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Rigid optically-active D_2 and D_3 macrocycles †

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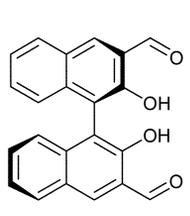
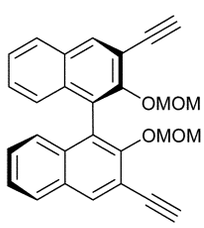
The synthesis and characterization of novel optically-active macrocycles, obtained by esterification reaction from a binaphthyl-containing diol and phthalic or terephthalic acids, and possessing overall D_2 or D_3 symmetry, is described.

Large macrocyclic structures with a high degree of shape-persistency have been the subject of increasing interest.[1] Traditionally macrocycles have been used as receptors and sensors for small organic molecules able to fit their cavity. Large and conformationally stable cyclic structures have recently been proposed as covalent scaffolds in order to form organic tubular structures by supramolecular association of the subunits. Striking examples of this strategy were published in recent years using different subunits, such as for example cyclic peptides,[2] phenylacetylene macrocycles,[3] or synthetic cyclic oligosaccharides.[4] We are interested in synthesizing chiral macrocycles which, by the introduction of suitable self-associating moieties, can assemble in columnar helical strucures with the aim of obtaining tailored material properties.[5] To achieve this, we have been exploring possible synthetic pathways for the rapid construction of macrocycles incorporating a source of axial chirality, such as binaphthyl-based macrocycles: chirality is expressed as a means of restricted rotation around the aryl–aryl bond and the conformational freedom of the unit is, therefore, limited.[6] Macrocycles incorporating two or more binaphthyl units have already been described in the literature: in recent examples the coupling of resolved, optically active binaphthols such as (*R*)-**1** with optically-active 1,2-diphenylethylenediamine furnished the [2 + 2] macrocycle only when one enantiomer of the diamine was used.[7] Diederich *et al*.[8] have reported the synthesis and characterization of a number of large macrocycles, incorporating mainly 3 or 4 binaphthyl units such as (*R*)-**2**, *via* efficient Glaser coupling of the terminal acetylenic units.



(R)-**1**



(R)-**2**

However, the [2 + 2] macrocycle was not obtained, probably because the number of binaphthyl units required for closing the macrocycle is dictated by the dihedral angle of the rigid binaphthyl unit.

In this communication, we report our investigations on the use of a simple cyclization protocol, based on an esterification reaction, in order to gain rapid access to macrocycles comprised of two or more binaphthol units. The compound (*R*)-3,3′-bis(hydroxymethyl)-2,2′-dimethoxy-1,1′-binaphthyl **3** was synthesized in several steps starting from racemic 1,1′-bi-2-naphthol as previously described.[9] The cyclization reactions were carried out in the presence of equimolar amounts of phthalic or terephthalic acids, respectively, in conditions developed for high yield room temperature polysterifications, using diisopropylcarbodiimide (DICD) as the coupling agent and 4-(dimethylamino)pyridinium 4-toluenesulfonate salt (DPTS) as the catalyst.[10]

The different sized macrocycles were well separated by flash chromatography in nonpolar solvents to give, the [2 + 2] adducts (*RR*)-**4** and (*RR*)-**6**, and the [3 + 3] macrocycles (*RRR*)-**5** and (*RRR*)-**7** (Fig. 1).

The [2 + 2] adducts were obtained as the main product in both cases, with yields of 16% and 18% respectively, whereas the [3 + 3] adducts were obtained with yields of 13% and 9%. ‡ Attempts to optimize reaction yields by using high dilution techniques resulted in almost negligible reactivity. Thus the cited yields refer to reactions carried out at 10–20 mmolar concentration of both reactants in CH_2Cl_2 for the macrocyclization reactions. The structure of the compounds was fully confirmed by mass spectrometric analyses. § The ^{1}H and ^{13}C NMR spectra reflected the highly symmetrical nature of the compounds. For example, the ^{1}H NMR spectra of compounds **4**–**7** showed at room temperature only one signal for each proton of the naphthyl moiety, as they are all related by symmetry operations both in the case of the [2 + 2] macrocycles, possessing D_2 overall symmetry, and the [3 + 3] macrocyles, possessing D_3 overall symmetry.

However, subtle but striking differences in the ^{1}H NMR spectra revealed how these macrocycles possess internal cavities of very different shapes and flexibility. For example, the resonances attributed to the methoxy protons of the binaphthyl moiety are clearly different comparing (*RR*)-**4** (2.88 ppm) with (*RR*)-**6** (3.48 ppm), containing phthalic or terephthalic acid moieties as spacers. When the macrocycles become larger and more flexible, the values for the chemical shifts for the OMe protons (3.06 ppm for (*RRR*)-**5** and 3.35 ppm (*RRR*)-**7**), tend towards the value recorded for precursor (*R*)-**3** (3.32 ppm). The diastereotopic methylene proton resonances appear as a well defined AB quartet in both (*RR*)-**4** and (*RR*)-**6**. Interestingly, in the case of both the larger (*RRR*)-**5** and (*RRR*)-**7** they appear as a collapsed signal. This suggests that in the larger macrocycles these protons experience a local environment which is substantially different from that of the more rigid (*RR*)-**4** and (*RR*)-**6** and of precursor (*R*)-**3**.[11]

A variable temperature ^{1}H NMR study, conducted on the (*RRR*)-**5** macrocycle (Fig. 2), showed, with the decrease of temperature, a splitting of the resonances in a well defined AB quartet. This indicates that the conformational preference present for the larger macrocycles at room temperature is not accessible at lower temperatures.

Circular dichroism spectroscopy of compounds **4**–**7** (Fig. 3) showed the exciton couplet typical of binaphthol moieties, corresponding to the maximum absorption band in the UV/Vis spectra (*ca*. 228 nm for all compounds). The intensity of the

† Electronic supplementary information (ESI) available: experimental details and ^{1}H NMR spectra for compounds **4**–**7**. See http://www.rsc.org/suppdata/ob/b3/b310751p/

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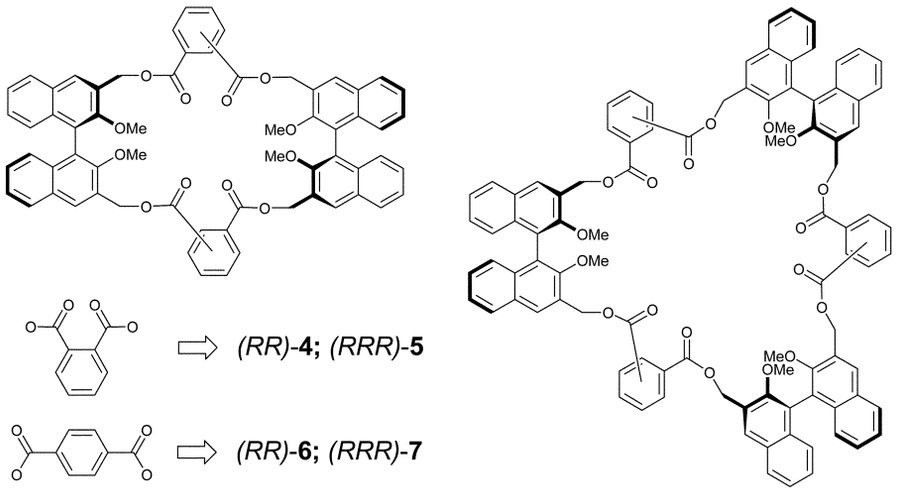

Fig. 1 Macrocycles (*RR*)-**4**, (*RR*)-**6** and (*RRR*)-**5**, (*RRR*)-**7**, obtained by condensation with phthalic and terephthalic acids, respectively.

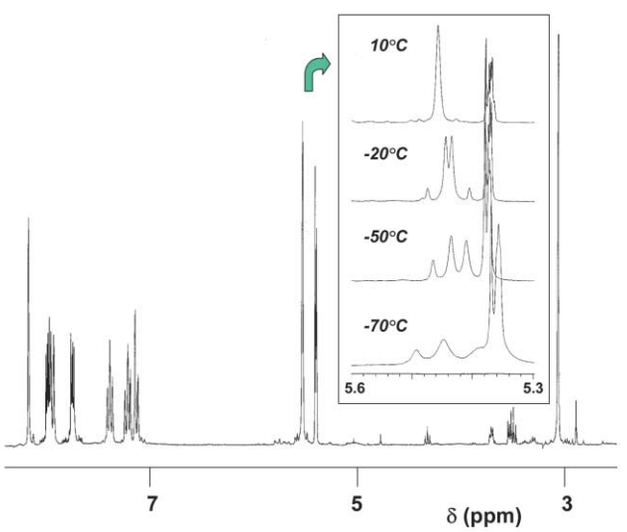

Fig. 2 Variable temperature ^{1}H NMR spectroscopy (300 MHz, CD_2Cl_2) for macrocycle (*RRR*)-**5**.

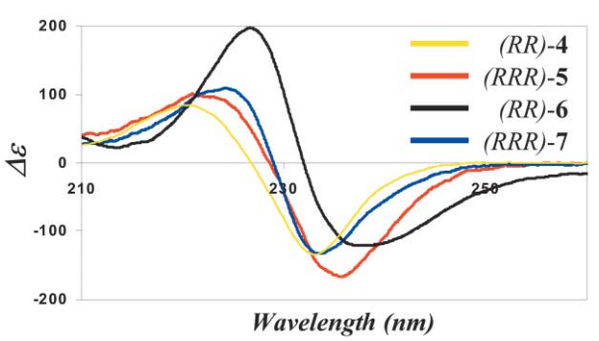

Fig. 3 Circular dichroism spectra for macrocycles **4**–**7** in THF ($c = 1$–6×10^{-5} M).

low energy component of the couplet (at 230–240 nm) ranges between values of −120 for (*RR*)-**6** and −160 for (*RRR*)-**5**; for 2,2′-binaphthol derivatives, these values have been directly related to variations of the dihedral angle between the naphthyl units as a consequence of the steric hindrance of the substituents in the 2,2′-positions.[12] Since compounds **4**–**7** possess the same substituent (OMe) in the 2,2′-positions, the differences between the above mentioned values should be ascribed to variations of the average dihedral angle of the binaphthyl units as a consequence of their incorporation in cyclized structures of differing sizes. Further experiments, such as the removal of the methoxy protecting groups, will give us useful insights on the conformational rigidity of these novel macrocycles, and will allow us to evaluate their potential as building blocks for the assembly of chiral nanoarchitectures.

Notes and references

‡ Other fractions, corresponding to cyclized products of higher dimensions, were also isolated at lower yields. Their ^{1}H NMR spectra were consistent with highly simmetrical compounds. Their mass spectra (ESI) showed unique species present in the samples. The differences observed between the measured and the calculated molecular ion peaks are attributed to an accuracy loss, associated with the instrument used, for molecules weighting more than 2000 Da.

§ For example, in the case of (*RR*)-**4** the MS-ESI spectrum shows a peak at $m/z = 1031$ ($[M + Na]^+$, 100%,), while the MS-ESI spectrum for (*RRR*)-**7** shows the corresponding peak at 1535 ($[M + Na]^+$, 100%).

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