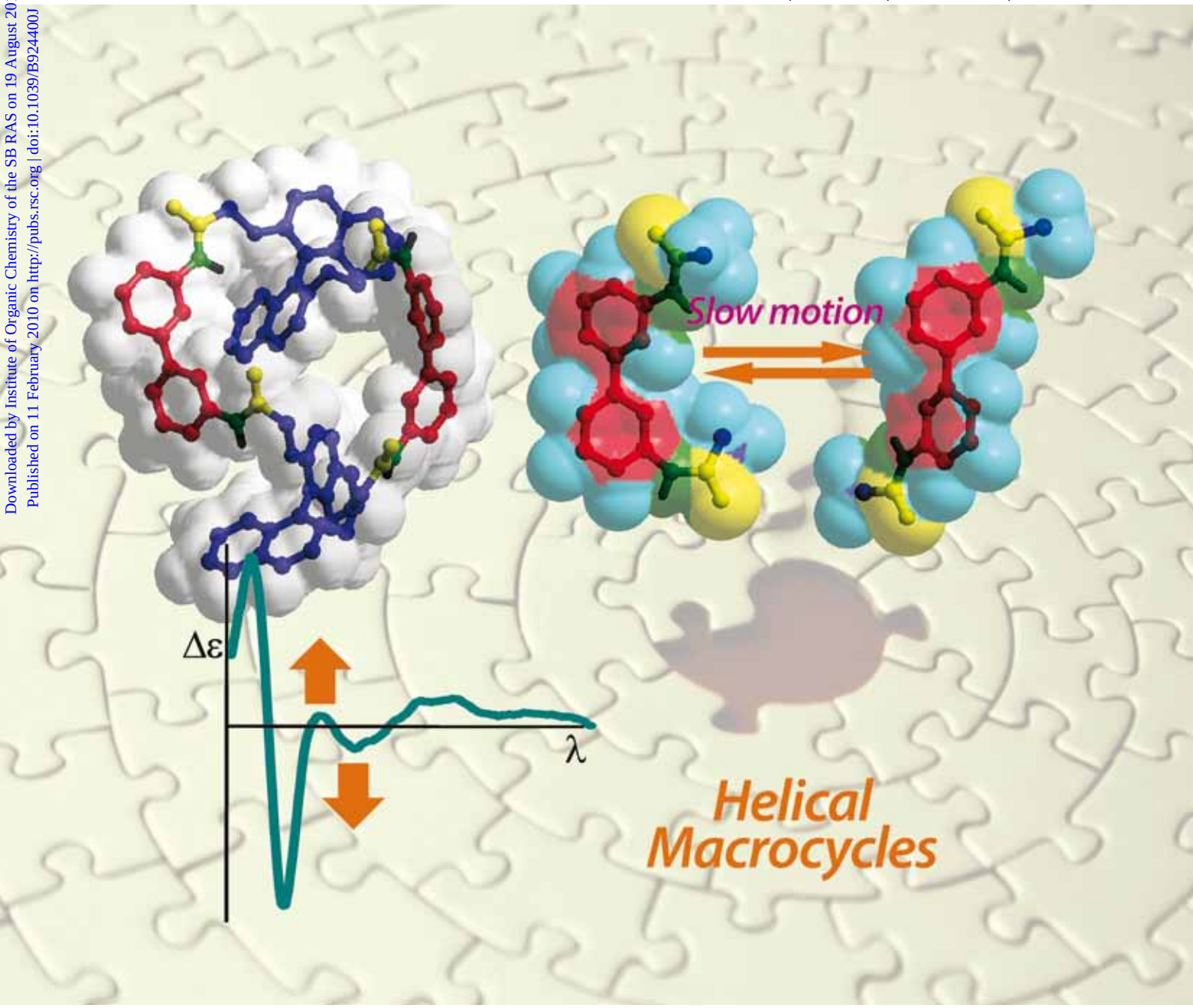
Organic & Biomolecular Chemistry

www.rsc.org/obc

Volume 8 | Number 8 | 21 April 2010 | Pages 1733–1976



ISSN 1477-0520

RSC Publishing

Locked chromophores as CD and NMR probes for the helical conformation of tetraamidic macrocycles†

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Received 20th November 2009, Accepted 15th January 2010
First published as an Advance Article on the web 11th February 2010
DOI: 10.1039/b924400j

A series of tetraamidic homochiral macrocycles have been built convergently upon the introduction in the covalent scaffold of two 1,1′-binaphthyl-2,2′-diol derivatives, joined by aromatic spacers of differing shapes and rigidity (*p*-phenyl, 4,4′-biphenyl, 3,3′-biphenyl) through aromatic amide functionalities, perfectly positioned to intramolecularly hydrogen bond the naphtholic oxygen acceptors of the binaphthyl units, in order to effectively lock the central chromophores in spatial proximity. The combination of several techniques, namely NMR and CD spectroscopies, and computational modeling, allows for a clear depiction of the structure and conformation of the macrocycles in solution. In the case of the shape "unstable" 3,3′-biphenyl spacer, the preferred conformation of a "wrapped" form in a relatively polar (EtOH) solvent is clearly signalled by CD spectroscopy by analyzing the changes in the shape of the induced CD signal deriving from the central, achiral chromophore absorption band. The rigid, covalent scaffold in which the two central 3,3′-biphenyl spacers are embedded raises the energetic barrier for the rotation around the aryl–aryl bonds of the spacers to a value (8.0 kcal mol^{-1}) much higher than the value calculated in the case of unlocked biphenyls.

Introduction

The modulation, manipulation and transcription of molecular chirality, both at the molecular and at the supramolecular level, have been the subject of intense research activity in recent years.[1] Since the concepts of chirality and directionality can be closely related, the control and signalling of chirality could in principle represent a key step in the design of a new generation of functional molecular motors and machines.[2] The use of circular dichroism (CD) spectroscopy as a detection tool can be particularly useful, as it can be complementary to other spectroscopic responses (*e.g.*, absorption or emission of light by a given chromophore in the analyte). Of particular interest is the induction of CD activity in absorption transitions related to non-chiral chromophores (either covalently or noncovalently linked to the source of chirality).[3] In these cases, CD spectroscopy offers an unique evaluation tool for the structural elucidation of conformational issues associated with the molecule or the supramolecular structure.[1,4]

The role of amide functionalities as hydrogen-bonding tools for the stabilization of certain conformations in assembled nanostructures has been elegantly exploited in several contexts for the creation and stabilization of foldamers,[5] and in the covalent synthesis of shape-persistent macrocycles.[6] On the other hand, amide functionalities have also been used as complementary, self-recognizing hydrogen-bonded systems in the assembly of diverse nanoobjects, such as, for example, organic nanotubes[7] and columnar assemblies.[8] Binol (1,1′-binaphthyl-2,2′-diol)-based synthons[9] are characterized by a C_2 symmetrical aromatic skeleton, and they possess a robust configurational stability in a broad range of reaction conditions; thus, they have become attractive chiral molecular modules for applications in several fields, spanning from asymmetric catalysis,[10] to chiral supramolecular recognition,[11] crystal engineering[12] and molecular electronics.[13] The synthesis and characterization of intriguing double-helically twisted cyclophanes or macrocycles have been elegantly developed and reported, these compounds showing peculiar electronic properties.[14] As the determination of the relationship between molecular structure and physical properties is a major issue in chemistry, compounds composed of strained and curved conjugated systems have been recently obtained and studied.[15] In this paper, we report on the construction of covalent helical objects, based on the introduction of aromatic amide segments locked within binaphthyl systems, on their peculiar conformational behavior, and finally, on how the molecular, helical shape is signalled by the achiral rigid spacing unit by NMR spectroscopy and by the induced CD response.

Results and discussion

Synthesis of precursors and macrocyclization

The synthesis of the axially chiral macrocycles was performed following a stepwise, convergent approach as illustrated in Scheme 1. In our design, the numbers of sp^3 hybridized carbon atoms included in the covalent architecture had to be minimized, in order to obtain rigid, shape-persistent homochiral macrocyclic scaffolds.[16] All compounds were obtained starting from the commercially available (*R*) enantiomer of 2,2′-dihydroxy-1,1′-binaphthyl **1**. Alkylation under mild basic conditions, by

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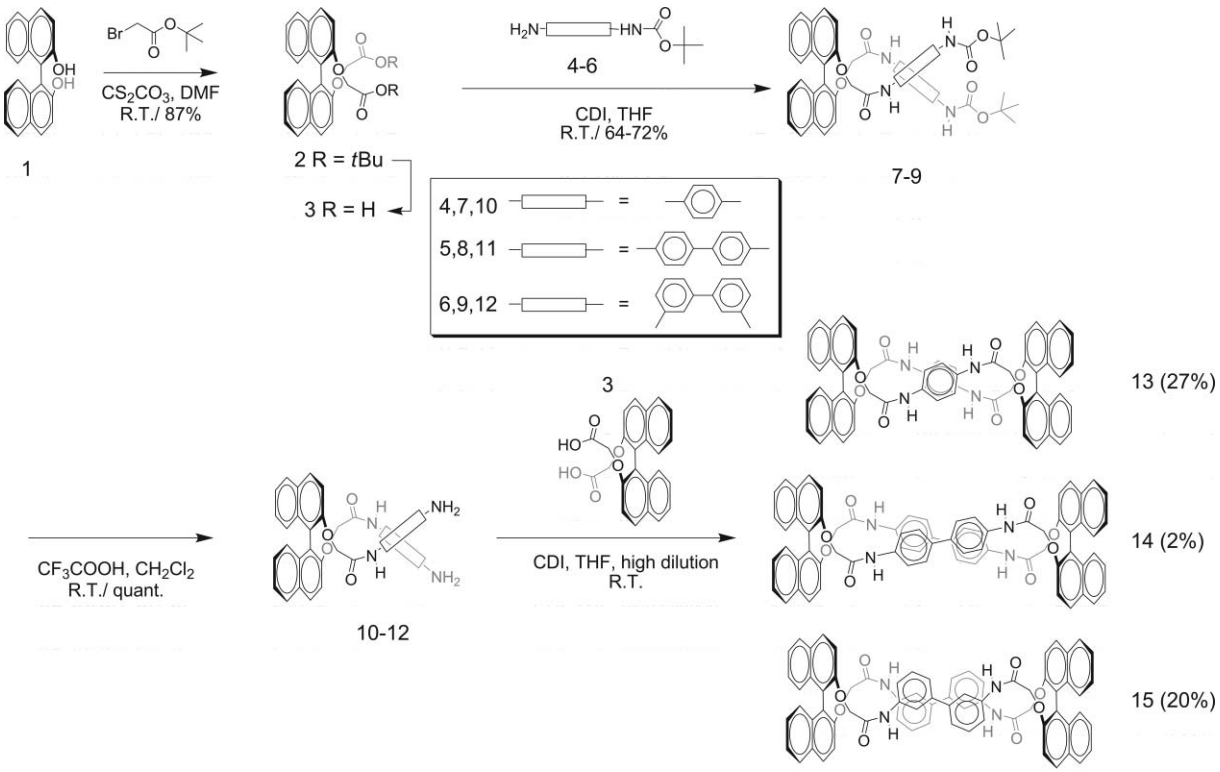
† Electronic supplementary information (ESI) available: Copies of NMR spectra for all compounds, additional NMR spectroscopic data, chiroptical data and computational details for **13** and **15**. See DOI: 10.1039/b924400j



Scheme 1 Synthesis of precursors and macrocycles.

adapting protocols previously reported for polyphenolic substrates,[17] afforded compound **2**, and, after deprotection of the *t*-butyl esters, the dicarboxylic acid **3** was obtained. Whereas mono-BOC-protected phenylene diamine **4** was available commercially, the corresponding aromatic amines **5** and **6** were obtained, using classical conditions, by statistical reaction using 1 equivalent of $(BOC)_2O$ with respect to the corresponding aromatic diamines, benzidine and 3,3′-diphenyldiamine,[18] in 47% and 32% yields, respectively. The amide-forming coupling reaction was initially tested in the case of **7** *via* formation of the acyl chloride ($COCl_2$, cat. DMF, CH_2Cl_2) and the subsequent addition of the monoprotected amine **4** (with excess Et_3N, CH_2Cl_2, reflux). Although the product was isolated and characterized, yields were substantially improved by the use of CDI as the coupling agent between the dicarboxylic acid and the amines **4–6**.[19] Subsequent deprotection of the BOC groups gave aromatic diamines **10–12**, which were used in the cyclization without further purification; the cyclization of these compounds with one equivalent of the dicarboxylic acid (*R*)-**3** was conducted in high dilution conditions (*ca.* 5 mM for each of the two fragments) to yield the homochiral macrocycles **13**, **14**, and **15** as white powders. Yields were much higher in the case of **13** (27%) and **15** (20%), whereas macrocycle **14** was only obtained in very low yield (2%), with a much higher amount of polymeric, baseline material obtained. It could not be completely purified but it was correctly identified by NMR and mass spectroscopies. The much lower yield in the case of **14** cannot be ascribed to a different reactivity of the benzidine-type aromatic amine when compared to the monophenyl and 3,3′-diphenyl aromatic amines, since the first amidation reaction to produce compounds **7–9** worked for all of the differently shaped amines equally well. Rather, it can be related to the mismatch in fit between the shape and dimensions of the aromatic spacers to be inserted and the unavoidable bite angle of the two binaphthyl units locking the macrocycle, as the length of the spacer imposes a certain rigid geometry and an associated overall strain/stability to the macrocycle.

The macrocycles showed different solubility behavior: whereas (*RR*)-**13** and (*RR*)-**14** were fully soluble in THF and polar solvents, but only sparingly soluble in chlorinated solvents, (*RR*)-**15** showed a good solubility also in these latter solvents.

NMR spectroscopy

The ^1H and ^{13}C NMR spectra of macrocycles **13** and **15** at room temperature showed the expected simple patterns in agreement with the D_2 symmetry of the molecules. The NMR spectra of macrocycles were fully assigned by means of appropriate 2D NMR spectroscopy (COSY, NOESY, HSQC and HMBC, as reported in the ESI†). A selection and comparison of the most significant resonances for the compounds described here is shown in Table S1. The N*H*COO*t*Bu signals in **7–9** appeared as broad singlets in all compounds at *ca.* 6.5–6.8 ppm, with virtually no shift with respect to the corresponding monoprotected amines **4–6**.[20]

An initial interesting observation is that the resonances associated to the CONH protons in precursors **7–9** were not identifiable in the NMR spectra run in $CDCl_3$ (at 5–10 mM concentrations, both at 200 MHz and 300 MHz), as they were broadened under the baseline as a consequence of their slow conformational equilibria on the NMR time scale, presumably *syn–anti* rotation around the aryl bonds (see Fig. 1, top left), in the context of the given molecular architecture. However, they appeared as sharp singlets in solvents competing for hydrogen bonds such as d_6-DMSO. In general, rotations related to CONH–aryl bonds are

more energetically demanding than rotations about CONH–alkyl bonds, because of the conjugation between the amide and aromatic groups. Energy minima are located in both the *syn* and *anti* conformations where aryl and amide groups are coplanar.[5a]

In contrast, macrocycles **13–15** showed one sharp singlet associated to the N*H*CO proton resonances at 200, 300 or 600 MHz, either in $CDCl_3$ (where possible), or in THF-d_8 or DMSO-d_6. This observation confirmed to us that the amide groups are involved in stabilizing hydrogen bonds, presumably with the adjacent aryl–alkyl ether oxygen acceptor atoms located in close proximity with the amide donor functionalities, in a five-membered ring hydrogen bonded system (Fig. 1, top right), as indicated by molecular modeling and inspection of CPK models for macrocycles **13–15**.[21] The presence of a single resonance for the NHCO protons also strongly suggested that their conformation (on the NMR time scale) is symmetry-related, just like each of the four different binaphthyl moieties are equivalent, as a consequence of the overall D_2 symmetry of the macrocyclic molecules (Fig. 2).

^{1}H NMR spectroscopy did not show any significant change by varying the macrocycle concentrations (5×10^{-5}–10^{-3} M, 600 MHz) in the case of compounds **13** and **15**, indicating the absence of any significant intermolecular aggregation induced by the self-recognition of amide bonds belonging to different molecules. In the case of macrocycle **15**, substantial variations in the chemical shifts are found by changing solvent (Table S1, ESI†), which indicates a switching of conformations, presumably involving the turning on or off of direct stacking interactions between the Binol and the spacing moieties (*vide infra*, molecular modeling), induced by the change of solvent polarity. As shown by Nuclear Overhauser Effect spectroscopy (NOESY), in cycles (*RR*)-**13** and (*RR*)-**15**, the irradiation on the signal resonances of the phenyl proton of the spacing units revealed proximity between the phenyl groups of the central chromophore and the proximal naphthalene ring of the binaphthyl unit. In particular, strong crossover signals were detected between protons G and protons E and F on the BINOL moieties, in both macrocycles.

Macrocycle **15** is composed of a flexible, 3,3′-disubstituted biphenyl system, and the slowing down on the NMR scale of the aryl–aryl free rotation would yield a family of conformations (whose extremes can be identified as *syn–anti*, Fig. 1 top left) which would break up the D_2 symmetry of the macrocycle, causing splitting of the signals.[22] On lowering the temperature, the behavior of compound **13** is indeed different from that of **15**. Whereas the ^{1}H spectrum of compound **13** in d_8-THF does not show any broadening ascribable to a dynamic effect down to −105 °C, the spectrum of compound **15** shows line broadening below −70 °C, followed by decoalescence of the NH signal and of the AB system belonging to the OCH_2 groups (see Fig. 3, right side), that both split into a 50 : 50 ratio.

This behavior indicates a loss of molecular symmetry, and could be ascribed, also by comparison with the behaviour of **13**, to the hindered rotation of the Ar–Ar bond of the biphenyl systems.[23] This rotational barrier is usually very small (about 2.2 kcal mol^{-1} in the case of biphenyl itself),[24] and not observable by NMR in the cases of simple biphenyls lacking *ortho*-substituents.[25] In the present case, however, the constraints imposed by the macrocycle can boost the energy of the coplanar transition state up to an NMR-observable value. From line shape simulation of the NH signal (indicated by the arrow in Fig. 3) and of the AB system (vertical dashes), an energy barrier of 8.0 ± 0.2 kcal mol^{-1} was derived.[26]

Chiroptical properties

The UV/Vis spectra of the two key macrocycles **13** and **15**, and the corresponding BOC-protected precursors (Fig. S1, ESI†),

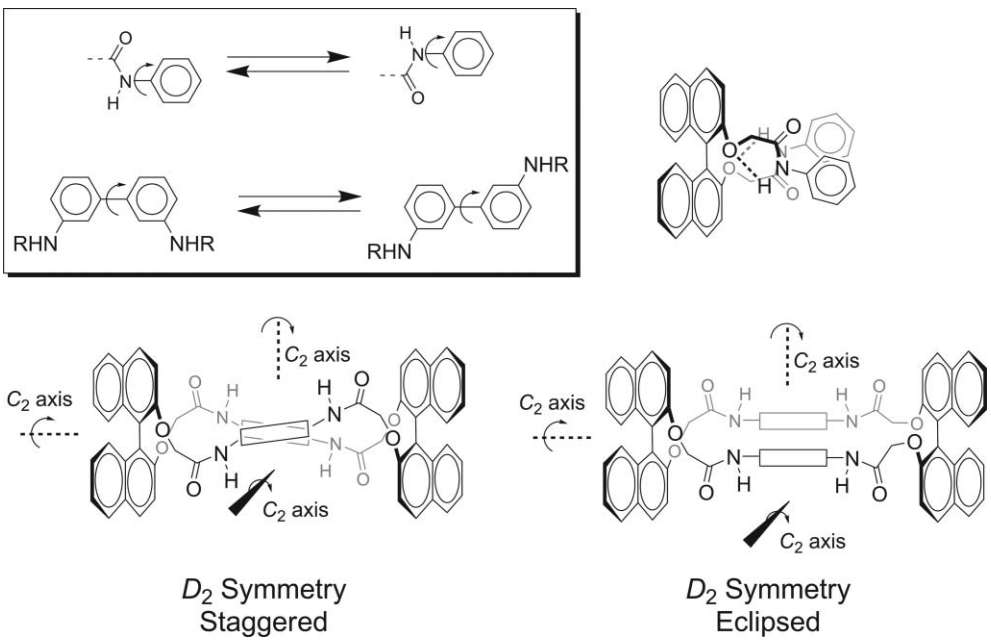


Fig. 1 Symmetry cartoon tools exemplifying: the conformational equilibrium in aromatic amides (top left); the key hydrogen bonding interaction locking the chromophores into a predetermined position (top right); the D_2 overall symmetry of the macrocycles **13–15** in two possible antipodal conformations (bottom).

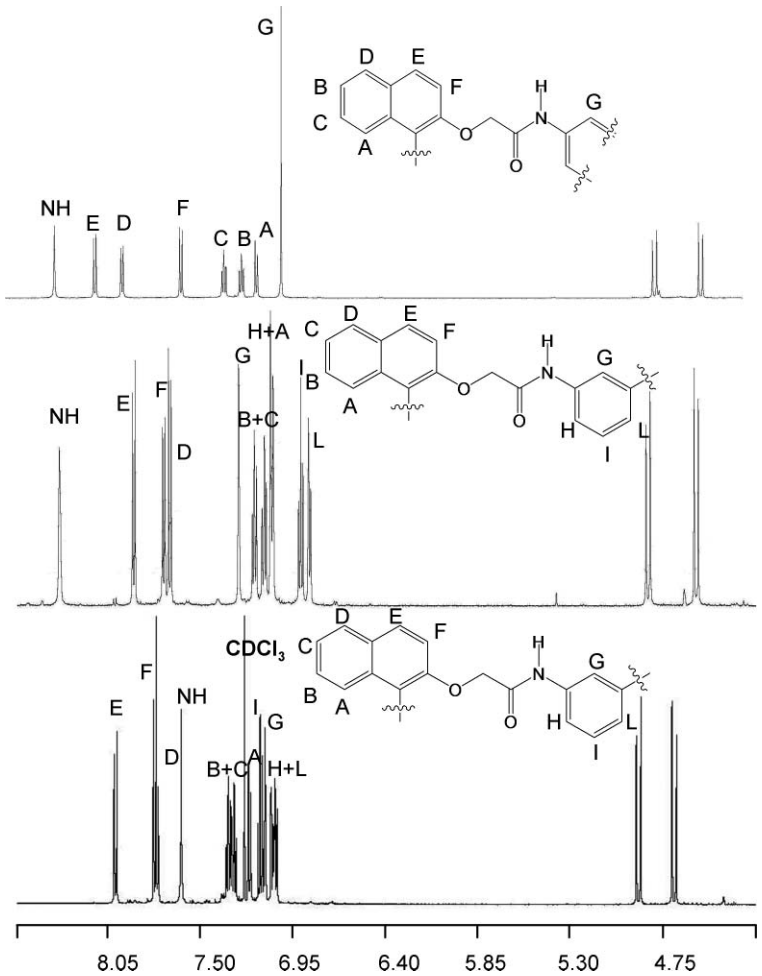


Fig. 2 ^{1}H NMR spectra (600 MHz) of macrocycle **13** (top, d_8-THF) and **15** (middle, d_8-THF; bottom, $CDCl_3$).

are characterized by the characteristic ^{1}B absorption band of the naphthyl fragment of the binaphthol unit (centered at 230 nm), with molar absorptivity values within the range reported for Binol alkyl-substituted compounds.[27] For precursor **2**, bands at *ca.* 280 and 330 nm, associated to the ^1L_a and ^1L_b transitions, respectively, are also clearly evident. In the case of the precursors and macrocycles, these latter bands are obscured by the bands associated to the second aromatic chromophores.‡ No substantial variation of the spectral structure within the range of concentrations allowed by the Lambert–Beer law could be detected, indicating, consistent with what was observed by NMR spectroscopy, that no aggregation phenomena are in place.

The measurements of the optical rotation (Table S2, ESI†), expressed as molar optical rotatory power, for this family of compounds reveal larger values for the macrocycles when compared with the respective precursors. The high contribution to the optical rotation at 589 nm in the case of macrocycles **13** and **15** hints at a well-defined helical conformation.[28] The CD spectra in EtOH are shown in Fig. 4. The most evident transition is the exciton couplet associated to the ^{1}B spectral region of the 2-naphthol chromophore (230 nm). Previous authors have shown a clear qualitative correlation between chiroptical response of Binol derivatives (in terms of $\Delta\varepsilon_{max}$ of the low-energy branch of the couplet) and the bite angle defined by the planes of the two naphthyl molecular modules of the binaphthyl fragment.[27] These data are reported in Table 1. It is evident how, in the unlocked precursors (**2**, or functionalized **7** and **9**), these angles are almost superimposable, and presumably the consequence of a similar degree of steric hindrance of the functionalized acetate substituents on the naphtholic oxygens, common to all three compounds.

On the contrary, the locking of the two chiral units within the rigid, covalent framework in both macrocycles **13** and **15** induced a bite angle in the binaphthyl region which is considerably different from the unlocked precursors, as the intensity of the low energy branch of the couplet (normalized, as two binaphthyl moieties per molecule are present) decreases (see Table 1). In the case of both macrocycles, therefore, the geometry of the spacing unit is not optimal to avoid additional strain in the binaphthyl units of the macrocycle.

‡ The clear absorption maxima for precursor **7** and macrocyle **13** (268 and 269 nm, respectively) matches the reported absorption band for *N*-(4-acetylaminophenyl)-acetamide ($\lambda_{max} = 265$ nm, $\varepsilon = 23\,000$ mol^{-1} dm^3 cm^{-1} in EtOH).[36] Also in the case of precursors **9** and macrocycle **15**, the absorption around 240 nm is considerably enhanced, consistent with that reported for the diacetyl 3,3′-diphenyldiamine ($\lambda_{max} = 242$ nm, $\varepsilon = 15\,000$ mol^{-1} dm^3 cm^{-1} in EtOH).[37] UV/Vis absorption spectra taken in THF or CH_2Cl_2 gave essentially identical results.

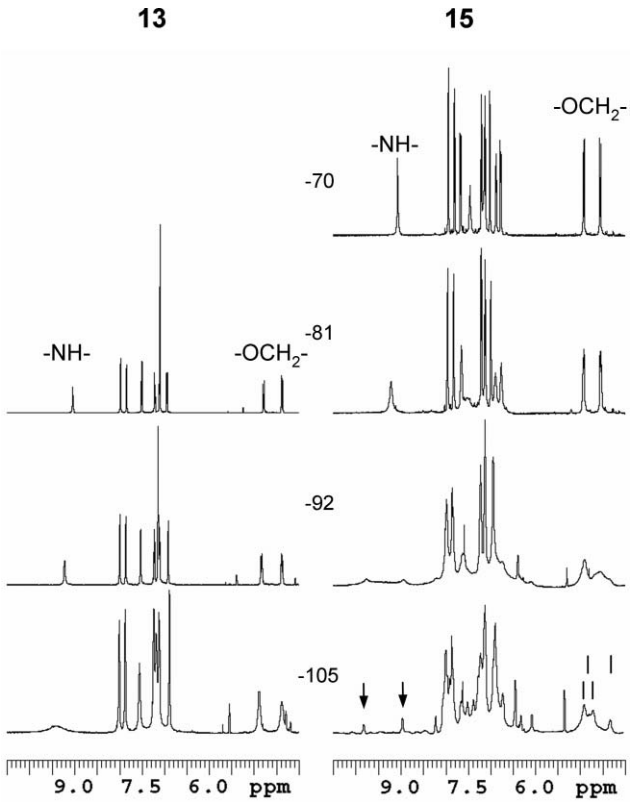


Fig. 3 Variable temperature NMR spectroscopy of macrocycle (*RR*)-**13** (left) and (*RR*)-**15** (right). The two arrows and the four lines (right) indicate the splitting of the proton resonances discussed in the text.

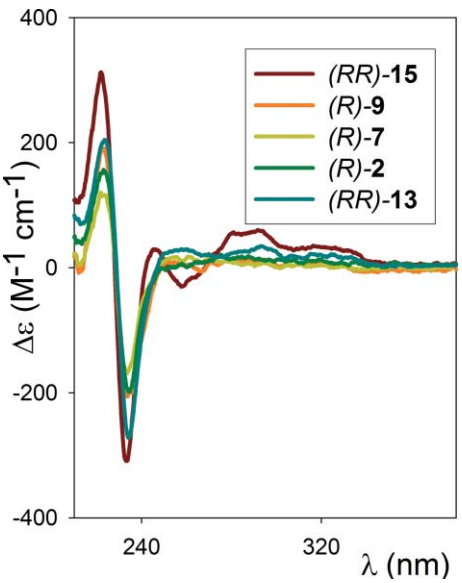


Fig. 4 CD spectra recorded in EtOH ($c = 1.5 \times 10^{-6}$ M).

Above the 220–240 nm region, the immediately evident feature in the CD spectra of macrocycle **15** is the presence of bisignate exciton-couplet-induced CD activity ($\Delta\varepsilon \sim 20$) in the absorption zone of the locked 3,3′-biphenyl chromophores (centered at 246 nm). The bisignate exciton signal, furthermore, is solvent dependent and temperature independent (Fig. 5, and ESI, Fig. S3†). It is bisignate in EtOH, and instead appears as a band entirely

Table 1 Values for the exciton couplet CD signal associated with the binaphthyl unit, and their calculated dihedral angles

Compound	$\Delta\varepsilon$/M^{-1} cm^{-1} [a]	λ/nm [b]	Calcd. angle CD [c]
(*RR*)-**15**	−154(309/2)	233	>90
(*RR*)-**13**	−136(272/2)	234	>90
(*R*)-**9**	−198	234	≈90
(*R*)-**7**	−168	233	≈90
(*R*)-**2**	−206	235	≈90

[a] Value taken on the low energy branch of the binaphthyl exciton couplet. [b] Wavelength of the lowest energy value of the bisignate exciton couplet signal. [c] Determined by comparison with tables and graphs reported in ref. 27 (constructed with data obtained with structurally variable alkyl-substituted 1,1′-binaphthyl-2,2′-diol molecular modules).

located in the negative spectral region in THF. It is not present in the case of macrocycle **13**; Time-Dependent Density Functional Theory (TD-DFT) calculations[4b,29] correctly simulate, in the case of compound **15**, the bisignate exciton couplet centered at 246 nm (Fig. S2, ESI†).

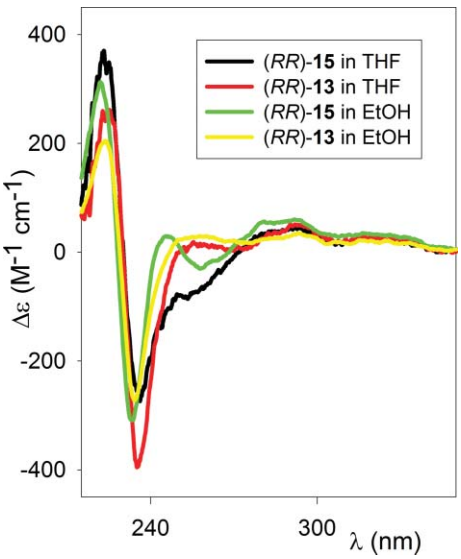


Fig. 5 Solvent-dependent CD spectroscopy of the two macrocycles.

Induced CD activity is observed, in this particular solvent, also in the 300 nm region, corresponding to the low energy transitions associated to the binaphthyl chromophore.[30] In the case of macrocycle **15**, therefore, hydrophobic interactions in a polar solvent favor a "wrapped" conformation of the spacer into a fully collapsed internal cavity, with the 3,3′-diphenyl spacer embedded and in close proximity with the binaphthyl unit; in the relatively less polar THF solvent, instead, a more dynamic situation is in place, although induced CD activity is clearly evident. Variable temperature CD studies (5–50 °C) in EtOH confirm, in the case of **15**, that the induced CD is persistent, indicating a stable molecular conformation; they tend to exclude, furthermore, that the observed signal is due to an intermolecular aggregation phenomenon since in this case an ample modulation of the signal is usually observed (Fig. S3, ESI†).[1b]

Computational studies

In order to better understand the behavior of **15** (and **13** as well), a conformational search has been carried out using Monte Carlo searching together with the MMFF94 molecular mechanics force field[31] (as implemented in Titan 1.0.5). At this stage, MM conformational search indicates that, for both compounds, the lowest energy conformation is by far more stable than all of the other energy minima. These structures were then subjected to minimization using DFT methods (B3LYP/6-31G(d) level).[32] There are some common features to the two structures: the amide functionalities show the tendency, in three cases out of four, to give the five-membered ring hydrogen bonded system highlighted in Fig. 1. The five atoms involved are in all cases defining an almost perfect plane; this seems to force the fourth amide functionality to dispose differently in order to minimize the strain of the second binaphthyl units (see Table 1). In both cases, furthermore, selected hydrogen atoms of the aromatic spacers are pointing towards the aromatic faces of one naphthyl fragment of the binaphthyl unit, in an edge-to-face disposition, confirming the proximity detected by NMR spectroscopy. In the case of **13** (Fig. 6), the two monophenyl spacers are disposed in a staggered-like conformation, but they seem too far away to interact by π–π stacking (centroid–centroid distance of 4.6 Å).

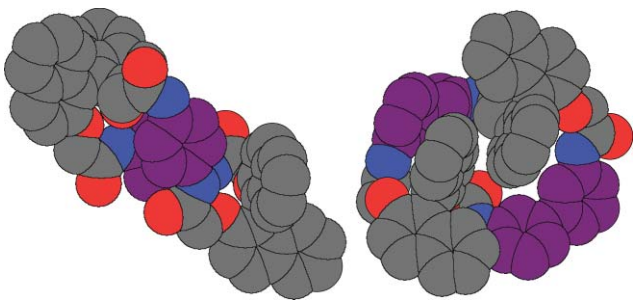


Fig. 6 Space-filling representation of the computationally optimized molecular structures of (*RR*)-**13** (left) and (*RR*)-**15** (right). The central *p*-phenylene (**13**) or *m*-biphenylene (**15**) spacers have been coloured in purple for clarity. Oxygen and nitrogen amide atoms are in red and blue, respectively. See text for details.

In the case of **15**, the increased distance allowed by the 3,3′-diphenyl spacers induces two naphthyl rings of the two different binaphthyls to stack over each other, practically filling the cavity of the macrocycle in an "all wrapped" conformation. There is also stacking between one phenyl of the spacer and one naphthyl of the binaphthyl unit and, as shown by NMR and by CD spectroscopy, this is a fully dynamic, yet persistent situation, that can be partially frozen at low temperatures. The two biphenyl moieties have different geometry, in that the nitrogens are *anti* in one of the biphenyl units, and *syn* in the second one, resulting in a C_1 molecular symmetry of the ground state.

Conclusion

We have reported on the synthesis of rigid, helical macrocycles built on the convergent introduction of axially-chiral binaphthyl units and aromatic segments of different shapes. The more rigid spacer in **13** makes the folding in a less polar "wrapped" conformation impossible, and this is probably the cause for its solubility only in more polar solvents. In the case of **15**, instead, the higher flexibility of the 3,3′-biphenyl spacer results in the possibility of switching the conformation when passing from relatively apolar (THF) to a relatively polar (EtOH) solvent. This difference is clearly signalled by CD spectroscopy, by analyzing the changes in the shape of the induced CD signal deriving from the central, achiral chromophore. The higher flexibility allows the maximization of noncovalent interactions between the central chromophore and the naphthyl units of each binaphthyl moiety, resulting in the slowing down of the aryl–aryl bond rotation, giving an extraordinarily high energy barrier for this equilibrium (about 8 kcal mol^{-1}). The induced CD effect and the NMR barrier in the case of **15**, both the result of an unusual collapsed intramolecular conformation, are unprecedented to our knowledge in covalent macrocyclic systems. Since the precise construction of nanoscale assemblies relies heavily on conformational issues at the molecular level, the clarification of the synthetic and of the dynamic conformational issues related to these macrocycles will be useful for the design of molecular modules as chiral seeds for the non-covalent assembly, in combination with suitable, complementary molecular units, of helical, oriented, robust nanoarchitectures.

Experimental

General experimental

All available compounds were purchased from commercial sources and used as received. 3,3′-Diamino-1,1′-biphenyl[18] and compound **6**[33] were prepared according to a literature procedure. Compounds THF (Na, benzophenone), Et_2O (Na, benzophenone) and CH_2Cl_2 (CaH_2) were dried and distilled before use. ^1H and ^{13}C NMR spectra were recorded from solutions in $CDCl_3$ at 200 or 300 MHz with the solvent residual proton signal as a standard. Spectra of compounds **13** and **15** were recorded at 600 MHz, using a triple resonance indirect probe for the RT spectra and bi-dimensional spectra. Variable temperature spectra of **13** and **15** were recorded using a customized probe. Temperature calibrations were performed before the experiments using a digital thermometer and a Cu/Ni thermocouple placed in an NMR tube filled with isopentane. The conditions were kept as identical as possible with the subsequent work, in particular the sample was not spun and the gas flow was the same as that used during the acquisition of the spectra. The uncertainty in temperature measurements can be estimated as ± 2 °C. Infrared spectra were recorded using NaCl disks or KBr powder using a diffuse reflectance accessory. Mass spectra were recorded using an electrospray ionization instrument. Melting points are uncorrected. Analytical thin layer chromatography was performed on silica gel, chromophore loaded, commercially available plates. Flash chromatography was carried out using silica gel (pore size 60 Å, 230–400 mesh). The UV/Vis spectroscopic studies were recorded using commercially available spectrophotometers. Optical rotations were measured on a polarimeter with a sodium lamp ($\lambda = 589$ nm) and are reported as follows: $[\alpha]_D^{rt}$ ($c = g$ (100 mL)$^{-1}$, solvent). CD spectroscopy was performed using an appropriate spectropolarimeter; spectra were recorded at 25 °C at a scanning speed of 50 nm min^{-1} and were background corrected. Molecular modelling calculations were performed using the Gaussian 03 suite of programs on a server equipped with 2 four-cores Xeon processors operating

at 2.66 GHz. The standard geometry optimization algorithm included in Gaussian 03 was used.[34] All of the calculations employed the B3LYP hybrid HF-DFT method[35] and the 6-31G(d) basis set. Harmonic vibrational frequencies were calculated for all stationary points. As revealed by the frequency analysis, imaginary frequencies were absent in all ground states.

Compound (*R*)-2

A suspension of (*R*)-**1** (778 mg, 2.72 mmol) and Cs_2CO_3 (5.3 g, 16.3 mmol) in DMF (40 ml) was stirred for 20 min at room temperature and then *t*-butyl bromoacetate (2.12 g, 10.9 mmol) was added at once. After 5 h of additional stirring, H_2O (40 mL), and the homogeneous solution was extracted with Et_2O, and then the organic phase dried (Na_2SO_4). Purification by flash chromatography (SiO_2; hexanes–ethyl acetate 97 : 3) yielded (*R*)-**2** as a colourless oil (1.24 g, 87%). $[\alpha]_D^{25}$ +40.7 (*c* 0.01 in CH_2Cl_2). IR (NaCl, nujol, cm^{-1}) 2980, 1750, 1622, 1592, 1368. ^{1}H NMR ($CDCl_3$, 200 MHz, 25 °C) δ = 7.96 (d, 2H; binaphthyl), 7.87 (d, 2H; binaphthyl), 7.31 (m, 2H; binaphthyl), 7.33 (m, 2H; binaphthyl), 7.22 (m, 2H; binaphthyl), 7.17 (m, 2H; binaphthyl), 4.26 (s, 4H; -OCH_2COO-), 1.51 (s, 18H; *t*-butyl). ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C) δ = 168.5 (-*C*OO*t*Bu), 153.3 (Cq), 133.5(Cq), 129.2 (Cq), 129.0 (CH), 127.4 (CH), 125.9 (CH), 125.2 (CH), 123.5 (CH), 120.0 (Cq), 115.0 (CH), 81.3 (-*C*(CH_3)$_3$), 67.2 (-O*C*H_2COO-), 27.4 (-C(*C*H_3)$_3$). Found: C, 74.5; H, 6.6. Calc. for $C_{32}H_{34}O_6$: C, 74.7; H, 6.7.

Compound (*R*)-3

A solution of (*R*)-**2** (606 mg, 1.15 mmol) in CH_2Cl_2–CF_3COOH 9 : 1 (30 mL) was stirred at room temperature for 15 h. The solvent was removed *in vacuo*, and the solid partitioned between H_2O and ethyl acetate. The organic layer was dried (Na_2SO_4) and the solvent removed *in vacuo* to obtain the free dicarboxylic acid (*R*)-**3**, which was used without further purification, in quantitative yield. ^{1}H NMR ($CDCl_3$, 200 MHz, 25 °C) δ = 8.1-7.7 (m, 4H; binaphthyl), 7.05-7.5 (m, 8H; binaphthyl), 4.6 (m, 4H; -OCH_2COO-).

Compound 6

Et_3N (1.06 g, 10 mmol) and $(BOC)_2O$ (2.28 g, 10 mmol) were added to a solution of 3,3′-diamino-1,1′-biphenyl (1.84 g, 10 mmol) in dry CH_2Cl_2. The mixture was stirred at room temperature for 15 h, then washed with H_2O. The organic layer was separated and dried (Na_2SO_4). The product was purified by column chromatography (SiO_2; hexanes–ethyl acetate: 9 : 1) to yield the title compound as a white solid (1.00 g, 3.54 mmol, 32%). ^{1}H NMR (d_6-DMSO, 300 MHz, 25 °C) δ = 9.25 (s, 2H; NH_2), 9.08 (s, 1H; -N*H*CO-), 7.31-7.78 (m, 6H; aromatic), 7.20 (dd 2H; aromatic), 1.49 (s, 9H, C(CH_3)$_3$). ^{13}C NMR (d_6-DMSO, 75 MHz, 25 °C) δ = 153.2 (NH*C*OOtBu), 141.3 (Cq), 141.2 (Cq), 140.5 (CH), 140.4 (CH), 129.7 (CH), 129.5 (CH), 120.8 (CH), 120.6 (CH), 117.7 (Cq), 117.6 (Cq), 116.8 (CH), 116.7 (CH), 79.4 (-*C*(CH_3)$_3$), 28.5 (-C(*C*H_3)$_3$). Found: C, 71.9; H, 7.2; N, 10.0. Calc. for $C_{17}H_{20}N_2O_2$: C, 71.8; H, 7.1; N, 9.9.

General procedure for amide formation to synthesize precursors 7–9

A solution of 1,1′-carbonyldiimidazole (1.47 mmol) in dry THF (8 mL) was added to a solution of (*R*)-**3** (0.49 mmol) in dry THF (15 mL). After 1.5 h of stirring at room temperature, a solution of *N*-BOC monoprotected aromatic diamines **4–6** (0.98 mmol) in dry THF (8 mL) was added and the solution was stirred for a further 15 h. The solvent was then removed *in vacuo*, and the reaction mixture purified by flash chromatography (SiO_2; hexanes–ethyl acetate 6 : 4 or 7 : 3) to yield **7–9** as white solids in 64–72% yields. Spectral data for compound **7** (72% yield): $[\alpha]_D^{25}$ +1.5 (*c* 0.002 in THF). ^{1}H NMR (300 MHz, ($(CD_3)_2CO$) δ = 8.35 (s, 2H), 8.25 (d, 2H), 8.06 (d, 2H) 7.30-7.77 (m, 10H), 6.97 (d, 4H), 4.70 (m, 4H), 1.49 (s, 18H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 166.5, 154.2, 137.0, 134.8, 133.4, 131.6, 131.2, 129.6, 128.4, 126.1, 125.7, 120.9, 120.6, 119.9, 119.5, 116.5, 80.2, 69.4, 28.9. Found: C, 70.9; H, 5.7; N, 7.0. Calc. for $C_{46}H_{46}N_4O_8$: C, 70.6; H, 5.9; N, 7.2. Spectral data for compound (*R*)-**8** (64% yield): $[\alpha]_D^{25}$ −3 (*c* 0.0017 in THF). ^{1}H NMR ($CDCl_3$, 200 MHz, 25 °C) δ = 8.15 (d, 2H; binaphthyl), 8.02 (d, 2H; binaphthyl), 7.60-7.29 (m, 20H; binaphthyl and benzidine), 6.86 (d, 4H; benzidine), 6.60 (s, 2H; -N*H*COOtBu), 4.66 (s, 4H; -OCH_2COO-), 1.56 (s, 18H; *t*-butyl). ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C) δ = 165.4 (-CH_2*C*ONH-), 152.7 (-NH*C*OOtBu), 152.1 (Cq), 137.5 (Cq), 136.8 (Cq), 135.3 (Cq), 135.0 (Cq), 133.4 (Cq), 130.7 (CH), 129.9 (Cq), 128.4 (CH), 127.8 (CH), 127.2 (2CH), 126.8 (2CH), 125.1 (CH), 124.9 (CH), 119.8 (2CH), 119.2 (Cq), 118.7 (2CH), 114.3 (CH), 80.6 (-*C*(CH_3)$_3$), 68.2 (-O*C*H_2COO-), 28.3 (-C(*C*H_3)$_3$). Found: C, 74.8; H, 6.1; N, 6.0. Calc. for $C_{58}H_{54}N_4O_8$: C, 74.5; H, 5.8; N, 6.0. Spectral data for compound (*R*)-**9** (68% yield): $[\alpha]_D^{25}$ −39 (*c* 0.006 in THF). ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ = 8.07 (d, 2H, binaphthyl), 7.83 (m, 2H; binaphthyl), 7.54 (d, 2H; binaphthyl), 7.50-7.30 (m, 8H; binaphthyl and biphenyl), 7.24 (d, 2H; binaphthyl) 6.74 (m, 4H; biphenyl), 4.67 (s, 4H; -OCH_2COO-), 1.58 (s, 18H; *t*-butyl). ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C) δ = 165.4 (-CH_2*C*ONH-), 152.7 (-NH*C*OOtBu), 141.5 (Cq), 141.4 (Cq) 138.7 (Cq), 136.6 (Cq), 133.2 (Cq), 130.7 (CH), 129.7 (Cq), 129.1 (CH), 129.0 (CH), 128.4 (CH), 128.1 (Cq), 127.6 (CH), 124.9 (CH), 124.8 (CH), 123.4 (CH), 122.0 (CH), 119.2 (Cq), 118.4 (CH), 118.0 (CH), 117.6 (CH), 117.3 (CH), 114.4 (CH), 80.5 (-*C*(CH_3)$_3$), 68.2 (-O*C*H_2COO-), 28.3 (-C(*C*H_3)$_3$). Found: C, 74.7; H, 6.0; N, 6.1. Calc. for $C_{58}H_{54}N_4O_8$: C, 74.5; H, 5.8; N, 6.0.

General procedure for the deprotection reaction to synthesize compound 10–12

A solution of **7–9** (0.1 mmol) in CH_2Cl_2–CF_3COOH 9 : 1 (5 mL) was stirred at room temperature for 15 h. The solvent was removed *in vacuo*, and the solid partitioned between a $NaHCO_3$ satd. solution and ethyl acetate. The organic layer was washed with H_2O, dried (Na_2SO_4) and the solvent removed *in vacuo* to obtain the free diamines **10–12**, which was used without further purification, in quantitative yield. Spectral data for (*R*)-**10**: ^{1}H NMR ($CDCl_3$, 200 MHz, 25 °C) δ = 8.09 (d, 2H; binaphthyl) 7.96 (d, 2H; binaphthyl), 7.83 (d, 2H; binaphthyl), 7.3-7.7 (m, 6H; binaphthyl), 7.11 (s, 2H; -N*H*COOtBu), 6.62 (d, 4H, *J* = 8; phenyl), 6.51 (d, 4H; phenyl), 4.6 (s, 4H; -OCH_2COO-), 3.4 (bs, 4H; NH_2). Spectral data for (*R*)-**11**: ^{1}H NMR ($CDCl_3$, 200 MHz, 25 °C) δ = 8.15

(d, 2H; binaphthyl), 8.0 (d, 2H; binaphthyl), 7.51-7.34 (m, 16H; benzidine and binaphthyl), 6.86-6.73 (m, 8H; benzidine), 4.65 (s, 4H; -OCH_2COO-). Spectral data for (*R*)-**12**: ^{1}H NMR ($CDCl_3$, 200 MHz, 25 °C) $\delta = 8.07$ (d, 2H; $J = 8$ Hz; binaphthyl), 7.87 (m, 2H; binaphthyl), 7.22-7.49 (m, 16H; biphenyl and binaphthyl), 6.74-7.04 (m, 8H; biphenyl), 4.66 (s, 4H; -OCH_2COO-).

General procedure for the cyclization reaction to synthesize 13–15

1,1′-carbonyldiimidazole (0.96 mmol) was added to a solution of (*R*)-**3** (0.32 mmol) in dry THF (63 mL). After 1.5 h of stirring at room temperature, compounds **10–12**, respectively, (0.32 mmol) were added at once and the solution was stirred for a further 15 h. The solvent was then removed *in vacuo*, and the reaction mixture purified by flash chromatography (SiO_2; hexanes–ethyl acetate 3 : 1 to 1 : 3) to yield **13–15** in 2–27% yields as white solids. Spectral data for macrocycle (*RR*)-**13** (27%): MS(ESI): *m*/*z* 971.5 ([*M* + Na]$^+$, 100%). $[\alpha]_D^{25}$ +247 (*c* 0.0008 in THF). IR (KBr, cm^{-1}) 3280 (broad), 1770, 1664, 1462, 1377. ^{1}H NMR (d_6-DMSO, 200 MHz, 25 °C) $\delta = 9.23$ (s, 4H; -N*H*CO-), 8.11 (d, 4H; binaphthyl), 7.98 (d, 4H, $J = 10$ Hz; binaphthyl), 7.59 (d, 4H; binaphthyl), 7.34 (t, 4H, binaphthyl), 7.27 (t, 4H; binaphthyl), 7.01 (s, 8H; phenyl), 6.95 (d, 4H, binaphthyl), 4.89 (d, 4H; -OCH_2COO-) 4.50 (d, 4H; -OCH_2COO-). ^{13}C NMR (d_6-DMSO, 75 MHz, 25 °C) $\delta = 166.2$ (-NH*C*OCH$_2$-), 152.9 (Cq), 133.4 (Cq), 129.4 (CH), 129.0 (Cq), 128.1 (CH), 126.7 (CH), 124.4 (CH), 123.8 (CH), 120.4 (2CH), 118.7 (Cq), 115.6 (Cq), 114.8 (CH), 66.6 (-O*C*H$_2$COO-). Found: C, 75.7; H, 4.7; N, 5.6. Calc. for $C_{60}H_{44}N_4O_8$: C, 75.9; H, 4.7; N, 5.9. Spectral data for macrocycle (*RR*)-**14** (4 mg, 2%): MS(ESI): *m*/*z* 1123.4 ([*M* + Na]$^+$, 100%). ^{1}H NMR (d_6-DMSO, 200 MHz, 25 °C) $\delta = 9.12$ (s, 4H; -N*H*CO-), 7.73 (d, 4H; binaphthyl), 7.60 (d, 4H; binaphthyl), 7.22 (d, 4H; aromatic), 6.88-6.99 (m, 22H; aromatic), 6.57 (d, 4H; benzidine), 4.58 (d, 4H; -OCH_2COO-), 4.18 (d, 4H; -OCH_2COO-). Spectral data for macrocycle **15** (20%): $[\alpha]_D^{25}$ +180 (*c* 0.001, THF). IR (KBr, cm^{-1}) = 3270 (broad), 1775, 1660, 1450, 1378. ^{1}H NMR (600 MHz, $CDCl_3$) $\delta = 8.02$ (d, 4H), 7.78 (d, 4H), 7.76 (d, 4H), 7.62 (s, 4H), 7.34 (t, 4H), 7.31 (t, 4H), 7.25 (d, 4H), 7.15 (m 4H), 7.09 (m, 8H), 7.05 (m, 4H), 4.94 (d, 4H), 4.72 (d, 4H).^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 165.8$, 152.1, 140.0, 136.2, 133.2, 130.4, 129.5), 128.5, 127.9, 127.0, 124.3, 124.2, 122.7, 119.0, 118.1, 117.6, 114.0, 68.3. MS (ESI) [*M* + Na]$^+$ 1123.4. Found: C, 78.7; H, 4.7; N, 4.8. Calc. for $C_{72}H_{52}N_4O_8$: C, 78.5; H, 4.8; N, 5.1.

Acknowledgements

Financial support from the University of Pavia, MIUR (PRIN 2004 "Ingegneria Cristallina di Materiali a Base Molecolare"), Regione Lombardia (INGENIO postdoctoral fellowship to CC) and Fondazione CARIPLO (2007–2009 "Self-Assembled Nanostructured Materials: A Strategy for the Control of Electrooptic Properties", DP) is gratefully acknowledged. AM acknowledges the financial support from University of Bologna (RFO funds) and MIUR (PRIN 2007, "Stereoselezione in Sintesi Organica, Metodologie e Applicazioni")

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