnaphthylboronic acid[36] were prepared according to the literature. 2-*tert*-Butylphenylboronic acid was prepared following known procedures[37] (see the Supporting Information for details).

General Procedure for 1−5. To a solution of 1,8-dibromobiphenylene (0.062 g, 0.2 mmol, in 2 mL of benzene) were added K_2CO_3 (2 M solution, 1.0 mL), the appropriate boronic acid (0.5 mmol, suspension in 2 mL of ethanol), and $Pd(PPh_3)_4$ (0.046 g, 0.04 mmol) at room temperature. The stirred solution was refluxed for 2−3 h, and the reaction was monitored by GC−MS to confirm the first coupling. After the mixture was cooled to room temperature, a second amount of boronic acid (0.5 mmol, suspension in 2 mL of ethanol) and $Pd(PPh_3)_4$ (0.046 g, 0.04 mmol) were added, and the solution was refluxed again for 2 h. Subsequently, $CHCl_3$ and H_2O were added, and the extracted organic layer was dried (Na_2SO_4) and evaporated. The crude products were prepurified by chromatography on silica gel (hexane/Et_2O 10:1) to obtain mixtures containing the target compounds, together with biphenylene, 1-bromobiphenylene, 1-aryl-biphenylene, and 1-aryl,8-bromobiphenylene as impurities. Analytically pure samples of **1**−**5** were obtained by semipreparative HPLC on a C18 column (5 μm, 250 × 10 mm, 5 mL/min, ACN/H_2O; see the Supporting Information for more details). Crystals suitable for X-ray analysis were obtained from chloroform, by slow evaporation, in the cases of **1** and **4**. Detailed spectroscopic data for compounds **2**−**5** are reported in the Supporting Information.

1,8-Di(*o*-tolyl)biphenylene (1). ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS): δ 1.89 (6H, s), 6.66 (6H, m), 6.80 (6H, m), 6.93 (2H, td, J = 7.4, 1.6 Hz). ^{13}C NMR (150.8 MHz, $CDCl_3$, 25 °C, TMS): δ 19.7 (CH_3), 115.6 (CH), 124.8 (CH), 127.1 (CH), 128.2 (CH), 128.2 (CH), 129.4 (CH), 130.3 (CH), 132.5 (q), 135.0 (q), 137.6 (q), 149.6 (q), 150.8 (q). HRMS(EI): *m*/*z* calcd for $C_{26}H_{20}$ 332.15650, found 332.1564.

1,8-Bis(2-methylnaphthalen-1-yl)biphenylene (6). To a solution of 1,8-dibromobiphenylene (0.062 g, 0.2 mmol, in 2 mL of benzene) were added K_2CO_3 (2 M solution, 1.0 mL), 2-methylnaphtylboronic acid (0.5 mmol, suspension in 2 mL of ethanol), and $Pd(OAc)_2$ (0.009 g, 0.04 mmol) at room temperature. The stirred solution was refluxed for 48 h, and the reaction was monitored by GC−MS to confirm the first coupling had achieved. Subsequently, $CHCl_3$ and H_2O were added, and the extracted organic layer was dried (Na_2SO_4) and evaporated. The crudes was prepurified by chromatography on silica gel (hexane/Et_2O 10:1) to obtain a mixture that was further purified by preparative HPLC on a C18 column (10 μm, 250 × 21.2 mm, 24 mL/min, ACN/H_2O 90:10 v/v), to obtain 0.052 g (60%) of 1-bromo-8-(2-methylnaphthalen-1-yl)biphenylene. To a solution of this intermediate, (0.052 g, 0.12 mmol, in 2 mL of benzene) were added K_2CO_3 (2 M solution, 1.0 mL), 2-methylnaphtylboronic acid (0.5 mmol, suspension in 2 mL of ethanol), and $Pd(PPh_3)_4$ (0.046 g, 0.04 mmol), the solution was stirred for 48 h, and the reaction was monitored by GC−MS. Subsequently, $CHCl_3$ and H_2O were added, and the extracted organic layer was dried (Na_2SO_4) and evaporated. The crude was prepurified by chromatography on silica gel (Hexane/Et_2O 10:1) to obtain purified mixtures containing the title compound and 1-(2-methylnaphthalen-1-yl)biphenylene as impurity. Separation of the two isomers **6a** and **6b** was obtained in two steps: the pair was first separated from the impurity by preparative HPLC on a C18 column (10 μm, 250 × 21.2 mm, 24 mL/min, ACN/H_2O 95:5 v/v), then the separation of the two isomers was obtained by joining a C18 and a C8 semipreparative HPLC columns (first column: Kromasil C18, 5 μm, 250 × 10 mm; second column: Luna C8(2), 5 μm, 250 × 10 mm, 5 mL/min, ACN/H_2O 90:10 v/v). A total amount of 0.015 g of the anti isomer **6b** (first eluted) and 0.005 g of the syn isomer **6a** (second eluted) were obtained.

1,8-Bis(2-methylnaphthalen-1-yl)biphenylene, Syn Isomer (6a). ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS): δ 2.09 (6H, s), 6.51 (2H, d, J = 8.2 Hz), 6.75−6.84 (10H, m), 7.17−7.23 (6H, m). ^{13}C NMR (150.8 MHz, $CDCl_3$, 25 °C, TMS): δ 20.5 (CH_3), 115.9 (CH), 123.8 (CH), 125.0 (CH), 125.05 (CH), 127.1 (CH), 127.2 (CH), 127.3 (CH), 128.3 (CH), 129.9 (q), 130.98 (q), 131.0 (q), 131.4 (CH), 131.8 (q), 133.1 (q), 150.8 (q), 151.3 (q). HRMS-(EI): *m*/*z* calcd for $C_{34}H_{24}$ 432.18780, found 432.1876.

1,8-Bis(2-methylnaphthalen-1-yl)biphenylene, Anti Isomer (6b). ^{1}H NMR (600 MHz, acetone-d_6 25 °C): δ 1.55 (6H, s), 6.33 (2H, d, J = 8.4 Hz), 6.50 (2H, d, J = 8.1 Hz), 6.87 (2H, d, J = 6.7 Hz), 6.92 (2H, dd, J = 8.1, 6.9 Hz), 7.27 (2H, d, J = 8.4 Hz), 7.31−7.37 (4H, m), 7.44 (2 H, d, J = 8.2 Hz), 7.67 (2H, d, J = 8.0 Hz). ^{13}C NMR (150.8 MHz, acetone-d_6, 25 °C): δ 19.7 (CH_3), 116.5 (CH), 124.3 (CH), 125.2 (CH), 125.5 (CH), 127.3 (CH), 127.6 (CH), 128.1 (CH), 128.9 (CH), 130.2 (q), 131.0 (CH), 131.72 (q), 131.74 (q), 132.5 (q), 133.1 (q), 150.8 (q), 151.6 (q). HRMS(EI): *m*/*z* calcd for $C_{34}H_{24}$ 432.18780, found 432.1877.

Enantioselective HPLC and CD Spectra. Separation of the two enantiomers of **6b** was achieved at 25 °C on a Chiralcel OJ-H 250 × 4.6 mm column, at a flow rate of 1.0 mL/min, using hexane/iPr-OH 95:5 v/v as eluent. In order to have the sufficient amount to record the CD spectra, 10 injections (50 μg each one) were collected. UV detection was fixed at 225 nm. UV absorption spectra were recorded at 25 °C in hexane on the racemic mixture, in the 190−400 nm spectral region. The cell path length was 0.1 cm, concentration was 1.43×10^{-4} mol L^{-1}. Maximum molar absorption coefficient was recorded at 218 nm (ϵ = 66670). CD spectra were recorded at 25 °C in hexane, with the same path lengths of 0.1 cm, in the range 190−400 nm; reported $\Delta\epsilon$ values are expressed as L $mol^{-1}cm^{-1}$.

NMR Spectroscopy. The spectra were recorded at 600 MHz for ^{1}H and 150.8 MHz for ^{13}C. The assignments of the ^{1}H and ^{13}C signals were obtained by bi-dimensional experiments (edited-gHSQC[38] and gHMBC[39] sequences). Temperature calibrations were performed before the experiments, using a Cu/Ni thermocouple immersed in a dummy sample tube filled with isopentane, and under conditions as nearly identical as possible. The uncertainty in the temperatures was estimated from the calibration curve to be ±1 °C. The line shape simulations were performed by means of a PC version of the QCPE program DNMR 6 no. 633, Indiana University, Bloomington, IN. Kinetic equilibration of compound **6** was obtained by heating a NMR sample of pure **6a** in DMSO-d_6 into a thermostatic oil bath, kept at +140 °C. NMR spectra were then recoded at regular times until the equilibrium was reached (see Figure S4 of the Supporting Information.)

Calculations. Geometry optimizations were carried out at the B3LYP/6-31G(d) level by means of the Gaussian 03 series of programs[15] (see the Supporting Information): the standard Berny algorithm in redundant internal coordinates and default criteria of convergence were employed. The reported energy values are not ZPE corrected. Harmonic vibrational frequencies were calculated for all the stationary points. For each optimized ground state the frequency analysis showed the absence of imaginary frequencies, whereas each transition state showed a single imaginary frequency. Visual inspection of the corresponding normal mode was used to confirm that the correct transition state had been found. NMR chemical shift calculations were obtained with the GIAO method at the B3LYP/6-311++G(2d,p)//B3LYP/6-31G(d) level. TMS, calculated at the same level of theory, was used as reference to scale the absolute shielding value. TDDFT calculations on the M,M enantiomer of **6b** were obtained at the B3LYP/6-31+G(d,p)//

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B3LYP/6-31G(d) level. In order to cover the whole 190−400 nm range, 60 transitions were calculated. The CD spectrum was then obtained by applying a 0.3 eV Gaussian band shape.[40]

Acknowledgment. L.L. and A.M. received financial support from the University of Bologna (RFO) and from MUR-COFIN 2005, Rome (national project "Stereoselection in Organic Synthesis").

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Supporting Information Available: Low-temperature NOE spectra of compounds **2** and **5**; VT-NMR spectra of **3**; kinetic data for compound **6**; calculated and experimental UV spectrum of **6b**; calculated velocity rotational length and CD spectrum of (*M*,*M*)-**6b**; X-ray data of compounds **1** and **4** (CIF); experimental procedure for the preparation of 2-*tert*-butylphenylboronic acid; spectroscopic data of compounds **2**−**5**; ^{1}H and ^{13}C NMR spectra and HPLC traces of **1**−**6**; chemical shift calculations and computational data of **1**−**6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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