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Atropisomeric (*R,R*)-2,2′-Bi([2]paracyclo[2](5,8)quinolinophane) and (*R,R*)-1,1′-Bi([2]paracyclo[2](5,8)isoquinolinophane): Synthesis, Structural Analysis, and Chiroptical Properties

Giacomo Ricci,[†] Renzo Ruzziconi,*[,†] and Egidio Giorgio[‡]

Dipartimento di Chimica, Università di Perugia, via Elce di Sotto, 8 06123 Perugia, Italy, and Dipartimento di Chimica, Università della Basilicata, Via N. Sauro 85, 85100 Potenza, Italy

ruzzchor@unipg.it

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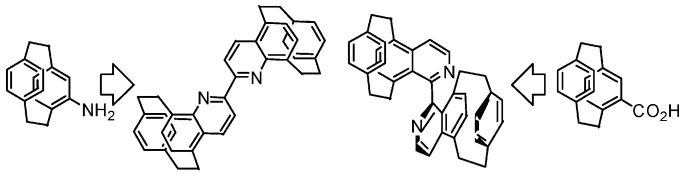

(*R,R*)-1 $[\alpha]_D^{20} = -10$ **(*R,R*)-2** $[\alpha]_D^{24} = +414$

Atropisomeric (*R,R*)-2,2′-bi([2]paracyclo[2](5,8)quinolinophane) [**(*R,R*)-1**] and (*R,R*)-1,1′-bi([2]-paracyclo[2](5,8)isoquinolinophane) [**(*R,R*)-2**] have been prepared in moderate overall yield (17 and 9%, respectively) by a four-step sequence starting from (*R*)-(−)-4-amino[2.2]paracyclophane and (*R*)-(−)-4-carboxy[2.2]paracyclophane, respectively. The structures have been determined on the basis of NOE ^{1}H NMR analysis and molecular mechanics (MM) calculations performed with a Spartan02 program, using the MMF94s force field. A preliminary, qualitative analysis of the chiroptical properties of these two compounds has also been attempted. The main spectral data can be interpreted in terms of an almost planar 2,2′-bisquinoline chromophore inserted in a paracyclophane structure in the case of **(*R,R*)-1**, while in the case of **(*R,R*)-2**, the main role is played by a distorted 1,1′-bisisoquinoline chromophore. On the basis of the above structural results, a hypothesis about the enantioselection capability of these two molecules has also been formulated.

Chiral C_2-symmetric N,N-donor ligands have recently received renewed attention as valuable ligands of transition metals in homogeneous stereoselective catalysis.[1] Among these, bisoxazolines,[2] semicorrines,[3] and salen-type chelating ligands [4] are the most widely used in transition-metal-catalyzed asymmetric reactions. Particular interest has been devoted to bipyridine-based ligands whose chirality is often due to the presence of stereogenic centers as substituents, mostly in the 6,6′ positions, of the heterocyclic ring.[5] However, applications to stereoselective syntheses of atropisomeric diazabiaryl derivatives exhibiting only axial chirality are little known. The reason for such scarce consideration rests in the poor conformational stability of the chiral atropisomers due to the low rotational barrier.[6] Conformational stability can be substantially increased by dialkyl substitution or anellation at 3,3′-position of the heterocyclic rings. In this case, it depends on the size of the

[†] Università di Perugia.

[‡] Università della Basilicata.

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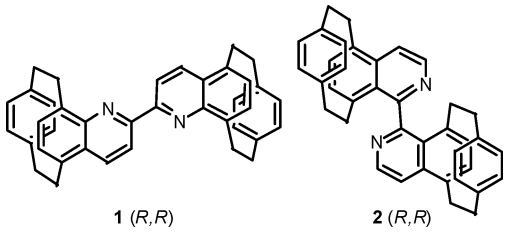
bridge. For instance, 3,3′ dimethylene- and trimethylene-bridged in 2,2′-pyridine and 2,2′-diquinoline undergo rapid conformational inversion, whereas the 3,3′-tetramethylene-bridged systems are conformationally so stable that the racemic mixture can be resolved.[7]

Conformationally very stable 2,2′-diazabiaryl ligands can also be obtained by alkyl substitution, or anellation, at the 3,3′position of the corresponding *N*-oxides. Accordingly, racemic mixtures of 3,3′-disubstituted 2,2′-bipyridine and 2,2′-biquinoline *N*,*N*′-dioxides have been easily resolved and the enantiomers successfully employed as ligands in several transition-metal-catalyzed enantioselective reactions.[8]

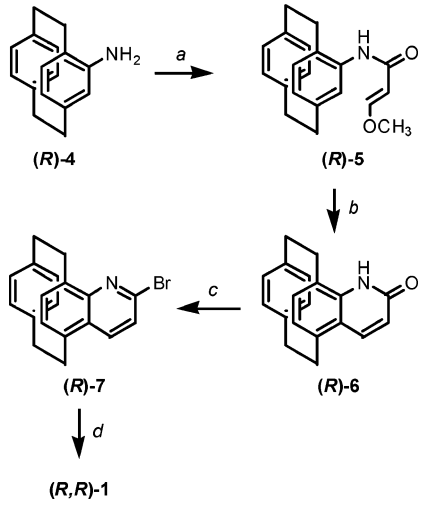
The low barrier to the rotation around the bond linking the heterocyclic moieties, created by the repulsion of the nitrogen lone pairs, is also responsible for the rapid one-step atropisomerization at the anti configuration of axially chiral 1,1′-biisoquinolines, especially when bulky alkyl groups are present in the 8,8′-positions.[9] Only *N*,*N*′-dioxide exhibits a substantial conformational stability allowing the racemic mixture to be easily resolved.[10]

The presence of chiral substituents of the same configuration at the *n*,*n*′-positions of C_2-symmetric diazabiaryl ligands inevitably induces diastereoisomerism. How the presence of stereogenic centers or other types of chirality affects the atropisomerism of this class of compounds and eventually the diastereomeric ratio (for instance, the (*R,P,R*)/(*R,M,R*)[11] ratio) of chiral diazabiaryl derivatives is still an intriguing question. Our interest in the chemistry of chiral [2.2]paracyclophane-based ligands [12] spurred us to investigate the contribution of the planar chirality to the conformational stability of some chiral biquinolinophanes. In this paper we report the synthesis, the structural analysis (by ^{1}H NMR spectroscopy and molecular mechanics calculations), and an unprecedented first qualitative investigation about the chiroptical properties of the (*R*,*R*)-2,2′-bi([2]paracyclo[2](5,8)quinolinophane) [**(*R,R*)-1**] and (*R,R*)-1,1′-bi([2]paracyclo[2](5,8)isoquinolinophane) [**(*R,R*)-2**] (Chart 1).

CHART 1



SCHEME 1[a]



[a] Key: (a) (1) BuLi, (2) MeOCH=CHCO$_2$Me, THF, rt; (b) conced HCl;(c) POBr$_3$, 120 °C, 1.5 h; (d) NiCl$_2$·6H$_2$O, PPh$_3$, Zn, DMF, 50 °C, 1 h.

Results and Discussion

(*R,R*)-2,2′-Bi([2]paracyclo[2](5,8)quinolinophane) [(*R,R*)-1]. (*R*)-(−)-4-Carboxy[2.2]paracyclophane [**(*R*)-3**] was the selected precursor of both biquinolinophane **(*R,R*)-1** and biisoquinolinophane **(*R,R*)-2**. From the acid **3**, (*R*)-(−)-4-amino[2.2]paracyclophane [**(*R*)-4**] was prepared in four steps in excellent overall yield (>95%) and on a multigram scale through a slightly modified Curtius rearrangement of the acylzide, followed by the alkaline hydrolysis of the resulting isocyanate. The lithium amide, obtained by the reaction of **(*R*)-4** with butyllithium, was made to react with ethyl 3-methoxyacrylate to obtain the corresponding amide **(*R*)-5** in 40% yield (Scheme 1). Acid-catalyzed cyclization converted **(*R*)-5** into the 2-quinolone **(*R*)-6** from which the expected 2-bromoquinolinophane **(*R*)-7** was obtained in fairly good yield by treatment with POBr$_3$. Finally, Ni(0)-catalyzed homocoupling of **(*R*)-7** in DMF [14] allowed the biquinolinophane **(*R,R*)-1** to be obtained in satisfactory yield (72%).

^{1}H NMR Analysis and Theoretical Calculations. ^{1}H NMR analysis turned out to be a valuable tool for drawing the structure of **(*R,R*)-1** in solution in its more stable conformation. Four AB systems can be identified in the range of aromatic protons which are attributable

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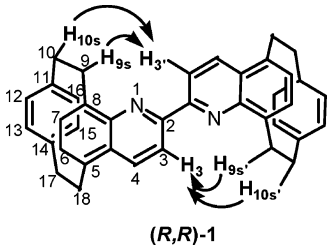

FIGURE 1. NOE in the most stable conformation of **(*R*,*R*)-1**.

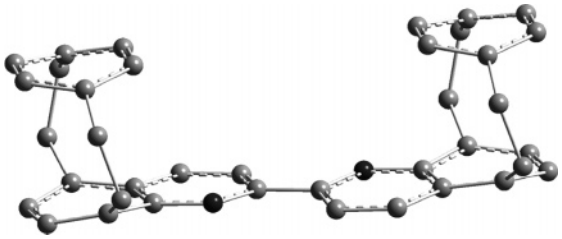

FIGURE 2. Most stable conformation of **(*R*,*R*)-1**.

to the four pair of protons of the quinolinophane moieties. The highest field AB system centered at δ 5.74 can certainly be attributed to the two protons (H-15 and H-16) of the phenyl ring overlooking the quinoline moiety and falling into the shielding cone of the heterocyclic ring.

In this respect, the most significant ^{1}H NMR signals fall at δ 8.17 and 8.86 ppm, assigned to H-4 and H-3, respectively, and at δ 4.54 and 3.83 assigned to the two protons H-9s and H-18s which are almost coplanar with the quinoline moiety and turned toward the heterocyclic ring (Figure 1).

The presence of a substantial NOE between H-3′ and H-9s is consistent with a stable conformation where the two 2,2′-bonded quinolinophane moieties are nearly coplanar, the nitrogen atoms being placed anti each other.

Furthermore, a weak NOE between protons H-3 and H-10′ suggests that the two quinoline moieties are slightly rotated around the C-2−C-2′ bond so that C-3−H-3 bond points to the middle of the C-9′−C-10′ bridge. A theoretical conformational analysis, performed with the Spartan02 program, using the MMFF94s force field,[15] seems to confirm the above conclusions. According to the calculations, **(*R*,*R*)-1** would exist in only one conformation (Figure 2) with the nitrogen atoms anti each other and a dihedral angle N−C−C−N of −173°.

$[\alpha]_D$, Absorption and Circular Dichroism (CD) Spectra. Biquinolinophane **(*R*,*R*)-1** shows low values of optical rotation ($[\alpha]_D$ +36 (*c* 0.027, THF) or −10 (*c* 0.11, $CHCl_3$)), which are also strongly solvent-dependent. The absorption and circular dichroism (CD) spectra of **(*R*,*R*)-1**, measured in THF, are reported in Figure 3.

Four main absorption regions can be easily identified in the UV spectrum: a first maximum is observed at about 360 nm (ϵ ca. 20 000), a second one is centered at about 300 nm (ϵ ca. 30 000) with a definite shoulder at 250 nm (ϵ ca. 20 000), followed by an intense absorption at 200 nm (ϵ ∼60 000, THF cutoff). The CD spectrum looks quite complex: in fact, the lowest-energy Cotton

(15) *Spartan02*; Wavefunction Inc., Irvine, CA, 2002.

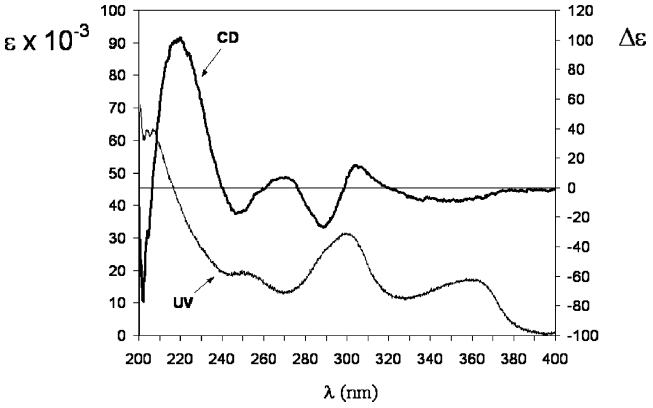

FIGURE 3. UV and CD spectra of **(*R*,*R*)-1**.

effect is located at ca. 360 nm ($\Delta\epsilon$ −10), followed by a sequence of positive/negative CD bands ($\Delta\epsilon$ +20, −25, +5, and −15 at 310, 290, 270, and 250 nm, respectively). The complex shape of the CD spectrum of **(*R*,*R*)-1** explains why its $[\alpha]_D$ is so low: notice that a series of positive/negative Cotton effects, having similar intensities, is present down to 240 nm. If one considers that the OR at the sodium D line can be calculated by the Kronig−Kramers transform, which can assume the following approximate form[16]

$$[\alpha]_D = (9151/MW)\Sigma_i(R_i\lambda_i^2/(589^2 - \lambda_i^2)) \qquad (1)$$

where MW is the molecular weight and R_i is the rotational strength corresponding to the electronic transitions occurring at λ_i, it results that the contributions coming from the sequence of CD bands at wavelengths longer than 240 nm tend to cancel each other and in practice only the 220 nm positive Cotton effect will provide a contribution to the $[\alpha]_D$. However, its absolute value would not be large, taking into account the distance, on the wavelength scale, from the sodium D line; i.e., the denominator of eq 1 will be large. Accordingly, a small value of the optical rotation at 589 nm would be expected. To formulate some spectrum/structure relationships, following an established procedure[17] based on the exciton coupling optical activity,[18] **(*R*,*R*)-1** could be considered, from the optical properties point of view, as an aggregate of the *transoid*-2,2′-bi(quinoline) chromophore and two, suitably disposed, *p*-xylene chromophores. Such a procedure requires knowledge of the spectroscopic properties of the two chromophores. Whereas the spectroscopic characteristics of *p*-xylene are well-known,[17] those of 2,2′-bis(quinoline) have not been reported. However it is reasonable to invoke the presence of such a chromophore because the absorptions at 360 and 300 nm in the UV spectrum of **(*R*,*R*)-1** cannot be ascribed to the simple quinoline chromophore (which absorbs below 300 nm [19]). By contrast, the NMR and

(16) To this end, the simple Kronig−Kramers transforms formulas (eq 10) of Moscowitz have been used: Moscowitz, A. Theory and analysis of rotatory dispersion curves. In Optical Rotatory Dispersion: Application to Organic Chemistry; Djerassi, C., Ed.; McGraw-Hill Publ.: New York, 1960; Chapter 12.

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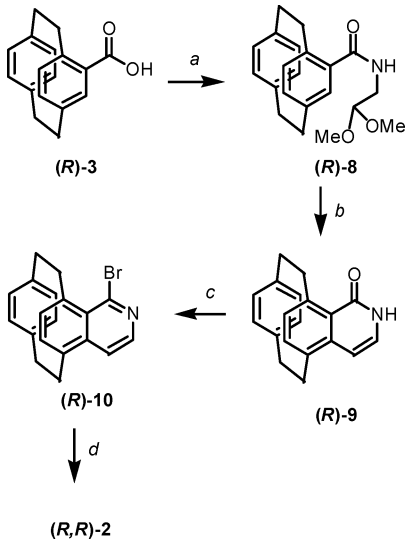
computational results discussed previously, point out that the most stable conformer of **(*R*,*R*)-1** contains an almost planar *transoid*-2,2′-bis(quinoline) group. Such a largely conjugate system could show absorption bands at much longer wavelengths than quinoline. Therefore, the analysis of the chiroptical properties of **(*R*,*R*)-1** in terms of exciton coupling optical activity requires the complete characterization of the above *transoid*-2,2′-bis(quinoline) chromophore followed by some coupled-oscillator calculations using, for instance, the DeVoe model.[20] Alternately, a quantum-chemical treatment of the CD spectrum (at a semiempirical or ab initio level)[21] could be carried out, but these kinds of analyses are well beyond the scope of the present paper and will be the object of a future study.

(*R*,*R*)-1,1′-Bi[2]paracyclo[2](5,8)isoquinolinophane [(*R*,*R*)-2]. In the synthesis of **(*R*,*R*)-2**, the acid **(*R*)-3** was treated with $SOCl_2$ and the resulting acyl chloride was made to react with aminoacetaldehyde diethyl acetal to give the amidoacetal **(*R*)-8** in 99% yield (Scheme 2). Cyclization of **(*R*)-8** in polyphosphoric acid at 100 °C gave the expected 1-isoquinolone **(*R*)-9** (47% yield) which was transformed into the 1-bromoisoquinolinophane **10** (45%) by treatment with $POBr_3$. Again, the Ni(0)-catalyzed homocoupling of **10** in DMF allowed the desired biisoquinolinophane **(*R*,*R*)-2** to be obtained in 42% yield.

^{1}H NMR Analysis and Theoretical Calculations. In the frequency range of the aromatic protons the ^{1}H NMR spectrum of 1,1′-biisoquinolinophane **(*R*,*R*)-2** is substantially different from that observed for 2,2′-quinolinophane **(*R*,*R*)-1** and some considerations may be useful for drawing the conformational structure. In this case too, four AB systems can be identified which are attributable to the four pairs of protons of the quinolinophane moieties.

The two doublets at δ 8.84 and 7.70 can be assigned to proton H-3 and H-4, respectively, whereas the AB system at δ 5.93−5.80 is certainly attributable to the two protons of the phenyl ring overlooking the quinoline moiety. Significantly, the signals of H-3 and H-3′ are shifted at upper field compared with the corresponding proton of **(*R*,*R*)-1** (Figure 4).

SCHEME 2[a]



[a] Key: (a) (1) $SOCl_2$, rt, 12 h, (2) $H_2NCH_2CH(OEt)_2$, Et_2O, 25 °C; (b) polyphosphoric acid, 110 °C, 30 min; (c) $POBr_3$, 100 °C, 7 h; (d) $NiCl_2{\cdot}6H_2O$, PPh_3, Zn, DMF, 50 °C, 1 h.

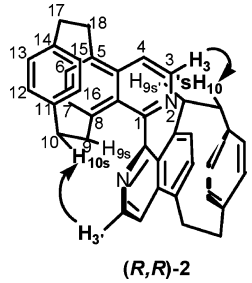


FIGURE 4. NOE of the most stable conformation of **(*R*,*R*)-2**.

With respect to **(*R*,*R*)-1**, the chemical shift values of the corresponding protons H-15 and H-16 in biisoquinolinophane **(*R*,*R*)-2** are significantly higher ($\Delta\delta$, +0.1 and 0.2 ppm, respectively). This is consistent with an almost perpendicular arrangement of the two C-1-C-1′-bonded isoquinoline moieties, with the protons H-15 and H-16 of one quinolinophane moiety falling into the deshielding cone of the other.

Moreover, the two protons of the ethylenic bridges turned toward the heterocyclic ring (H-9s and H-10s) resonate at abnormally high field (δ 0.88 and 1.96, respectively) compared with the corresponding proton in biquinolinophane **(*R*,*R*)-1** (δ 4.55 and 3.2, respectively). The most plausible explanation is that the two isoquinoline moieties are rotated around the C-1−C-1′ bond defining a substantial dihedral angle θ. In such way, H-9s and H-10s protons of one quinolinophane moiety fall into the shielding cone of the other. Thus, H-9, the proton of the bridge resonating at the lowest field in 2,2′-biquinolinophane **(*R*,*R*)-1** becomes the highest field resonating proton in 1,1′-biisoquinolinophane **(*R*,*R*)-2**. NOE experiments also confirm this conformational hypothesis. Accordingly, a substantial interaction is observed between the protons H-3 and H-10′ and to a lesser extent between the proton H-4-and H-9′. Therefore, the conformation *pR*,*aS*,*pR* (chiral axis nomenclature) or *R*,*P*,*R* (helix nomenclature) can be unequivocally assigned to the biisoquinolinophane **(*R*,*R*)-2**.

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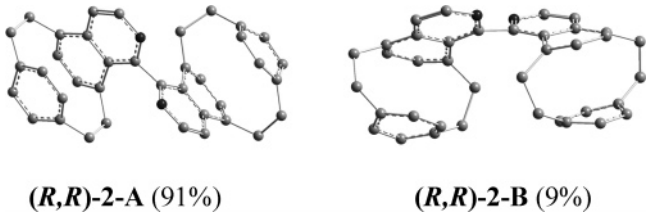


FIGURE 5. Conformations of **(*R*,*R*)-2:** (a) more stable; (b) less stable.

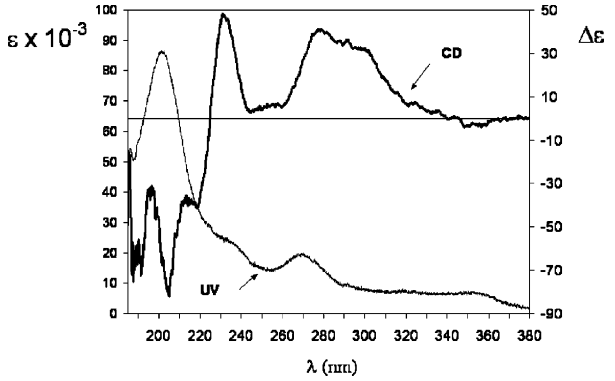


FIGURE 6. UV and CD spectra of **(*R*,*R*)-2**.

The above NMR conclusions are in keeping with the results of molecular mechanics calculations, similar to those carried out previously.[15] In fact, two conformers have been identified for **(*R*,*R*)-2**: the conformer **(*R*,*R*)-2-A** having the (*R*,*P*,*R*) configuration, where the two isoquinoline rings define a dihedral angle θ of about 72° (Figure 5a), and the conformer **(*R*,*R*)-2-B** has a (*R*,*M*,*R*) configuration, where the same angle is −134° (Figure 5b).

According to the energy values provided by these calculations, conformer **(*R*,*R*)-2-A** is largely prevalent (91%).

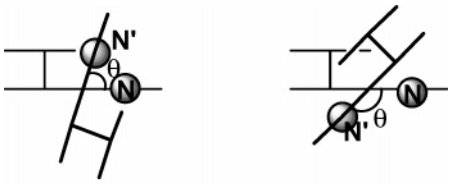
$[\alpha]_D$, Absorption ,and Circular Dichroism (CD) Spectra. Biisoquinolinophane **(*R*,*R*)-2** shows $[\alpha]_D$ +468 (*c* 0.5, $CHCl_3$), +556 (c 0.05, MeOH), +437 (*c* 0.027, CH_3CN), which are very strong positive values that are slightly solvent-dependent.[22] The UV and CD spectra of **(*R*,*R*)-2**, measured in CH_3CN, are reported in Figure 6.

In the electronic spectrum four main regions of absorption can be easily identified: a long absorption tail occurs from 360 nm down to 290 nm (ϵ ca. 10 000), a maximum is centered at about 270 nm (ϵ ca. 20 000) with a definite shoulder at 240 nm (ϵ ca. 25 000), followed by an intense absorption maximum (ϵ ca. 90 000) at about 205 nm. The CD spectrum shows a very broad, intense Cotton effect located between 340 and 260 nm ($\Delta\epsilon_{max}$ +30, and +40 at 290 and 275 nm, respectively), followed by a sequence of positive/negative CD bands ($\Delta\epsilon$ +50 and $\Delta\epsilon$ −35 at 220 and 235 nm, respectively). Below 220 nm, at least one other negative CD band can be observed at 205 nm ($\Delta\epsilon$ −80). The high value of optical rotation measured for **(*R*,*R*)-2** can be explained following the same reasoning as for **(*R*,*R*)-1**. Now the two lowest energy (at 280−300 and 235 nm) positive Cotton effects dominate (they are near 589 nm and provide an OR value at the sodium D line of +811, i.e., a value which is larger than the experimental one!). The contributions coming from the higher energy and negative CD bands (below 220 nm, far away from 589 nm) are certainly smaller and can only reduce the 811 value, and therefore, a large OR value is expected.

It is noteworthy that the UV spectrum of **(*R*,*R*)-2** closely resembles that of 8,8′-dimethyl-1,1′-biisoquinoline [**(*R*)-11**],[9a] which exhibits an almost constant absorption (ϵ about 10 000) in the region down to 250 nm, followed by a broad high intensity (ϵ ca. 70 000) band in the 250−200 nm region, with a maximum at ca. 220 nm. These absorption features are related to a distorted 1,1′-biisoquinoline chromophore: the dihedral angle θ between the aryl planes [9a] being 102° (when evaluated from the crystal structure) or 90.2° (by AM1 calculations). The CD spectrum of this derivative is quite simple: for the (*R*) absolute configuration we have a positive Cotton effect ($\Delta\epsilon$ + 10 ca.) at ca. 320 nm, followed by a strong negative couplet (−160, +240 ca.) centered at 230 nm. It is well-known, since the seminal paper of Mason and coworkers [23a] on the analysis of CD spectra of biaryl derivatives, that the strong couplet effect is due to the exciton coupling of the intense electronic transitions of the aryl chromophores, polarized along the axis. Furthermore, the shapes of both the UV and CD spectra depend on the value of the dihedral angle θ. In particular, for large angles (θ in the range of 80−100°) the absorption band is broad in the 220 nm spectral range and a negative couplet corresponds to the *R* configuration of the biaryl. With this information it is now possible to return to the spectra of **(*R*,*R*)-2**, by attempting a qualitative interpretation. First of all, as noticed above, the comparison of the absorption spectra shows that both **(*R*,*R*)-2** and (*R*)-8,8′-dimethyl-1,1′-biisoquinoline [**(*R*)-11**] strongly contain the same distorted 1,1′-biisoquinoline chromophore, the difference in shape occurring in the 250−200 nm range could be due to the fact that while the dihedral angle of **(*R*)-11** is of the order of 90−100°,[9a] the present MM calculation gives a much smaller dihedral angle (72°) in **(*R*,*R*)-2**. This is in keeping with the UV spectrum of **(*R*,*R*)-2**, where a sequence of less intense (longer wavelength)/more intense (shorter wavelength) absorption bands is observed between 250 and 200 nm, characteristic of a biaryl possessing a small θ angle.[23] In addition, our MM calculations show that the (*R*,*R*) planar chirality of **(*R*,*R*)-2** induces a positive twist of the 1,1′-biisoquinoline moiety. Thus, according to the Mason analysis, a positive couplet should be expected in the 250−200 nm spectral region, i.e., where the coupling of the allowed, long-axis polarized electronic transition of the biaryl chromophore occurs, as experimentally observed (Figure 6). In summary, even a simple, qualitative

(22) These OR values are also obtained at different concentrations, and it is well-known that this experimental parameter may also affect the OR measurement. Eliel, E. L.; Wilen, S. H. *Stereochemistry of organic compounds*; J. Wiley and Sons: New York, 1994; Chapter 13, p 1076. Polavarapu, P. L. *Chirality* **2002**, *14*, 768.

(23) (a) Mason, S. F.; Seal, R. H.; Roberts, D. R. *Tetrahedron* **1974**, *30*, 1671. (b) Rosini. C.; Rosati, I.; Spada, G. P. *Chirality* **1995**, *7*, 353.; (c) Di Bari, L.; Pescitelli, G.; Salvadori, P. *J. Am. Chem. Soc.* **1999**, *121*, 7988. (d) Rosini, C.; Superchi, S.; Peerlings, H. W. I.; Meijer, E. W. *Eur. J. Org. Chem.* **2000**, 61. (e) Di Bari, L.; Pescitelli, G.; Marchetti, F.; Salvadori, P. *J. Am. Chem. Soc.* **2000**, *122*, 6395. (f) Bandin, M.; Casolari, S.; Cozzi, P. G.; Proni, G.; Schmohel, E.; Spada, G. P.; Tagliavini, E.; Umani-Ronchi, A. *Eur. J. Org. Chem.* **2000**, 491. (g) Proni, G.; Spada, G. P.; Lustenberger, P.; Welti, R.; Diederich, F. *J. Org. Chem.* **2000**, *65*, 5522.



(*R*,*R*)-2-A (θ = +72°) **(*R*,*R*)-2-B** (θ = -134°)

FIGURE 7. Dihedral angles of the two quinoline moieties in the more stable conformer **(*R*,*R*)-2-A** and in the less stable conformer **(*R*,*R*)-2-B**.

analysis of the UV/CD spectra of **(*R*,*R*)-2** can reveal some interesting spectrum/structure correlations. Unfortunately, the distorted 1,1′-biisoquinoline moiety cannot be considered responsible for all the spectral features of **(*R*,*R*)-2**; in fact, the shape of its CD spectrum is more complex than that of **(*R*)-11**. In particular, in the case of **(*R*,*R*)-2**, the 350−250 nm range possesses a positive, broad, and very intense Cotton effect, while a negative, well-defined, and less intense CD band is observed for **(*R*)-11**. In addition, the intensity of the couplet at 220−230 nm in the spectrum of **(*R*,*R*)-2** is much smaller than that of a model compound **(*R*)-11** (note that θ in **(*R*)-11** is 90−100° and shows a couplet with $\Delta\epsilon$ −200, +200, a distortion of 72° should induce an even more intense couplet).[23] These observations suggest that a "perturbed", distorted 1,1′-biisoquinoline chromophore, is really responsible for the spectroscopic properties of **(*R*,*R*)-2** is where by "perturbation" we intend the effect of the paracyclophane moieties which cannot be neglected in order to completely explain the optical activity of this molecule.

Conclusions

Atropisomeric (*R*,*R*)-2,2′-bi[2]paracyclo[2](5,8)quinolinophane [**(*R*,*R*)-1**] and (*R*,*R*)-1,1′-bi[2]paracyclo-[2](5,8)-isoquinolinophane [**(*R*,*R*)-2**] can be prepared in moderate overall yield (17 and 9%, respectively) by a four-step sequence starting from (*R*)-(−)-4-amino[2.2]paracyclophane and (*R*)-(−)-4-carboxy[2.2]paracyclophane, respectively.

^{1}H NMR experiments and theoretical calculations are in excellent accordance in drawing the structure of both 2,2′-biquinolinophane **(*R*,*R*)-1** and 1,1′-biisoquinolinophane **(*R*,*R*)-2** exhibiting both planar and axial chirality. The low rotational barrier around the C-2-C-2′ bond allows **(*R*,*R*)-1** to exist as a mixture of (*R*,*P*,*R*) and (*R*,*M*,*R*) conformational diastereoisomers both having the nitrogen atoms anti each other. According to our MM calculations 1,1′-biisoquinolinophane **(*R*,*R*)-2** seems to strongly prefer the (*R*,*P*,R) conformation (91%) with a dihedral angle between the two quinoline moieties of about 72°. The minor conformer exhibits opposite axial chirality (*R*,*M*,*R*) with a dihedral angle of −134°. The energy difference between the two conformers (ca. 1.3 kcal/mol) has to be ascribed most probably to the steric repulsion between the two phenyl groups overlapping the quinoline moieties in the minor conformer (Figure 7).

The structural information obtained by a theoretical conformational analysis is fully confirmed by the analysis (although preliminary and very qualitative) of the chiroptical properties of these molecules. In fact, for **(*R*,*R*)-1** the main source of optical activity can be found in the presence of the paracyclophane moiety, i.e., the molecular chirality is only due to insertion of the (almost planar) 2,2′-biquinolino chromophore in a paracyclophane structure. By contrast, in **(*R*,*R*)-2** the paracyclophane structural motif only constitutes a (relatively small) perturbation which only slightly modifies the main source of optical activity, i.e., the presence of a distorted 1,1′-biisoquinoline chromophore. These results can be useful to (at least preliminary) predict the ability of these ligands to induce steroselectivity in asymmetric catalysis. Biquinolinophane **(*R*,*R*)-1**, where the nitrogen atoms are in an anti spatial relationship, should coordinate metal ions poorly, while **(*R*,*R*)-2** has the same atoms in a relative disposition which is suitable for efficient coordination. As a result, if a direct correlation between coordination capability and induced enantioselectivity exists, we can expect that the former compound will provide low enantioselection values in asymmetric reactions while better results should be obtained in reactions employing the latter ligand. Further studies are needed to fully understand the spectrum/structure correlations in these molecules and to verify the reliability of the present prediction of the enantioselection capability of these two ligands.

Experimental Section

(*R*)-(−)-4-Amino[2.2]paracyclophane [(*R*)-4]. (*R*)-(−)-4-Carboxy[2.2]paracyclophane [**(*R*)-3**] (10.0 g, 40 mmol) was made to react 12 h with $SOCl_2$ (20 mL) at 20 °C under stirring. Excess chlorinating reagent was evaporated at reduced pressure, toluene (20 mL) was added to the residue, and the mixture was evaporated again at reduced pressure to remove any trace of $SOCl_2$. Acetone (100 mL) was added to the resulting gray solid, and the solution was poured into a previously prepared solution of NaN_3 (10 g, 0.15 mol) in H_2O (50 mL) and acetone (35 mL). The mixture was made to react at 20 °C for 1 h, and then it was poured into ice−water (300 mL) and extracted with diethyl ether (3 × 100 mL). The collected extracts were dried with Na_2SO_4, and the solvent was evaporated at reduced pressure. Toluene (125 mL) was added to the resulting white solid, and the solution was refluxed until the starting acyl azide disappeared (TLC, SiO_2, eluent light petroleum/diethyl ether 9:1). Usually 2 h are enough to complete the conversion of the acyl azide into the corresponding isocyanate. Toluene was evaporated at reduced pressure, the residue was dissolved in THF (100 mL), and 40% aqueous tetrabutylammonium hydroxide (30 mL) was added in portions while stirring. After the addition was completed, the mixture was refluxed for 5 min before it was poured into iced water (600 mL). The white solid was filtered and washed with water until neutrality, and dried in the presence of P_2O_5 until constant weight (7.7 g, 95% from the acid). Mp: 241−243 °C dec. $[\alpha]^{20}_D = -71$ (*c* 0.58, $CHCl_3$). ^{1}H NMR δ: 7.16 (dd, J = 7.6 and 1.9 Hz, 1 H), 6.58 (dd, J = 7.7 and 1.9 Hz, 1 H), 6.38 (dd, J = 7.7 and 1.9 Hz, 2H), 6.25 (d, J = 7.5 Hz, 1 H), 6.12 (dd, J = 7.5 and 1.7 Hz, 1 H), 5.37 (d, J = 1.7 Hz, 1 H), 3.46 (broad s, 2 H), 3.14−2.91 (m, 6 H), 2.85−2.78 (m, 1 H), 2.70−2.60 (m, 1 H). ^{13}C NMR δ: 144.9, 141.0, 138.9, 138.8, 135.2, 133.4, 132.4, 131.4, 126.7, 124.1, 122.8, 122.2, 35.3, 34.9, 32.9, 32.2. IR (KBr) 3472, 3385 cm^{-1}. MS *m/z*: 223 (M^+, 26), 119 (100), 104 (5), 91 (16). Anal. Calcd for $C_{16}H_{17}N$: C, 86.05; H, 7.67; N, 6.27. Found: C, 85.92; H, 7.81; N, 6.38.

(*R*)-[2]Paracyclo[2](5,8)quinolinophan-2(1*H*)-one [(*R*)-6]. Butyllithium (19.0 mL 1.59 M in hexane, 30 mmol) was added to a solution of (*R*)-(−)-4-amino[2.2]paracyclophane [**(*R*)-4**] (6.8 g, 30 mmol) in THF (100 mL) at −30 °C. The

temperature was raised to 20 °C, ethyl 3-ethoxyacrylate (2.2 g, 15 mmol) was added, and the mixture was allowed to react for 2 h before it was poured into water and extracted with diethyl ether (3 × 50 mL). The collected organic phases were dried with Na_2SO_4, and the solvent was evaporated at reduced pressure. Aqueous HCl (36% w/w) was added to the resulting brown solid, and the mixture was vigorously stirred for 24 h. The yellow solid, identified as **(*R*)-*N*-([2.2]paracyclophan-4-yl)-3-methoxyacrylamide** [**(*R*)-5**] by its ^{1}H NMR spectrum, was filtered, washed with water, and dissolved in $CHCl_3$. The organic solution was dried with Na_2SO_4 before the solvent was evaporated at reduced pressure leaving a sticky brown material. Chromatography on silica gel (eluent, ethyl acetate/light petroleum 8:2) allowed pure **(*R*)-6** (3.3 g, 40%) to be isolated.

(*R*)-5. ^{1}H NMR δ: 8.31 (broad s, 1 H), 7.02 (s, 1 H), 6.76 (d, J = 7.6 Hz, 1 H), 6.56−6.42 (AB system, J_{AB} = 7.6 Hz, 2 H), 6.45−6.39 (m, 5 H), 4.13 (s, 3 H), 3.22 (dd, J = 14.3 and 9.7 Hz, 1 H), 3.16−2.97 (m, 5 H), 2.87−2.76 (m, 2 H).

(*R*)-6. Mp: 251−256 dec. ^{1}H NMR (DMSO-d_6) δ 10.99 (s, 1 H), 7.66 (d, J = 9.7 Hz, 1 H), 6.68−6.50 (AB system, J_{AB} = 7.5 Hz, 2 H), 6.41 (d, J = 9.7 Hz, 1 H), 6.47−6.35 (AB system, J_{AB} = 7.8 Hz, 2 H), 6.16 (dd, J = 7.6 and 1.3 Hz, 1 H), 5.97 (dd, J = 7.6 and 1.3 Hz, 1 H), 3.78 (dd, J = 13.2 and 10.0 Hz, 1 H), 3.51 (t, J = 11.5 Hz, 1 H), 3.03−2.61 (m, 6 H). ^{13}C NMR (DMSO-d_6) δ 162.5, 139.2, 139.1, 138.8, 138.6, 137.9, 136.3, 133.0, 132.9, 128.6, 127.6, 126.4, 125.8, 121.4, 120.4, 34.3, 33.3, 31.8, 30.9. IR (KBr) ν_{max}: 3688 cm^{-1}. Anal. Calcd for $C_{19}H_{17}NO$: C, 82.88; H, 6.22; N, 5.09. Found: C, 82.78; H, 6.29; 5.16.

(*R*)-(+)-2-Bromo[2]paracyclo[2](5,8)quinolinophane [(*R*)-7]. Quinolone **(*R*)-6** (1.5 g, 4.4 mmol) was added to $POBr_3$ (11.5 mL, 32.4 g, 0.11 mol), and the mixture was allowed to react at 20 °C while stirring for 1 h. It was then poured on ice, and the aqueous phase was cautiously neutralized with $NaHCO_3$ and extracted with $CHCl_3$ (3 × 50 mL). The collected organic phases were dried with Na_2SO_4, and the solvent was evaporated at reduced pressure. Chromatography of the residue on silica gel (eluent, light petroleum/diethyl ether 8:2) allowed pure 2-bromoquinolinophane **(*R*)-7** (1.1 g, 60%) to be isolated. Mp: 115−117 °C. $[\alpha]^{20}_D$ = +94 (c = 0.5, $CHCl_3$). ^{1}H NMR δ: 7.76 (d, J = 8.6 Hz, 1 H), 7.44 (d, J = 8.6 Hz, 1 H), 6.96 (d, J = 7.2 Hz, 1 H), 6.82 (d, J = 7.2 Hz, 1 H), 6.45 (tight AB system, J = 7.0 Hz, 2 H) 5.75 (d, J = 7.9 Hz, 1 H), 5.58 (d, J = 7.9 Hz, 1 H), 4.18 (ddd, J = 12.5, 9.6 and 3.0 Hz, 1 H), 3.72−3.63 (m, 1 H), 3.16−2.76 (m, 6 H). ^{13}C NMR δ: 150.1, 139.6, 139.5, 137.8, 137.7, 137.4, 135.1, 134.3, 132.7, 132.2, 131.7, 129.1, 128.8, 127.6, 124.4, 34.5, 34.5, 32.3, 31.4. IR ν_{max}: 3068, 3019, 2931, 1577, 1489, 1111, 465, 420 cm^{-1}. Anal. Calcd for $C_{19}H_{16}BrN$: C, 67.47; H, 4.77; N, 4.14. Found: C, 67.31; H, 4.59; 4.23.

(*R,R*)-(−)-2,2′-Bi([2]paracyclo[2](5,8)quinolinophane) [(*R,R*)-1]. Zinc dust (0.07 g, 1.1 mmol) was added to a solution of $NiCl_2{\cdot}6H_2O$ (0.24 g, 1.0 mmol) and triphenylphosphine (1.0 g, 4.0 mmol) in DMF (5 mL), and the mixture was stirred at 50 °C for 1 h. (*R*)-(+)-2-Bromo[2]paracyclo[2](5,8)quinolinophane [**(*R*)-7**] (0.4 g, 1.2 mmol) was added, and the mixture was allowed to react at 50 °C for 30 min. The white precipitate was filtered, washed first with DMF (5 mL) and then with CH_3OH (5 mL), and dissolved in hot $CHCl_3$ (250 mL). The solid impurities were filtered off, and the solvent was evaporated at reduced pressure. The resulting white solid was washed with ethyl acetate and dried in a vacuum to recover pure 2,2′-bi([2]paracyclo[2](5,8)quinolinophane) [**(*R,R*)-1**] (0.22 g, 72%). Mp: 300 °C dec. $[\alpha]^{20}_D$ = −10 (c = 0.1, $CHCl_3$). ^{1}H NMR δ: 8.86 (d, J = 8.6 Hz, 1 H), 8.17 (d, J = 8.6 Hz, 1 H), 7.03 (d, J = 7.2 Hz, 1 H), 6.86 (d, J = 7.2 Hz, 1 H), 6.54 (tight AB system, 2 H), 5.77−5.72 (tight AB system, J = 7.6 Hz, 2 H), 4.54 (tight m, 1 H), 3.83 (m, 1 H), 3.21−2.91 (m, 6 H). ^{13}C NMR δ: 153.3, 148.7, 139.4, 138.6, 137.7, 137.6, 133.8, 133.5, 132.6, 132.2, 131.6, 130.4, 128.8, 127.4, 118.0, 34.9, 34.6, 32.3, 31.9. IR ν_{max}: 3.68, 3034, 2932, 1592, 1498 cm^{-1}. Anal. Calcd for $C_{38}H_{32}N_2$: C, 88.34; H, 6.24; N, 5.42. Found: C, 88.12; H, 6.31; 6.29.

(*R*)-(−)-*N*-(2,2-Dimethoxyethyl)[2.2]paracyclophane4-carboxyamide [(*R*)-8]. (*R*)-4-Chlorocarbonyl[2]paracyclo[2]-(5,8)paracyclophane (5.5 g, 20 mmol), prepared as above, was added to a solution of aminoacetaldehyde dimethyl acetal (4.8 g, 46 mmol) in diethyl ether (75 mL) at 0 °C while stirring. After 1 h at 20 °C, H_2O (150 mL) was added, the organic phase was separated, and the aqueous phase was further extracted with CH_2Cl_2 (3 × 50 mL). The collected organic phases were washed with brine and dried with Na_2SO_4. After the solvent was evaporated at reduced pressure, a white solid was recovered that was identified as (*R*)-(−)-*N*-(2,2-dimethoxyethyl)-4-carboxyamido[2.2]paracyclophane (6.9 g, 99%) on the basis of their spectroscopic and analytical properties. Mp: 132−134 °C. $[\alpha]^{20}$ = −89 (c = 0.5, $CHCl_3$). ^{1}H NMR δ: 6.78 (broad d, J = 7.9 Hz, 1 H), 6.68 (d, J = 1.9 Hz, 1 H), 6.59 (dd, J = 7.8 e 1.8 Hz, 1 H), 6.54 (tight m, 2 H), 6.49 (d, J = 7.8 Hz, 1 H), 6.42 (broad d, J = 8.0 Hz, 1 H), 5.79 (broad s, 1 H), 4.50 (t, J = 5.2 Hz, 1 H), 3.69 (ddd, J = 12.8, 10.1 and 2.5 Hz, 1 H), 3.64−3.52 (m, 2 H), 3.45 (s, 3 H), 3.44 (s, 3 H), 3.23−2.85 (m, 7 H). ^{13}C NMR δ: 159.2, 150.2, 140.1, 139.7, 139.2, 139.1, 135.9, 135.0, 132.6, 132.5, 132.4, 131.7, 131.6, 102.7, 54.4, 41.1, 35.3, 35.2, 35.1, 34.8. IR ν_{max}: 3441, 3009, 2931, 1651, 1514, 1131, 1072, 454 cm^{-1}. The product was pure enough to be used in the following step without further purification.

(*R*)-(+)-[2]Paracyclo[2](5,8)isoquinolinophan-1(2*H*)-one [(*R*)-9]. Pulverized (*R*)-(−)-*N*-(2,2-dimethoxyethyl)-4-carboxyamido[2.2]paracyclophane (3.4 g, 10.0 mmol) was added in portions to vigorously stirred polyphosphoric acid (270 g) and preheated at 100 °C, and the resulting mixture was allowed to react for 30 min before it was poured on triturated ice. The aqueous phase was extracted with $CHCl_3$ (3 × 50 mL), and the collected organic phases were dried with Na_2SO_4. After solvent, evaporation the gummy red product was washed with diethyl ether and the residue was chromatographed on silica gel (eluent, ethyl acetate/light petroleum 1:1.) to recover a product that identified as (*R*)-(+)-[2]paracyclo[2](5,8)isoquinolinophan-1-one (1.3 g, 47%) on the basis of the following spectroscopic and analytical characteristics. Mp: 238−240 °C. $[\alpha]^{20}_D$ = +451 (c = 0.5, $CHCl_3$). ^{1}H NMR δ: 11.01 (broad s, 1 H), 7.17 (d, J = 7.2 Hz, 1 H), 6.82−6.73 (AB system, J = 7.5 Hz, 2 H), 6.56 (dd, J = 7.9 and 1.8 Hz, 1 H), 6.48 (d, J = 7.2 Hz, 1 H), 6.44 (dd, J = 7.9 and 1.8 Hz, 1 H), 6.29 (dd, J = 7.8 and 1.8 Hz, 1 H), 6.19 (dd, J = 7.8 and 1.9 Hz, 1 H), 4.78 (ddd, J = 12.0, 9.5 and 1.9 Hz, 1 H), 3.60−3.53 (m, 1 H), 3.23−3.09 (m, 3 H), 3.03−2.93 (m, 3 H). ^{13}C NMR δ: 164.1, 142.4, 140.6, 139.9, 138.1, 136.6, 135.9, 133.5, 133.2, 132.2, 129.9, 128.4, 127.6, 127.3, 104.6, 36.1, 34.4, 34.2, 33.1. IR ν_{max}: 3674, 3407, 3019, 2935, 2861, 1639, 1449, 1314, 1225, 1103, 871 cm^{-1}. Anal. Calcd for $C_{19}H_{17}NO$: C, 82.88; H, 6.22; N, 5.09. Found: C, 82.71; H, 6.28; 5.17.

(*R*)-(+)-1-Bromo[2]paracyclo[2](5,8)isoquinolinophane [(*R*)-10]. (*R*)-(+)-[2]paracyclo[2](5,8)isonolinophan-1(2*H*)-one (0.8 g, 3.2 mmol) was allowed to react with $POBr_3$ (10 mL) for 7 h at 100 °C. After cooling, the reaction mixture was poured into triturated ice (100 g), and the resulting mash was neutralized with 50% aqueous KOH and extracted with diethyl ether (3 × 50 mL). The collected extracts were dried with Na_2SO_4, and the solvent was evaporated at reduced pressure. Chromatography of the remaining gummy product on silica gel (eluent, ethyl acetate/petroleum ether 7:3) allowed a reddish solid (0.3 g) to be isolated which was recrystallized from ethanol after treatment with decolorizing carbon. A white crystalline product was obtained which was identified as (*R*)-1-bromo[2]paracyclo[2](5,8)isoquinolinophane (0.44 g, 45%) on the basis of the following spectroscopic and analytical characteristics. Mp: 224−226 °C. $[\alpha]^{20}_D$ = +193 (c = 0.5, $CHCl_3$). ^{1}H NMR δ 7.77−7.43 (AB system, J_{AB} = 8.6 Hz, 2 H), 6.97−6.81 (AB system, J_{AB} = 7.3 Hz, 2 H), 6.45 (s, 2 H), 5.75−5.57 (AB system, J_{AB} = 7.9 Hz, 2 H), 4.16 (ddd, J = 12.2, 9.3, and 2.5 Hz, 1 H), 3.69−3.63 (m, 1 H), 3.16−2.90 (m, 5 H), 2.84−2.70 (m, 1 H). ^{13}C NMR δ: 141.6, 141.5, 141.0, 139.0, 137.6, 137.5, 136.9, 136.0, 134.7, 132.4, 131.5, 130.4, 129.6, 129.4,

118.1, 38.0, 34.9, 34.0, 32.5. IR ν_{max}: 3020, 2941, 2863, 1588, 1311, 1222, 1212, 1056, 823 cm^{-1}. Anal. Calcd for $C_{19}H_{16}BrN$: C, 67.47; H, 4.77; N, 4.14. Found: C, 67.55; H, 4.69; 4.25.

(*R,R*)-(+)-1,1′-Bi([2]paracyclo[2](5,8)isoquinolinophane) [(*R,R*)-2]. Zinc dust (0.06 g, 0.9 mmol) was added to a stirred solution of $NiCl_2 \cdot 6H_2O$ (0.20 g, 1.0 mmol) and triphenylphosphine (1.2 g, 4.6 mmol) in DMF (15 mL) at 50 °C. After 1 h, (*R*)-(+)-2-bromo-[2]paracyclo[2](5,8)quinolinophane (0.4 g, 1.2 mmol) was added, and the mixture was allowed to react at 50 °C for 1.5 h. H_2O (50 mL) was added, and the aqueous phase was acidified with 20% aqueous HCl (10 mL) and extracted with diethyl ether (3 × 25 mL). Aqueous NaOH (50%) was added to the aqueous phase and it was extracted again with diethyl ether (3 × 25 mL). The collected organic phases were dried with Na_2SO_4, and the solvent was evaporated at reduced pressure. Chromatography of the remaining solid on silica gel (eluent, 9:1 petroleum ether/diethyl ether) allowed 130 mg (43%) of a white solid to be recovered to which the structure of (*R,R*)-1,1′-bi([2]paracyclo-[2](5,8)isoquinolinophane) was assigned on the basis of the following spectroscopic and analytical properties. Mp: 280 °C dec. $[\alpha]^{24}_D = +414$ ($c = 0.5$, $CHCl_3$), $[\alpha]^{30}_D = +566$ ($c = 0.05$, MeOH). ^1H NMR δ: 8.82 (d, $J = 5.6$ Hz, 1 H), 7.69 (d, $J = 5.6$ Hz, 1 H), 6.77 (d, $J = 7.2$ Hz, 1 H), 6.45 (d, $J = 7.2$ Hz, 1 H), 6.37 (dd, $J = 7.8$ and 1.6 Hz, 1 H), 6.24 (dd, $J = 7.8$ and 1.3 Hz, 1 H), 5.91 (dd, $J = 7.8$ and 1.7 Hz, 1 H), 5.83 (dd, $J = 7.8$ and 1.7 Hz, 1 H), 3.92−3.67 (m, 1 H), 3.18−2.93 (m, 3 H), 2.41 (t, $J = 11.1$ Hz, 1 H), 2.32−2.25 (m, 1 H), 1.97−1.89 (m, 1 H), 0.86 (ddd, $J = 13.8$, 9.6 and 1.7 Hz, 1 H). ^{13}C NMR δ: 158.4, 142.0, 139.0, 138.9, 137.7, 137.0, 135.8, 134.4, 133.8, 131.9, 131.3, 130.3, 129.4, 129.2, 118.0, 35.6, 34.3, 34.2, 32.5. IR ν_{max}: 3059, 3023, 2942, 1592, 1319 cm^{-1}. Anal. Calcd for $C_{38}H_{32}N_2$: C, 88.34; H, 6.24; N, 5.42. Found: C, 88.15; H, 6.35; 5.58.

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Supporting Information Available: ^1H and ^{13}C NMR spectra of all the reported new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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