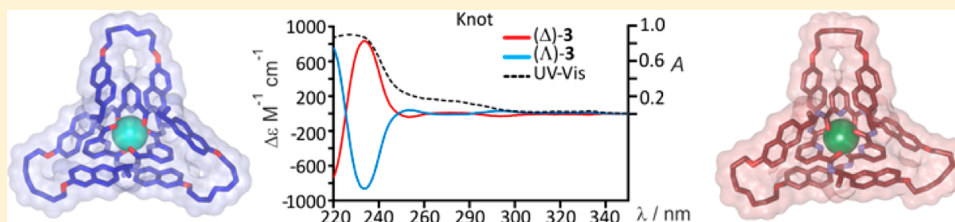# Lanthanide Template Synthesis of Trefoil Knots of Single Handedness

Gen Zhang, Guzmán Gil-Ramírez, Augustinas Markevicius, Colm Browne, Iñigo J. Vitorica-Yrezabal, and David A. Leigh*

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S *Supporting Information*

ABSTRACT: We report on the assembly of 2,6-pyridinedicarboxamide ligands (**1**) with point chirality about lanthanide metal ion (Ln^{3+}) templates, in which the helical chirality of the resulting entwined 3:1 ligand:metal complexes is covalently captured by ring-closing olefin metathesis to form topologically chiral molecular trefoil knots of single handedness. The ligands do not self-sort (racemic ligands form a near-statistical mixture of homoleptic and heteroleptic lanthanide complexes), but the use of only (*R,R*)-**1** leads solely to a trefoil knot of Λ-handedness, whereas (*S,S*)-**1** forms the Δ-trefoil knot with complete stereoselectivity. The knots and their isomeric unknot macrocycles were characterized by NMR spectroscopy, mass spectrometry, and X-ray crystallography and the expression of the chirality that results from the topology of the knots studied by circular dichroism.

INTRODUCTION

Knots are significant structural features of circular DNA[1] and about 1% of proteins in the Protein Data Bank (PDB)[2] and are believed to play an important role in the properties of both natural and synthetic polymers.[3] For many (but not all) knots, their topology alone is sufficient to confer chirality.[4] As such chirality is a consequence of the three-dimensional constraints on the loop as a whole, it may be that this form of topological stereochemistry could ultimately prove useful for applications in which the expression of chirality is particularly important (chiral recognition, asymmetric catalysis, chiral liquid crystal phases, materials for nonlinear optics, etc.).[5] The simplest prime knot—the trefoil knot—is topologically chiral, possessing D_3-symmetric Λ-helical chirality in its most symmetrical representation if the loop crosses over and then under (a positive crossing) three times when traced in a clockwise fashion (Δ- if the crossings have the opposite sense).[4] Although a number of small-molecule trefoil knots have been prepared to date,[6−11] their stereoselective synthesis remains a significant challenge,[12] with only one designed stereoselective route,[9] and two examples of chiral trefoil knots formed unexpectedly during macrocyclization reactions,[10] reported to date.

We recently described[11] the synthesis of a racemic molecular trefoil knot through the organization, and subsequent ring closing olefin metathesis (RCM), of three 2,6-pyridinedicarboxamide-based ligands coordinated to a lanthanide ion template.[13] In the initial assembly process the three tridentate ligands bind to the nine-coordinate metal ion to form complexes with Λ- or Δ-handedness (analogous to the arrangement of three bidentate ligands around an octahedral metal ion),[14] both of which are present, in equal numbers, in the unit cell of the X-ray crystal structure. Introducing chiral centers close to the donor atoms of the ligands should induce the formation of lanthanide−ligand complexes of single handedness[15] which, we reasoned, upon ring closure might transfer the point chirality of the ligands to the topological chirality of the resulting knot.

RESULTS AND DISCUSSION

Ligand (*R,R*)-**1** (Scheme 1) and its enantiomer (*S,S*)-**1** (see Supporting Information) were prepared in five steps from commercially available building blocks. The enantiomeric purity (>99% ee) of the chiral intermediates and the final ligands was confirmed by chiral HPLC analysis (see Supporting Information). Treatment of (*R,R*)-**1** with $Ln(CF_3SO_3)_3$ (Ln = Eu or Lu) in a 3:1 ratio in acetonitrile, followed by precipitation with dichloromethane, gave the corresponding $Ln((R,R)$-**1**$)_3(CF_3SO_3)_3$ complexes in 83% (Eu) and 89% (Lu) yields. The 3:1 ligand:metal stoichiometry was confirmed by electro-spray ionization mass spectrometry (ESI-MS; m/z 1082 $[Lu((R,R)$-**1**$)_3][CF_3SO_3]^{2+}$, 672 $[Lu((R,R)$-**1**$)_3]^{3+}$). The symmetry of the ^1H NMR spectra of the complexes showed all three ligands to be in equivalent environments, which is only possible if a single handedness of the metal−ligand complex is present (later shown to be Λ- when using three (*R,R*)-ligands).

Scheme 1. Stereoselective Lanthanide Template Synthesis of a Molecular Trefoil Knot, Λ-(R^6)-3^a
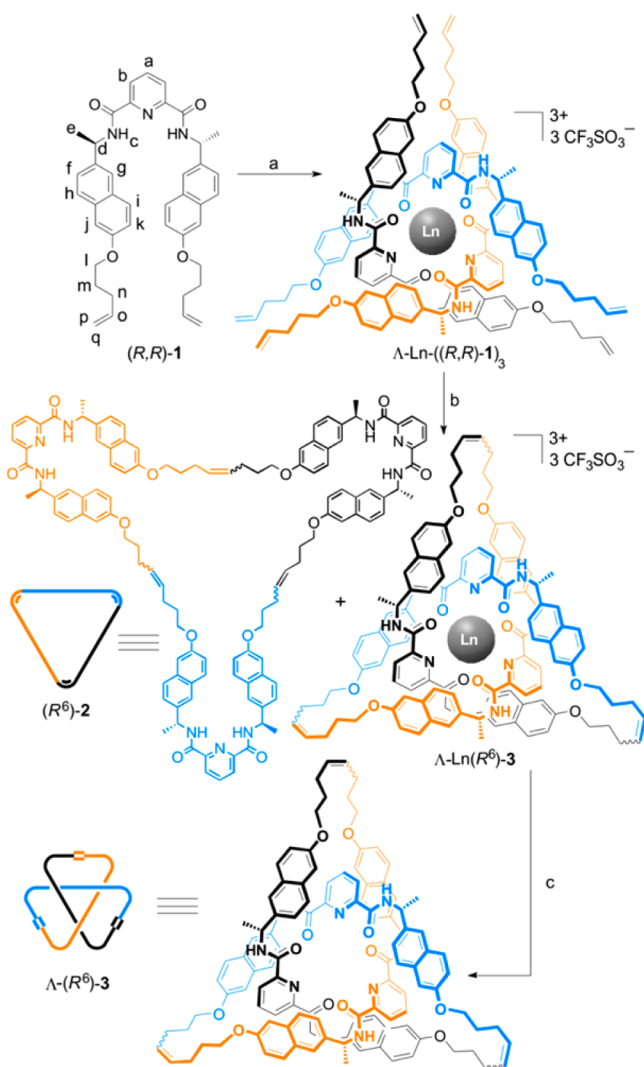
^{a}A similar synthetic sequence starting from (S,S)-1 afforded Δ-(S^6)-3 (see Supporting Information). (a) Ln(CF$_3$SO$_3$)$_3$, MeCN, RT, 2 h, 89% (Ln = Lu); 83% (Ln = Eu). (b) (1) Hoveyda−Grubbs (second generation) catalyst (50 mol %), CH$_2$Cl$_2$/MeNO$_2$, 50 °C, 18 h; (2) Na$_5$DTPA, DMF, RT, 45 min, 62% (Ln = Lu); 55% (Ln = Eu). (c) TEAF, DMSO, 80 °C, 5 min, 74%.

To join the ligand termini to form the trefoil knot, Λ-Lu((R,R)-1)$_3$(CF$_3$SO$_3$)$_3$ was treated with second generation Hoveyda−Grubbs catalyst (50 mol %, 17% loading per connection) in CH$_2$Cl$_2$/CH$_3$NO$_2$ (3:1, v/v) at 50 °C for 18 h (Scheme 1, step b1). Following quenching of the reaction with ethyl vinyl ether, addition of dichloromethane precipitated a mixture of the trefoil knot complex Λ-Lu(R^6)-3(CF$_3$SO$_3$)$_3$ and the isomeric unknot macrocycle complex Λ-Lu(R^6)-2(CF$_3$SO$_3$)$_3$.[16]

The two topological isomers were separated by exploiting their significantly different binding affinities for Ln^{3+} ions.[11] Treatment of the mixture of the unknot and trefoil knot metal complexes in dimethylformamide (DMF) with the chelating agent pentasodium diethylenetriaminepentaacetate (Na$_5$DTPA) smoothly removed the lutetium from the unknot macrocycle, forming (R^6)-2, while the trefoil knot complex Λ-Lu(R^6)-3(CF$_3$SO$_3$)$_3$ remained intact (Scheme 1, step b2). The

metal-free unknot macrocycle (R^6)-2 (15% isolated yield) could then be extracted with dichloromethane leaving behind the pure trefoil knot complex Λ-Lu(R^6)-3(CF$_3$SO$_3$)$_3$ in 62% isolated yield. Treatment of pristine Λ-Lu(R^6)-3(CF$_3$SO$_3$)$_3$ with tetraethylammonium fluoride (TEAF) in dimethyl sulfoxide (DMSO) at 80 °C afforded the wholly organic trefoil knot Λ-(R^6)-3 in 74% yield (Scheme 1, step c).

An analogous route was used to convert Eu((R,R)-1)$_3$(CF$_3$SO$_3$)$_3$ into Λ-Eu(R^6)-3(CF$_3$SO$_3$)$_3$ (Scheme 1) and, starting from (S,S)-1, a similar set of procedures led to the stereoselective synthesis of trefoil knot Δ-(S^6)-3, unknot macrocycle (S^6)-2 and the corresponding Lu(III) and Eu(III) salts (see Supporting Information).

The ^{1}H NMR spectrum (600 MHz, DMSO-d_6, 298 K) of unknot macrocycle (R^6)-2 (Figure 1b) is similar to that of
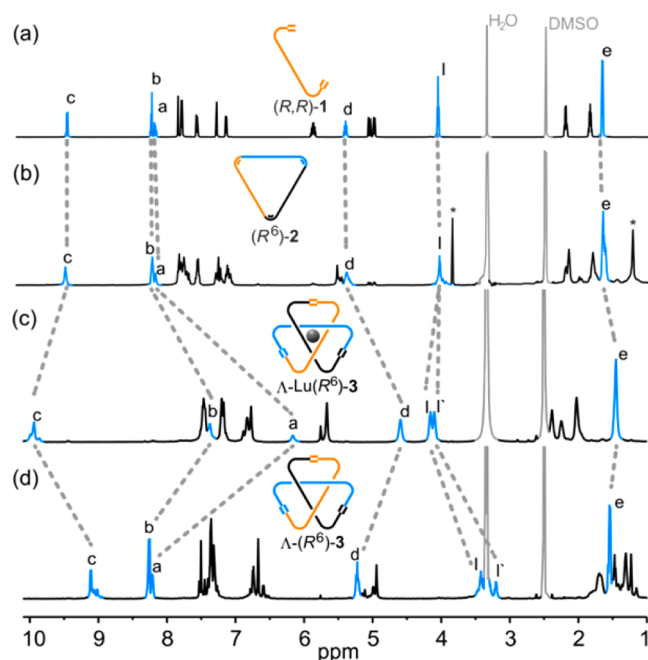
Figure 1. ^{1}H NMR spectra (600 MHz, DMSO-d_6, 295 K) of (a) ligand (R,R)-1, (b) unknot macrocycle (R^6)-2, (c) lutetium-trefoil-knot complex Λ-(R^6)-Lu3(CF$_3$SO$_3$)$_3$, and (d) demetalated trefoil knot Λ-(R^6)-3. The lettering refers to the proton assignments shown for (R,R)-1 in Scheme 1. * = impurity.

ligand (R,R)-1 (Figure 1a), other than the disappearance of the terminal alkene proton signals of (R,R)-1 at 5.06 and 4.99 ppm. In contrast, the ^{1}H NMR spectrum of the isomeric demetalated trefoil knot Λ-(R^6)-3 (Figure 1d) shows significant changes in several resonances, including upfield shifts of the H$_l$ protons (Δδ ∼ 0.66 ppm), presumably as a result of the positioning of these residues face-on to aromatic rings in the compact structure of the knot.

Slow diffusion of diethyl ether into saturated methanolic solutions of Λ-Eu(R^6)-3(CF$_3$SO$_3$)$_3$ or Δ-Lu(S^6)-3(CF$_3$SO$_3$)$_3$ afforded single crystals suitable for X-ray diffraction (see Supporting Information). The solid-state structures confirm the molecular topology and show that (R^6)-3 is a trefoil knot of Λ-handedness, while (S^6)-3 is of Δ-handed topology (Figure 2). The knotted ligand wraps around the central metal ion to give a trigonal prismatic coordination geometry with the Ln−O (Eu−O 2.380(8)−2.454(9) Å; Lu−O 2.307(8)−2.361(8) Å) and Ln−N (Eu−N 2.548(2)−2.583(1) Å; Lu−N 2.435(8)−
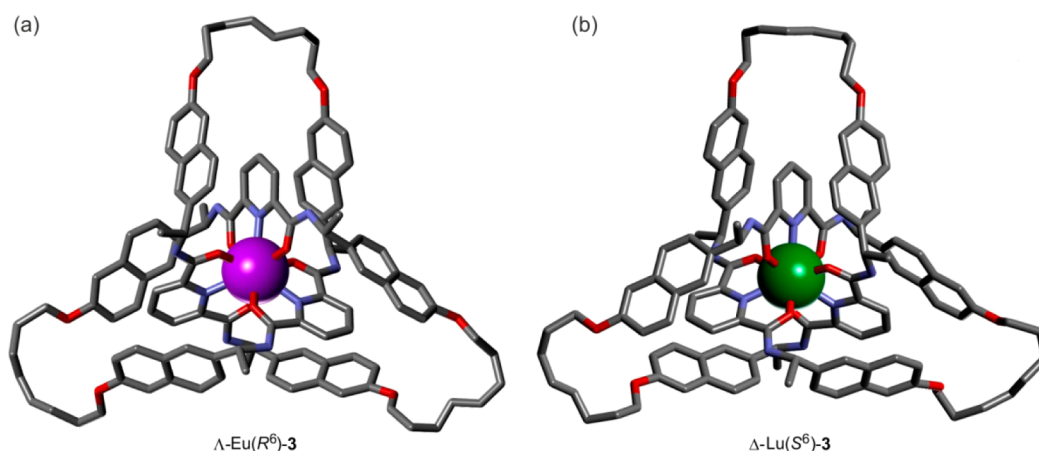
Figure 2. X-ray crystal structures of (a) Λ-Eu-(R^6)-**3**(CF$_3$SO$_3$)$_3$ and (b) Δ-Lu-(S^6)-**3**(CF$_3$SO$_3$)$_3$ shown in framework representation. Hydrogen atoms, solvent molecules, and counterions are omitted for clarity. The europium atom is shown in purple; lutetium, green; nitrogens, purple; oxygens, red; and carbons, gray. Selected metal−heteroatom bond lengths (Å): Eu−O 2.413(8), 2.428(8), 2.454(9), 2.407(9), 2.417(8), 2.454(8), 2.380(9) and Eu−N 2.583(8), 2.548(9), 2.569(8); Lu−O 2.361(8), 2.307(8), 2.323(9), 2.332(9), 2.320(8) and Lu−N 2.435(8), 2.473(9), 2.457(8).

2.473(9) Å) distances in the expected ranges for pyridine-2,6-dicarboxamide complexes.[15,17] Aromatic stacking interactions between each pyridine ring and two naphthalene groups arrange the ligand into a tight compact structure around the metal. This arrangement is consistent with the ^{1}H NMR chemical shifts for the pyridine and naphthalene groups in the trefoil knot complexes in solution (Figure 1c). The steric constraints are such that changing the stereochemistry of any of the asymmetric carbon centers in the knot could not be tolerated by the complex. Disorder in the olefin region of the chains in the X-ray crystal structure indicate that a mixture of E and Z olefins are formed during the RCM reaction.

The syntheses of trefoil knots Λ-(R^6)-**3** and Δ-(S^6)-**3** are apparently completely stereoselective in terms of knot handedness, and molecular models indicate that lanthanide complexes of the diastereomeric knots of opposite topological handedness (i.e., Δ-Ln(R^6)-**3** or Λ-(S^6)-**3**) would not be able to form. Clearly the transfer of point chirality from the three tridentate ligands coordinated to the lanthanide ion to the topological chirality of the trefoil knot is highly effective. However, we found that when combined with Lu^{3+} ions, a racemic mixture of (R,R)-**1** and (S,S)-**1**-d_4 ligands (the latter deuterium labeled to enable analysis of the constitution of the complexes by mass spectrometry) does not self-sort into a 1:1 mixture of Λ-Lu((R,R)-**1**)$_3$ and Δ-Lu((S,S)-**1**-d_4)$_3$ but instead forms a near-statistical mixture of diastereoisomeric complexes (Figure 3). Furthermore, RCM of this mixture does not yield more of Λ-Lu(R^6)-**3** or Δ-Lu(S^6)-**3**-d_{12} than would be expected from the amount of Λ-Lu((R,R)-**1**)$_3$ and Δ-Lu((S,S)-**1**-d_4)$_3$ present initially, so there is also no self-sorting during the reaction to covalent capture the knots.[18] Although the stereochemistry of (R,R)/(S,S)-**1** is sufficient to generate a lanthanide complex of single helical handedness in a homoleptic complex (demonstrated by ^{1}H NMR, *vide supra*), there appears to be little energy difference between this structure and heteroleptic complexes containing ligands of opposing point chirality.

Previously a small number of studies have compared either the properties of a trefoil knot and its unknot macrocyclic isomer[6b,7k,10b] or the properties of trefoil knot enantiomers.[8] The synthetic availability of both enantiomers of **1**, and the ability to make both the unknot and trefoil knot isomers, means that for the first time differences in properties can be compared
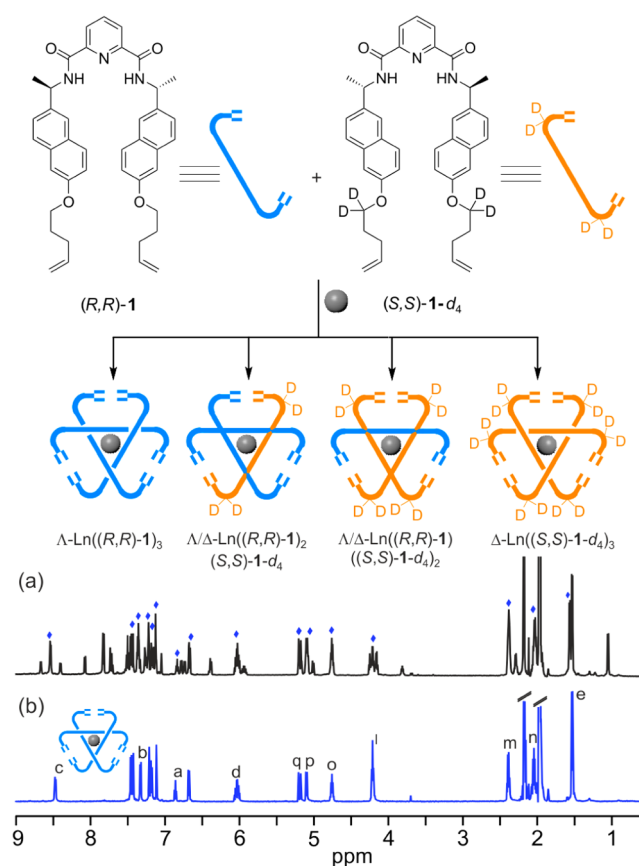
Figure 3. Lack of self-sorting of (R,R)-**1** and (S,S)-**1**-d_4 upon coordination to Ln^{3+} ions. (a) ^{1}H NMR spectrum (600 MHz, CD$_3$CN, 295 K) of the product distribution arising from a 1:1 mixture of (R,R)-**1** and (S,S)-**1**-d_4 in the presence of 0.33 equiv of Lu(OTf)$_3$ (proton resonances for homoleptic complex Λ-Lu((R,R)-**1**)$_3$ labeled with blue diamonds). Mass spectrometry indicates the formation of a near-statistical mixture of homoleptic and heteroleptic Lu**1**$_3$ complexes. (b) ^{1}H NMR spectrum (600 MHz, CD$_3$CN, 295 K) of (R,R)-**1** in the presence of 0.33 equiv of Lu(OTf)$_3$ (i.e., Λ-Lu((R,R)-**1**)$_3$).

between *both* topological isomers (unknot and trefoil knot) *and* topological enantiomers (Λ- and Δ-knots).

The UV−visible absorption (UV−vis) spectra of (R,R)/(S,S)-**1** (see Supporting Information), unknot macrocycle (R^6)/(S^6)-**2** (e.g., Figure 4b), and trefoil knot Λ-(R^6)/Δ-(S^6)-
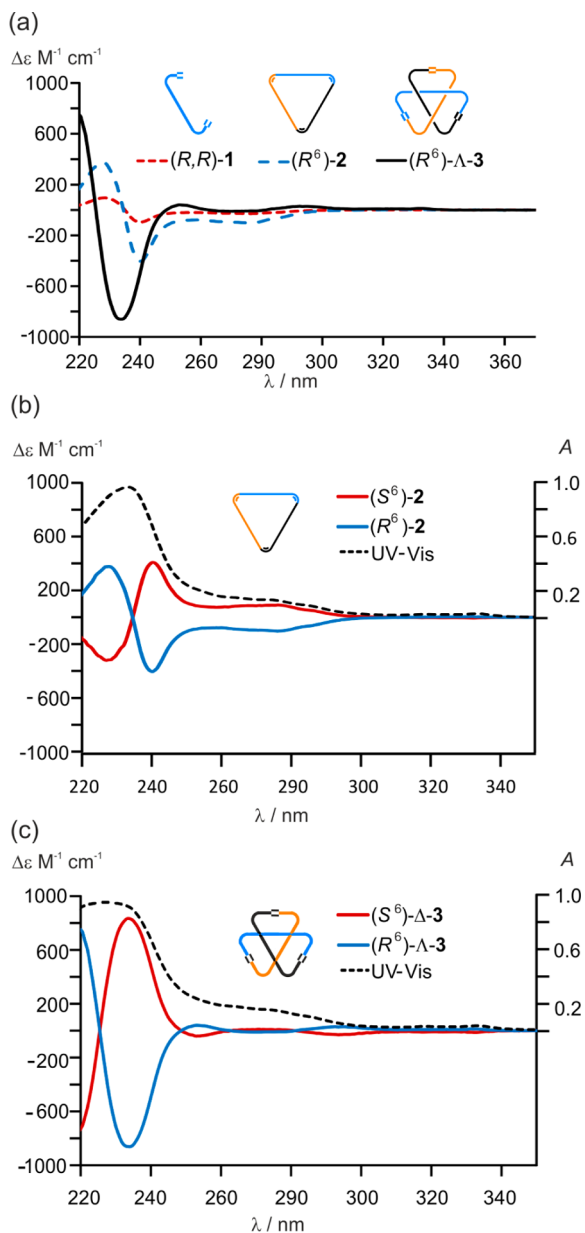
Figure 4. Overlay of the UV−vis (2.7 × 10^{-5} M, CH$_2$Cl$_2$, 298 K; scale right-hand axis) and CD spectra (2.7 × 10^{-5} M [except (R,R)-**1** 7.8 × 10^{-5} M], CH$_2$Cl$_2$, 298 K; scale left-hand axis) of (a) ligand (R,R)-**1**, unknot macrocycle (R^6)-**2** and trefoil knot Λ-(R^6)-**3**; (b) unknot macrocycles (R^6)-**2** and (S^6)-**2**; and (c) trefoil knots Λ-(R^6)-**3** and Δ-(S^6)-**3**. The CD spectra are normalized for molarity rather then absorbance intensity at a particular wavelength, so the unknot macrocycle and trefoil knot spectra arise from 3× more chromophores than (R,R)-**1**.

3 (e.g., Figure 4c) have similar profiles with absorption bands at λ = 233 nm (pyridyl n−π^*) and 275 nm (naphthalene π−π^*) in the expected ranges[17] for 2,6-pyridinedicarboxamides. The molar absorptivity (ε of (R^6)/(S^6)-**2** is 3-fold that of (R,R)/(S,S)-**1**, consistent with each molecule of the unknot macrocycle having 3× the chromophores of the tridentate ligand. However, the trefoil knot Λ-(R^6)/Δ-(S^6)-**3** shows a 1.4-

fold decrease in absorbance at 233 nm compared to the unknot (R^6)/(S^6)-**2** isomer (see Supporting Information). This may be a consequence of the compact arrangement of the pyridyl groups in the knot leading to more effective through-space coupling of the n−π^* transitions.[19]

The circular dichroism (CD) spectra of ligand (R,R)-**1**, unknot macrocycle (R^6)-**2** and trefoil knot Λ-(R^6)-**3** are shown in Figure 4a. The $\Delta\varepsilon$ of (R^6)-**2** is 3-fold that of (R,R)-**1**, again in line with the number of chromophores in each molecule, but other than this the spectra of (R,R)-**1** and (R^6)-**2** are very similar, both a reflection of the influence of the chiral centers on the adjacent chromophores. However, the induced CD signal for the trefoil knot (Λ-(R^6)-**3**) is almost 3× stronger than that of the unknot macrocycle (R^6)-**2** in the range 220−248 nm, showing that in these molecules the single element of topological chirality has a much greater effect on the asymmetry of the chromophore environment than the six asymmetric carbon atoms. In addition a hypsochromic shift ($\Delta\lambda$ = 8 nm) of the exciton coupling for the pyridyl n−π^* transitions is observed for Λ-(R^6)-**3** compared to (R^6)-**2**, indicating a larger HOMO−LUMO band gap in the trefoil knot.

The CD spectra of the trefoil knot enantiomers (Figure 4c), Λ-(R^6)-**3** and Δ-(S^6)-**3**, have exciton couplings of equal and opposite sign with maxima at 233 nm, confirming their opposite chirality. The negative exciton-couplet is consistent with the absolute configuration of the handedness of the knot (R^6)-**3** being Λ.[19] The CD spectra of the unknot enantiomers (R^6)-**2** and (S^6)-**2** also have profiles of equal and opposite sign (Figure 4b). It should be noted that in the absence of a coordinating lanthanide ion, the trefoil knots likely do not adopt well-defined helical conformations (whereas the Ln-complexed knots possess D_3-helical symmetry; Figure 2), but rather the CD spectrum is the summation of different dissymmetric[20] and asymmetric conformations adopted by the topologically chiral knot, interconverted through intramolecular reptation.[7c]

■ CONCLUSIONS

The complexation of tridentate ligands possessing point chirality to lanthanide ions can be used to transfer chiral information from asymmetric stereocenters to topological stereochemistry in a short and efficient synthesis of molecular trefoil knots of single handedness. Although the knot synthesis is completely stereoselective, a racemic mixture of the tridentate ligands does not self-sort during complex formation. The solid-state structures of lutetium and europium complexes of the chiral trefoil knots (examples of both handedness) were determined by X-ray crystallography, revealing the interactions and steric constraints that control and direct the assembly and chiral induction process. The simplicity and flexibility of the synthetic pathway mean that for the first time differences in the properties of both topological isomers (unknot macrocycle and trefoil knot) and topological enantiomers (Λ- and Δ- knots) can be compared. We find that the single element of topological stereochemistry (trefoil knot versus unknot macrocycle) has a much greater influence on the asymmetry of the chromophore environment (manifested in the CD spectrum) than the six asymmetric carbon centers present in the molecules. This supports the notion[5] that molecular knots of single handedness could ultimately prove useful in chemical processes where the transfer or expression of chirality plays a crucial role.

ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b07069.

    Synthesis, electronic absorption, circular dichroism, NMR, MS and X-ray crystallography data (PDF)
Additional characterization data (CIF)
Additional characterization data (CIF)

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Notes
The authors declare no competing financial interest.

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