Versatile Bottom-up Approach to Stapled π-Conjugated Helical Scaffolds: Synthesis and Chiroptical Properties of Cyclic *o*-Phenylene Ethynylene Oligomers**

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In memory of Christian Claessens

Carbon nanocoils (CNCs) are carbon allotropes with tubular diameters as small as 20 nm, and present interesting technological applications.[1] They have been used to generate magnetic fields through chiral electric currents, thus emulating the behavior of a solenoid,[2] and have shown pseudoelastic properties allowing elongations of up to 42% without permanent deformation.[3] Although in a broad sense [*n*]-helicenes and *o*-phenylenes can be considered CNCs, they feature extremely rigid backbones in the axial direction (helix propagation)[4] and densely packed π systems. This fact hinders the expected chiral electron transport (ET) because of competitive ET through the π-stacked aromatic rings, thus limiting their use as a nanocoil.[5] Considering the structural features of these CNCs, we were interested in the conformationally flexible open-chain *o*-phenylene ethynylene oligomers (*o*-PEOs), which were mainly developed by Tew and co-workers[6] and can adopt helical arrangements by supramolecular interactions.[7] Nevertheless, such arrangements are solvent dependent and may not be suitable for applications demanding a permanent shape.[8] Within this context, the covalent stapling[9] of conformationally dynamic *o*-PEOs would lead to the corresponding less-tight helical compounds. These loops would have a helical conductive backbone, but the potential ET through the π-stacked aromatic rings could be avoided by tuning the space defined by the staple (spacer group). This is essential to emulate the behavior of a macroscopic solenoid. Moreover, if the spacer group is conforma-

tionally flexible, the structure could be either compressed or stretched mechanically without significant energy variation. The stretching process of a very flexible chain could lead to a long-range pseudoelastic behavior. Additionally, the introduction of chiral spacers could lead to flexible, optically active structures adopting a helical shape, in which chiral currents could be potentially induced.[10] Moore and co-workers have reported a family of chiral *m*-PEOs using diastereoselective complexation with chiral guests[11,12] or by introducing a chiral moiety as substituent within the oligomer chain.[13] The introduction of chirality into *o*-PEOs has been considerably less studied.[6] To the best of our knowledge, *o*-PEOs and *m*-PEOs with cyclic structures closed by a chiral unit have not been reported up to date.

Recently, we described the synthesis of simple organic compounds which exert elementary electronic functions,[14] by using a bottom-up approach. Herein, we disclose a similar approach to synthesize the smallest members of a new CNC family, which would be able to retain their striking properties. Surprisingly, the stapling of simple foldamers has been scarcely reported in literature.[15] We show that *o*-PEOs functionalized with simple oxygenated functions such as allylic ethers and benzylic alcohols can be conveniently stapled using simple stapling reactions such as esterification with diacid derivatives or alkene metathesis reactions. Notably, remarkable chiroptical responses could be achieved with the introduction of a very simple and available optically

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active staple such as a tartrate diester. A significant transfer of chirality from the stereogenic centers to the helical framework in these new cyclic structures was observed.

The starting *o*-PEOs **A**–**H** were prepared using Sonogashira couplings.[16] We chose open-chain *o*-PEOs derivatives **A** and **D**, having a *para* substitution pattern at the terminal aryl ring, the *meta*-substituted analogues **B** and **E**, and the *meta,para*-substituted derivative **C** (Scheme 1). These substitution patterns allowed evaluation of the influence of the different geometries on the properties of the final stapled products. Compounds **F**, **G**, and **H**, having two *meta,meta*-disubstituted terminal aromatic rings were also obtained so as to place two linkers in the closed targets. Benzyl alcohols (**A**–**C**, **F**) or allyl ethers (**D**, **E**, **G**, and **H**) situated on the terminal aryl groups of the *o*-PEOs systems (Scheme 1) facilitated the attachment to the spacer. Thus, compounds bearing the free hydroxy groups were esterified with different diacids, previously activated as acid chlorides, as spacers.[17] The results, shown in Scheme 1, evidenced that open-chain difunctionalized compounds **A**–**C** were able to efficiently accommodate diesters derived from malonate (**1**, **5**, and **7**), succinate (**2**), and glutarate (**4**). Compounds **3** and **6**, having an L-tartrate moiety, were obtained as a 80:20 mixture of diastereomers, as determined by HPLC. This evidenced the presence of two chiral elements in the structures: the stereogenic centers present in the L-tartrate unit and a new chiral helical fragment. All the structures were fully characterized by ^{1}H and ^{13}C NMR spectroscopy, MS, and, in most cases, by X-ray diffraction.[16]

The X-ray analysis confirmed our hypothesis of the partial disconnection between the superposed benzene rings (Figure 1). The distance between the aromatic superposed rings, ranging from 4.5 to 5.6 Å, was longer than the typical π–π stacking distance (3.5–3.8 Å). The helical arrangement of these stapled structures was also seen in the X-ray structure. The unit cell of the crystal obtained for **3** (Figure 1 b) consisted of two different helical diastereoisomers (*M,R,R* and *P,R,R*), although **3** had been synthesized as a 80:20 mixture of both diastereomers.

Comparison of UV/vis spectra provided evidence of the change from conformationally flexible *o*-PEOs to the close-shaped systems.[16] The wide absorption band appearing in the open structures at about $\lambda_{max} = 270$ nm, resulting from the aromatic chromophores, was red shifted in all cases to $\lambda = 300$ nm after the stapling reaction.[18] The CD spectra of compounds **3**, **6**, **11**, **15**, and **17**, having the (−)-*O,O*′-dipivaloyl-L-tartrate moiety, are depicted in Figure 2. Taking into account the presence of both *M*- and *P*-helical diastereomers in these derivatives, the chiroptical responses are noteworthy. In the region of $\lambda < 270$ nm, the CD absorptions of the tartrate moiety[19] overlap with bands corresponding to the aromatic framework. As the *R,R* configuration of the

stereogenic carbon atoms of the tartrate is the same in all cases, the presence in this region of positive bands in the
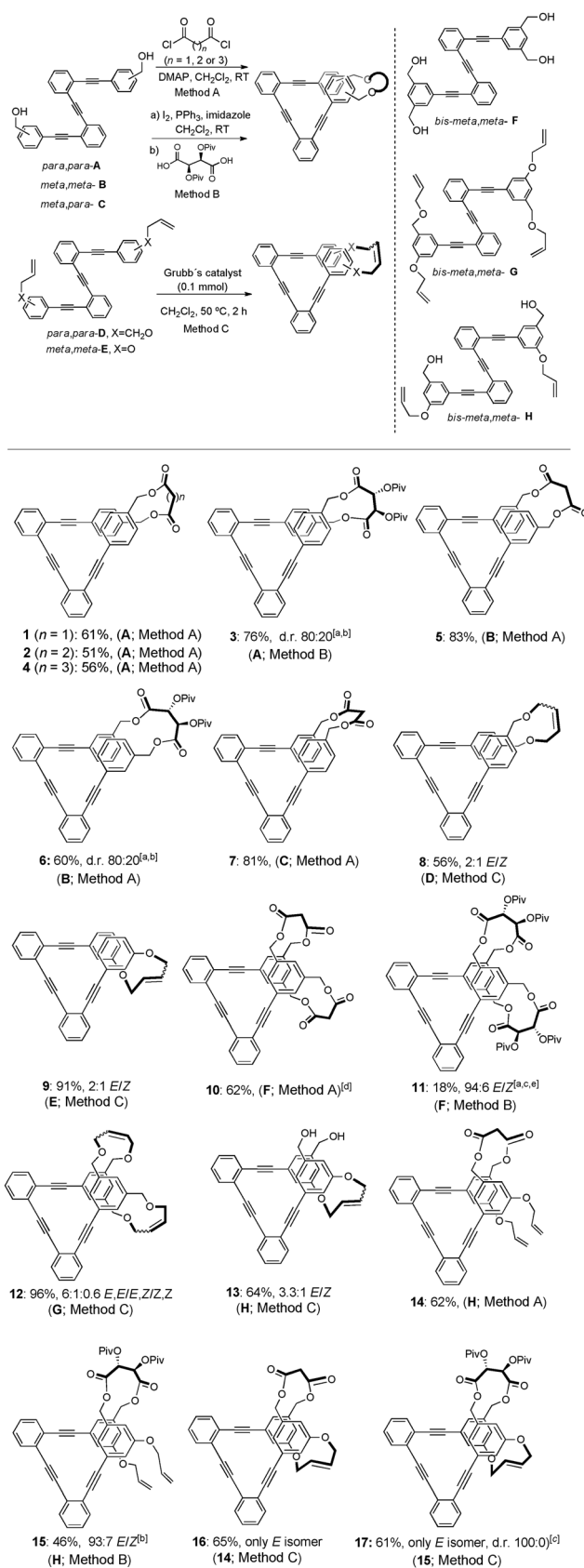
Scheme 1. Synthesized CNCs **1**–**17** from *o*-PEOs **A**–**H**. [a] Yield based on recovered starting material.[16] [b] Chiralpack IC column using *n*-hexane/*i*PrOH (90:10) as the eluent with a 0.5 mL min^{-1} flow rate. [c] Chiralpack IB column using *n*-hexane/*i*PrOH (90:10) as the eluent with a 0.5 mL min^{-1} flow rate. [d] Used 2 equiv of malonyl chloride. [e] Used 2 equiv of (−)-*O,O*′-di-pivaloyl-L-tartaric acid.
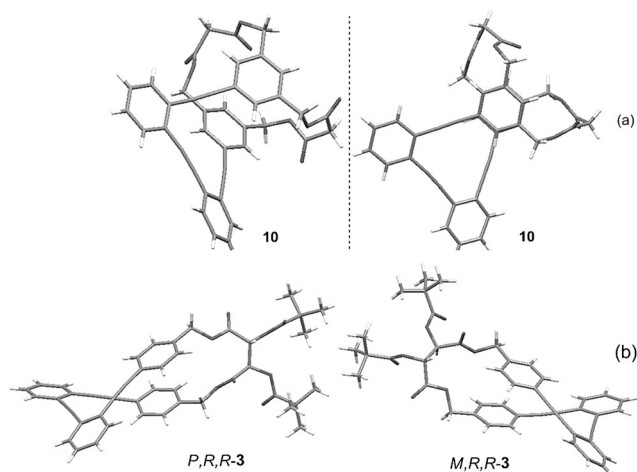
Figure 1. Representative X-ray structures: a) **10** (side view left and top view right). b) *P,R,R*-**3** and *M,R,R*-**3**.[27]

Figure 2. CD spectra (1×10^{-5} M in CH_2Cl_2). a) Mono and doubly stapled derivatives (−)-**3**, (+)-**6**, (+)-**11**, (+)-**15**, and (−)-**17**. b) Pure diastereomers (*M,R,R*)-**3** (solid line) and (*P,R,R*)-**3** (dotted line), 80:20 mixture of (*M,R,R*)-**3**, and (*P,R,R*)-**3** (dash-dot line). c) TD-PBE0/6-31G* spectra[25] of (*M,R,R*)-**3**/(*P,R,R*)-**3** (80:20; solid line) and (*P,R,R*)-**3**/(*M,R,R*)-**3** (80:20; dotted line).

monotartrates **6** and **15**, and negative ones in **3** (Figure 2a) indicated a significant contribution of the aromatic chiral helical framework to these absorptions. The CD bands in the region $\lambda > 270$ nm were also of opposite sign for **3** when compared with those of **6** and **15**. The *p*-substituted mono-stapled tartrate **3** gave a chiroptical response in the region of about $\lambda = 295$ nm, which was much more intense ($\Delta\varepsilon = 47.35$) and pseudoenantiomeric to that of the *meta*-substituted analogues **6** ($\Delta\varepsilon = -5.07$) and **15** ($\Delta\varepsilon = -12.21$). Thus the chiral L-tartrate unit was able to induce a helix of different configuration depending on the relative *m* or *p* positions of the benzyl alcohols in the initial *o*-PEOs precursors. The intensity of these bands significantly depends on the relative substitution of the terminal aromatic rings. Pure (*M,R,R*)-**3**[20] and (*P,R,R*)-**3** diastereomers could be obtained after separation of the 80:20 mixture initially obtained by HPLC using a chiral stationary phase.[16] As can be seen in Figure 2b pseudoenantiomeric CD bands were observed for each diastereomer. The absorptions of the 80:20 mixture of **3** were very similar to those of the (*M,R,R*)-**3** diastereomer. The theoretical simulation of the ECD spectra[16] of the two possible (*M,R,R*) and (*P,R,R*) helical structures of **3** as well as that of the 80:20 and 20:80 mixtures of both diastereomers (Figure 2c), allowed the identification of the absolute configuration of the major species contributing to the 80:20 mixture of **3** experimentally obtained. Theoretical ECD spectra were calculated[21] in the frame of time-dependent density functional theory (TDDFT), by combining the PBE0 functional,[22] and the 6-31G* basis set[23] as implemented in Gaussian09 program suite.[24] As can be seen, the ECD curve for the 80:20 mixture of (*M,R,R*)-**3** and (*P,R,R*)-**3** featured a negative band in the $\lambda = 330$–400 nm spectral region, a very intense positive absorption at about $\lambda = 300$ nm, and another negative band at about $\lambda = 270$ nm. The qualitative agreement with the experimental ECD spectrum obtained for the 80:20 mixture of **3** and pure (*M,R,R*)-**3** (Figure 2b) is very good and allowed assignment of the (*M,R,R*)-**3** configuration to the major diastereomer. A pseudoenantiomeric ECD spectrum was calculated for the reverse diastereomer ratio (Figure 2c),
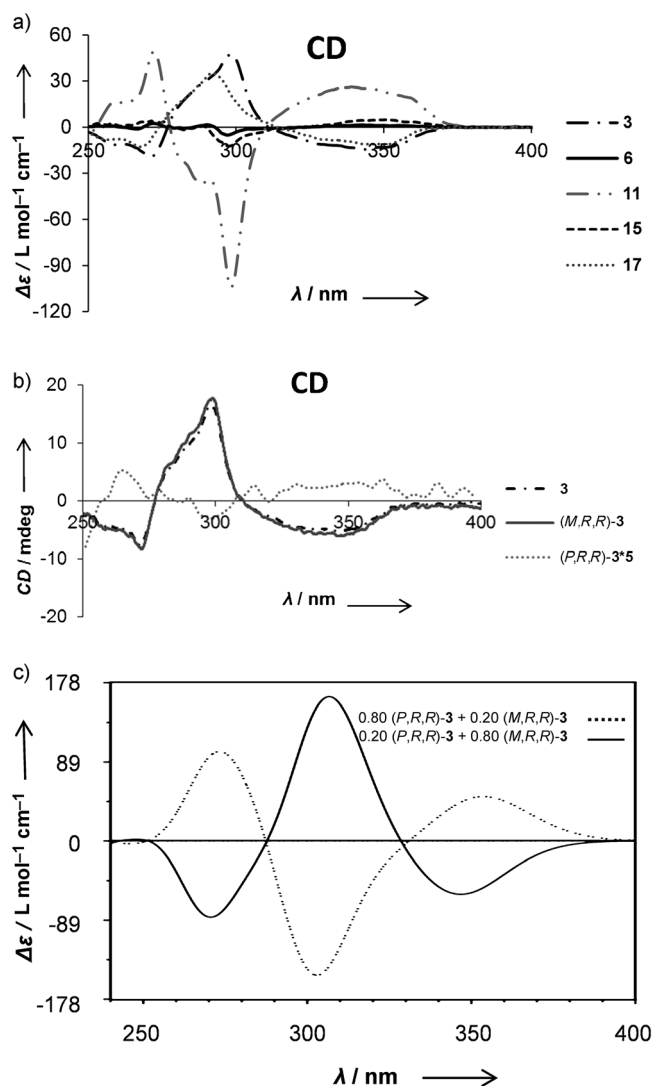
and is in agreement with the ECD spectra experimentally recorded for the pure diastereoisomer (*P,R,R*)-**3**.

Pseudoenantiomeric chiroptical responses were also experimentally observed in the CD spectra of the doubly stapled *meta*-substituted derivatives **11** [$\Delta\varepsilon$ (298 nm) = −105.14], having two tartrate moieties, and **17** [$\Delta\varepsilon$ (292 nm) = 35.02], having one tartrate and one 2-butene linker (Figure 2a). As we were dealing with mixtures of (*P,R,R*) and (*M,R,R*) diastereomers, the positive broad bands at about $\lambda = 360$ nm for **6** and **15** suggested that the major diastereomer in this case the *P*-configured helical moiety.[20] In a similar way, the configuration of the major diastereomers present in **11** and **17** were assigned as (*P,R,R*) and (*M,R,R*), respectively. Thus, a preferred handed *P* helicity was induced when one (−)-*O,O′*-di-pivaloyl-L-tartaric acid was introduced as a chiral staple in the *m*-substituted *o*-PEOs **B** and **H**, to fix

the major helical structure in **6** and **15**. The same *P* helicity was induced when two L-tartrate units acted as staples to close the *meta,meta*-disusbtituted tetraol *o*-PEO **F**, thus leading to **11**. The opposite *M* helicity was induced when the *p*-substituted *o*-PEO **A** was transformed into the monostapled derivative **3** and when the *meta,meta*-disubstituted **F** was transformed sequentially, by the L-tartrate reaction and olefin metathesis, into **17**. This remarkable chirality induction is due to an intramolecular central-to-helix chirality transfer and the configuration of the major diastereomer formed is structure dependent.

Theoretical calculations also allowed prediction of pseudoelastic behavior for these systems. An inspection of the potential energy profile of compound **1**, chosen as a model, when submitted to mechanical stress, was calculated. DFT calculations (M06/6-31G*)[26] revealed two different regimes for the compression and the lengthening (Figure 3). An almost quadratic behavior was observed at small elongations (± 0.2 Å) with an estimated Hook force constant of 20.2 kcal Å^{-2} mol^{-1}.[4] In the lengthening regime, except for small elongations, the system dependence was practically linear and elongations up to 2 Å (55% longer) were accessible with low-energy requirements (< 3 kcal mol^{-1}). This pseudoelastic behavior is quite similar to that of CNCs.[3]
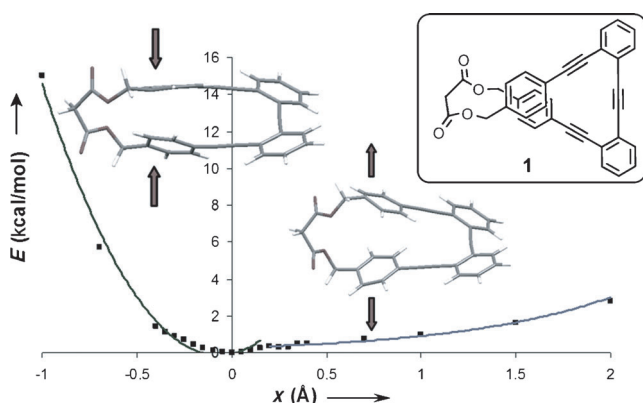

Figure 3. Potential energy profile of compound **1** toward elongation.

In conclusion, we have developed a versatile synthesis of flexible helical π-conjugated cyclic nanocoils from easily prepared *o*-PEOs, which retain some of their interesting properties. Our approach allowed the preparation of homochiral systems by introduction of L-tartrate esters. This simple chiral unit was able to induce either *P* or *M* configurations in the helical systems, as evidenced by the chiroptical responses observed. These helices could work as nanosolenoids, nanosprings, pressure sensors (when submitted to an external source of pressure), or adaptative ligands for metals because of their flexible backbone. The method described herein is general enough to envision further synthetic applications en route to larger chiral coils with different connecting groups.

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