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Stereoselective Synthesis of Molecular Square and Granny Knots

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Supporting Information Placeholder

ABSTRACT: We report on the stereoselective synthesis of both molecular granny and square knots through the use of lanthanide-complexed overhand knots of specific handedness as three-crossing ‘entanglement synthons’. The composite knots are assembled by combining two entanglement synthons (of the same chirality for a granny knot; of opposite handedness for a square knot) in three synthetic steps: First, a CuAAC reaction joins together one end of each overhand knot. Ring-closing olefin metathesis (RCM) then affords the closed-loop knot, locking the topology. This allows the lanthanide ions necessary for stabilizing the entangled conformation of the synthons to subsequently be removed. The composite knots were characterized by ^1H and ^{13}C NMR spectroscopy and mass spectrometry, and the chirality of the knot stereoisomers compared by circular dichroism. The synthetic strategy of combining building blocks of defined stereochemistry (here overhand knots of Λ - or Δ -handed entanglement) is reminiscent of the chiron approach of using minimalist chiral synthons in the stereoselective synthesis of molecules with multiple asymmetric centers.

INTRODUCTION

Most of the small-molecule knots¹ synthesized to date are trefoil² (3_1)³ knots, the simplest non-trivial knot topology. The few examples of more complex synthetic molecular knots^{4,5} are highly symmetrical,⁶ with the strand crossings assembled in one or two steps using frameworks designed to only tolerate the particular crossing pattern required. Unfortunately such strategies are not extendable to many knot topologies, which often lack sufficient symmetry in their crossing arrangements. Alternative synthetic approaches will need to be developed in order to access at the molecular level the majority of knot topologies.^{1a}

Knots are topologically distinct from each other in terms of the number of times a strand crosses itself, the arrangement (relative stereochemistry) of each crossing compared to other crossings, and the handedness (chirality) of the crossing sequence as a whole.^{1a,3} Constitutionally identical but differently knotted molecular strands are thus stereoisomers. The stereochemical relationship between strand crossings in knots is somewhat reminiscent of that between asymmetric centers in orthodox organic molecules (Figure 1): The topological stereoisomerism of knots is determined by the relative orientation (over, under) of each strand crossing; conventional organic stereoisomerism is determined by the relative handedness of stereogenic elements (centers, planes, axes, helices, etc). For example, the dimerization of a molecular fragment with an (*R*)-asymmetric center gives an (*R,R*)-molecule which is the enantiomer of the (*S*)-building block dimer and a diastereomer of the *meso*- (*R,S*)-compound (Figure 1a). In the case of knots, joining two trefoil tangles (a three-

crossing entanglement with an over-under-over-under-over-under crossing sequence) of the same handedness (Λ - or Δ -) forms a single enantiomer of a granny knot ($-3_1\#-3_1$ or $+3_1\#+3_1$)^{1a,3}, whereas combining trefoil tangles of opposite handedness forms the diastereomeric, topologically achiral, square knot ($+3_1\#-3_1$)^{1a,3} (Figure 1b).

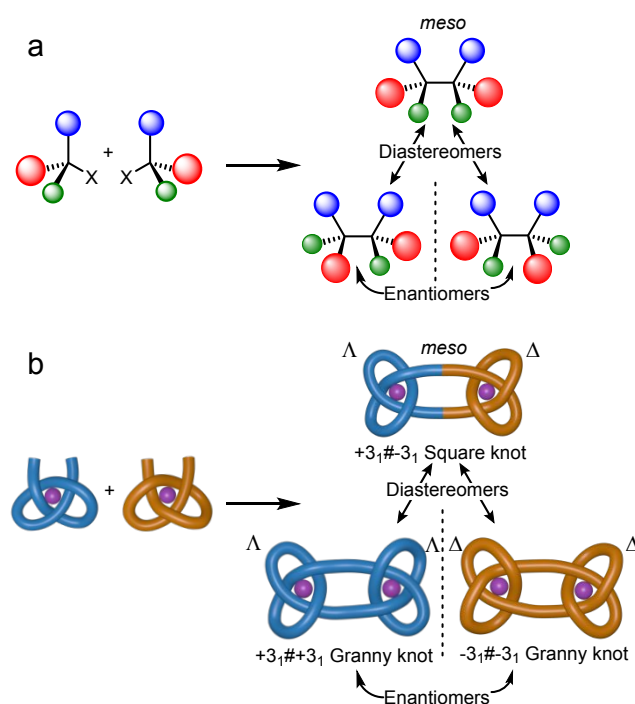


Figure 1. Parallels in the structural relationship between asymmetric centers in chiral molecules and strand crossings in knots. (a) Stereochemical consequences of combining two one-asymmetric-center synthons. (b) Topological consequences of combining two three-crossing entanglement synthons.

Granny and square knots are examples of composite knots, that is closed-loops consisting of two or more ring-opened prime knots joined together.³ The synthesis of composite knots⁵ is complicated by the difficulty in controlling knotting stereochemistry.^{1a} In the sole reported attempt at the synthesis of composite knots for more than 20 years,^{5a} Sauvage's group carried out the cyclodimerization of linear Cu(I) helicates. However, there was no attempt to control stereochemistry and the result was an inseparable mixture of granny and square knots, together with

topologically-trivial macrocycles.^{5a} Recently, symmetrical interwoven grids^{5b,7} and circular helicates^{5c} have been used to control the relative stereochemistry of strand crossings in the synthesis of a granny knot and a nine-crossing composite knot.^{5b,5c} However, those strategies did not control absolute stereochemistry (chirality) either, nor are these approaches readily extendable to topologies with less symmetrical crossing patterns.^{1a,f}

Given the stereochemical parallels between asymmetric centers and strand crossings, we wondered whether strategies used in conventional asymmetric synthesis could be usefully applied to the stereoselective synthesis of different molecular knot topologies. The ‘chiron approach’⁸ is a simple but effective approach for constructing molecules with multiple asymmetric centers. Minimalist chiral synthons, usually derived from cheap and readily available natural products, are combined to form the target molecule stereoselectively. However, a complication in trying to extend such an approach from asymmetric centers to strand entanglements is that although most asymmetric carbon atoms are configurationally fixed, an entanglement is a conformation that can be undone by bond rotations in a strand with open ends.

It has previously been shown that tris(2,6-pyridinedicarboxamide) ligands can be tied into overhand knots^{5a,9} (three-crossing entanglements or ‘trefoil tangles’) upon coordination to lanthanide(III) ions.¹⁰ The handedness of the entanglement can be controlled by introducing asymmetry at the benzylic positions of the ligand backbone: sterics dictate that only the Λ -overhand knot conformation forms from the (*R,R,R,R,R,R*)-strand while the (*S,S,S,S,S,S*)-enantiomer generates the Δ -overhand knot (Figure 2).¹¹ Crucially, as long as a lanthanide ion remains coordinated, the strand entanglement remains in place with its handedness retained. This makes the coordinated unit a potential ‘entanglement synthon’ with open ends for constructing knots by adding together crossings. Once a linear combination of such synthons is macrocyclized to form a closed loop the crossing sequence will become topologically fixed and the metal ions can

be safely removed without the entanglement being able to unravel.

Accordingly, we decided to use lanthanide-coordinated overhand knots as entanglement synthons to selectively construct composite knots with different stereochemistries. A CuAAC coupling step followed by ring closing metathesis (RCM) was used to combine two overhand knots to form open-ended and closed-loop six-crossing strands of precise stereochemical composition.¹² The approach was exemplified through the stereoselective synthesis of a topologically achiral square knot, Λ,Δ -**1**, and the enantioselective synthesis of granny knots Λ,Λ -**1** and Δ,Δ -**1** (Figure 2).

RESULTS AND DISCUSSION

Suitable ligand strands containing a terminal alkene at one end of the tris(2,6-pyridinedicarboxamide) strand and either alkyne (**L1**) or azide (**L2**) groups at the other, were prepared as outlined in the Supporting Information. The lengths of the spacers linking the alkene, alkyne and azide groups to the rest of the strand proved important for achieving efficient macrocyclization to the closed-loop composite knots.¹³ Each synthon was treated with Lu(CF₃SO₃)₃ in MeCN at 80 °C to generate the corresponding overhand knots, Λ -**L1**•[Lu], Δ -**L1**•[Lu], Λ -**L2**•[Lu] and Δ -**L2**•[Lu] in 73-85 % yields. In all cases the folding-threading process to form the overhand knot was found to be complete after 16 h, as evidenced by electrospray ionization mass spectrometry (ESI-MS, Figures S4 and S5) and ¹H NMR spectroscopy (Spectra S19-S22). Signals diagnostic of the entangled conformations of the **L1**•[Lu] and **L2**•[Lu] complexes include large upfield shifts of the pyridine H_{b1,b2} protons due to their proximity to aromatic rings in the overhand knots. The handedness of the entanglements, dictated by point chirality in the ligand strands, was confirmed by circular dichroism (Spectrum S34).

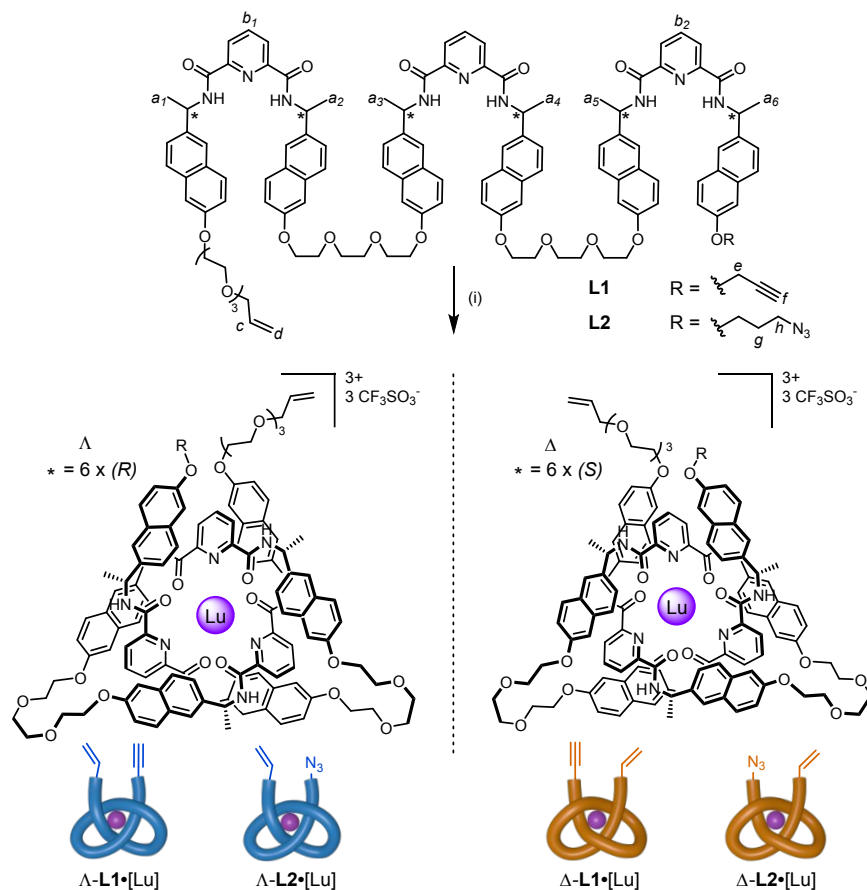
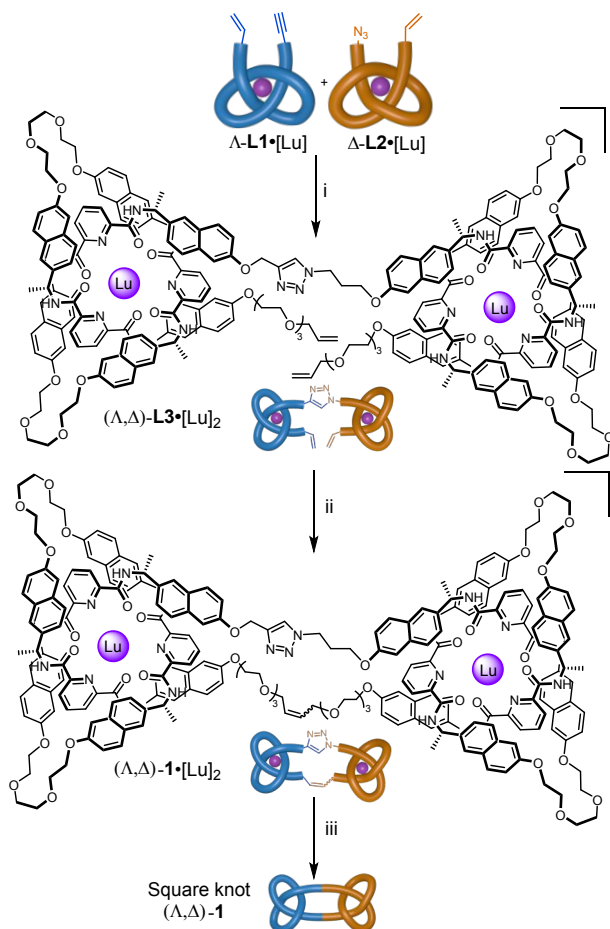


Figure 2. Lanthanide coordination induces folding and threading of **L1/L2** to form entanglement synthons: alkene and alkyne- or azide-bearing overhand knots of single handedness (Λ or Δ). Reagents and conditions: (i) $\text{Lu}(\text{CF}_3\text{SO}_3)_3$, MeCN, 80 °C, 16 h. Yields: 81% (Λ -**L1**•[Lu]), 82% (Δ -**L1**•[Lu]), 85% (Λ -**L2**•[Lu]), 73% (Δ -**L2**•[Lu]).

Scheme 1. Synthesis of double overhand knot (Δ,Δ)-L3**•[Lu]₂ and square knot (Δ,Δ)-**1**.**



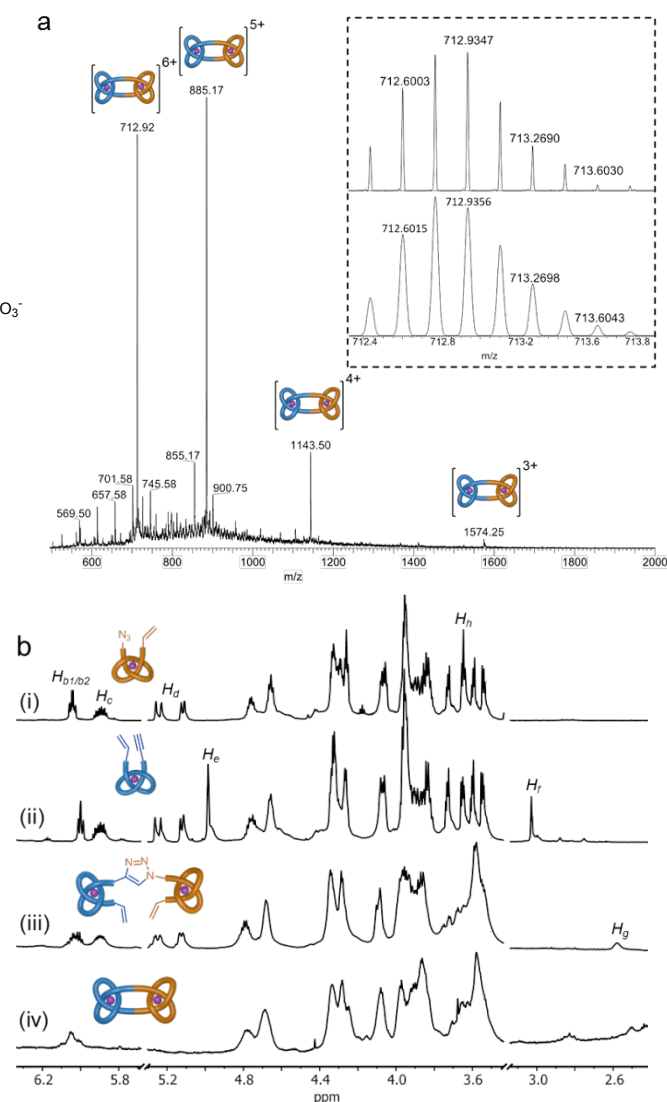
Reagents and conditions: (i) $\text{Cu}(\text{MeCN})_4(\text{CF}_3\text{SO}_3)$, Tentagel-TBTA, MeCN/MeOH 1:1, RT, 16 h, 70 %. (ii) Hoveyda-Grubbs 2nd generation catalyst, $\text{MeNO}_2/\text{CH}_2\text{Cl}_2$ 1:1, 30 %. (iii) Et_4NF , MeCN , RT, 5 min, 95 %.

To generate the square knot, $\Delta\text{-L1}\cdot[\text{Lu}]$ was first connected to $\Delta\text{-L2}\cdot[\text{Lu}]$ through a CuAAC reaction, giving the double overhand knot (Δ,Δ)-**L3**•[Lu]₂ in 70% yield after purification by size exclusion chromatography (Scheme 1). ¹H NMR spectroscopy showed the absence of an alkyne proton H_f at ~3.0 ppm, together with shifts in the resonances corresponding to the azide α -protons H_h (3.65-4.81 ppm) and β -protons H_g (2.19-2.53 ppm), and the propargylic α -protons H_e (3.94-4.98 ppm) (Figure 3b, i-iii).

Macrocyclization of (Δ,Δ)-**L3**•[Lu]₂ occurred over 14 hours at 50 °C in a $\text{MeNO}_2/\text{CH}_2\text{Cl}_2$ (1:1) solvent mixture using the 2nd generation Hoveyda-Grubbs catalyst.¹⁴ After work-up, size exclusion chromatography afforded the metallated molecular square knot, (Δ,Δ)-**1**•[Lu]₂, in 30 % yield. The isolated pure material is only a fraction of the amount actually formed. The closed knot is difficult to separate from closely running bands that

contain products resulting from incomplete olefin metathesis and the presence of other anions (¹H NMR analysis of the reaction mixture indicates that olefin metathesis proceeds in ~80 % conversion per alkene).

The closed-loop structure of (Δ,Δ)-**1**•[Lu]₂ was confirmed by ¹H NMR spectroscopy (e.g. loss of terminal alkene protons H_d ; Figure 3b), ESI-MS (molecular ion mass corresponds to loss of C_2H_4 , Figure 3a) and high resolution mass spectrometry (HR-MS; the isotope distribution of the molecular ion confirming the molecular formula, Figure 3a inset). Diffusion ordered spectroscopy (DOSY) shows that the composite knots diffuse with a larger hydrodynamic radius than the overhand knot



Coordination complex $(\Lambda, \Delta)\text{-1}\cdot[\text{Lu}]_2$ was smoothly demetallated with tetraethylammonium fluoride in MeCN, affording the metal-free square knot $(\Lambda, \Delta)\text{-1}$ in 95 % yield within 5 minutes at RT (Supporting Information Section 4.2). In line with other complex intertwined organic compounds,^{4d,e,5b,c} the ^1H NMR of $(\Lambda, \Delta)\text{-1}$ is broad (Figure S2), presumably due to conformational dynamics of the strand (e.g. reptation¹⁵) being significantly impeded by the entanglement. Slight sharpening of the ^1H NMR spectrum occurs at elevated temperatures (Spectrum S34). This may be a result of the loosening of intra-strand amide-amide hydrogen bonding as well as increased reptation. Remetallation of the wholly organic knot could be accomplished through treatment with excess lutetium trifluoromethanesulfonate (MeCN, 80 °C, 18 h; Figure S3).

Enantioselective syntheses of each enantiomer of the granny knot composite knot were achieved in a similar fashion to the square knot (Figure 4). Starting from the three-crossing entanglement synthons with Λ -handedness, $\Lambda\text{-L1}\cdot[\text{Lu}]$ and $\Lambda\text{-L2}\cdot[\text{Lu}]$, granny knot $(\Lambda, \Lambda)\text{-1}\cdot[\text{Lu}]_2$ was isolated in 26 % yield over two steps (Figure 4a). Its enantiomer $(\Delta, \Delta)\text{-1}\cdot[\text{Lu}]_2$ was synthesized from the two Δ -entanglement synthons in 16 % overall yield (Figure 4b). The identity of each composite knot was confirmed by NMR spectroscopy and HR-MS. Demetallation of the granny knot $(\Lambda, \Lambda)\text{-1}\cdot[\text{Lu}]_2$, under similar conditions to those used for the square knot, afforded $(\Lambda, \Delta)\text{-1}$ in 92 % yield (Supporting Information Section 4.2), with no appreciable difference in rate between the two topoisomers. The topology-based stereochemical differences between $(\Lambda, \Lambda)\text{-1}$ and $(\Delta, \Delta)\text{-1}$ are insufficient to significantly influence the reactivity of the labile lanthanide-ligand interactions.

The ^1H and ^{13}C NMR spectra of the granny and square knot are essentially indistinguishable (Spectra S27-S30). However, the composite knot diastereomers differ significantly in circular dichroism measurements (Figure 5). The CD spectra of the lanthanide complexes of the granny knot enantiomers $(\Lambda, \Lambda)\text{-1}$ and $(\Delta, \Delta)\text{-1}$ are symmetrical in terms of curve shape and have exciton couplings of equal and opposite sign with maxima at 253 nm, demonstrating the chirality (of opposite handedness) of their structures.¹⁶ The exciton couplets are consistent with the absolute configuration of the entanglement helicities of the synthons.¹⁰ The CD response of the square knot coordination complex is virtually, but not quite, baseline (Figure 5, green trace). The very small Cotton effect likely stems from the triazole ring in the composite knot strand connecting to the two entanglement synthons in non-identical ways: through a carbon atom of what was the alkyne group in $\Lambda\text{-L1}\cdot[\text{Lu}]$ and a nitrogen atom of what was the azide group in $\Delta\text{-L2}\cdot[\text{Lu}]$. The resulting break in the symmetry in the chemical constitution of the knot strand results in the molecule not having a perfect plane of symmetry between its two halves: The square knot prepared from $\Lambda\text{-L1}\cdot[\text{Lu}]$ and $\Delta\text{-L2}\cdot[\text{Lu}]$ would not be superimposable on one prepared from the enantiomeric building blocks, $\Delta\text{-L1}\cdot[\text{Lu}]$ and $\Lambda\text{-L2}\cdot[\text{Lu}]$. Although $(\Lambda, \Delta)\text{-1}$ is topologically achiral, because of the chemical make up of the strand it is not a true *meso*-compound. Accordingly, its lanthanide complex elicits a very small, but finite, CD response.

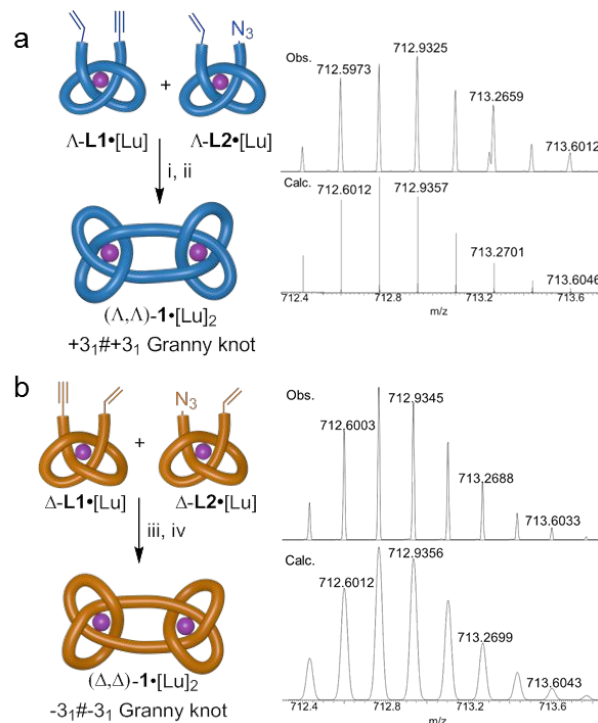


Figure 4. (a) Synthesis and HR-MS of granny knot complex $(\Lambda, \Lambda)\text{-1}\cdot[\text{Lu}]_2$. Conditions: (i) $\text{Cu}(\text{MeCN})_4(\text{CF}_3\text{SO}_3)$, Tentagel-TBTA, MeCN/MeOH 1:1, RT, 16 h, 79 %. (ii) Hoveyda-Grubbs 2nd generation catalyst, $\text{MeNO}_2/\text{CH}_2\text{Cl}_2$ 1:1, 33 %. (b) Synthesis and HR-MS of granny knot complex $(\Delta, \Delta)\text{-1}\cdot[\text{Lu}]_2$. Conditions: (iii) $\text{Cu}(\text{MeCN})_4(\text{CF}_3\text{SO}_3)$, Tentagel-TBTA, MeCN/MeOH 1:1, RT, 16 h, 52 %. (iv) Hoveyda-Grubbs 2nd Gen, $\text{MeNO}_2/\text{CH}_2\text{Cl}_2$ 1:1, 31 %. For each of the ion isotopic distributions, the experimentally observed spectrum is shown above the theoretically calculated spectrum.

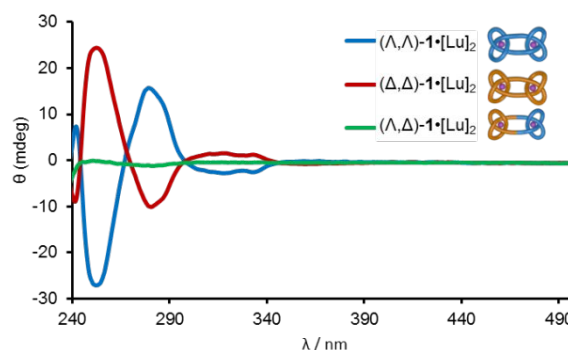


Figure 5. Circular dichroism spectra (1.0×10^{-4} M, MeCN, 298 K) of granny knots $(\Lambda, \Lambda)\text{-1}\cdot[\text{Lu}]_2$ (blue) and $(\Delta, \Delta)\text{-1}\cdot[\text{Lu}]_2$ (red) and square knot $(\Lambda, \Delta)\text{-1}\cdot[\text{Lu}]_2$ (green). Normalized for absorbance.

CONCLUSIONS

Three molecular six-crossing composite knots of different topologies, $-3_1\#-3_1$ (granny), $+3_1\#+3_1$ (granny) and $+3_1\#-3_1$ (square), were synthesized stereoselectively through a strategy involving joining together entanglement synthons of particular handedness to form a linear strand with multiple tangles that are each held in place by coordination to lanthanide cations. Subsequent macrocyclization of each strand locks its topology, forming a closed loop, 199 atoms long, from which the metal ions

can be removed without the knot being able to unravel. Tris(2,6-pyridinedicarboxamide) ligands were shown to be suitable 3₁ entanglement synthons of either handedness (chirality predetermined by choice of asymmetric centers on the ligand strand). The resulting granny knots are enantiomers (each with six alternating crossings) that exhibit pronounced equal and opposite CD spectra. The diastereomeric square knot is topologically achiral (two non-alternating crossings and four alternating crossings), but a lack of symmetry in the chemical constitution of the knot strand means this example is not a true *meso*-compound.

The synthetic strategy is related to both the chiron approach⁸ of conventional asymmetric synthesis and tangle theory,^{1a,3} a way that mathematicians understand and (de)construct complex knot topologies through simpler fragments termed ‘tangles’. The new approach may prove useful for the preparation of other complex molecular knots and entangled materials that lack high symmetry in their crossing patterns.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI. Synthetic procedures and NMR, MS, CD, UV/Vis data and molecular models (PDF).

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Notes

The authors declare no competing financial interests.

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(12) In preliminary studies we were unable to find spacers of a length and conformation that tolerated the one-step combination of entanglement synthons to form composite knots (e.g. dimerization of an entangled bis-alkene to form a granny knot; or combination of an entangled bis-azide and bis-alkyne of different handedness to form a square knot).

(13) Molecular modeling indicates that a double overhand knot such as (Λ,Δ)-**L3**•[Lu]₂ adopts a conformation that places the reactive endgroups a relatively long distance away from each other, hence the use of relatively short spacers to the azide and alkyne for the CuAAC step that couples the synthons and relatively long and flexible chains for the subsequent RCM ring closure (see Figure S11).

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(16) There is a small difference in intensity of the CD responses recorded for the two isolated granny knots when the spectra are normalized for UV-absorbance (Figure 5). This likely results from a trace impurity in (Δ, Δ)-**1**. No epimerization of asymmetric centers occurs during any of the synthetic steps (the resulting diastereomers are detectable by ¹H NMR^{10a,11a}) and folding to an entanglement of opposite handedness is not possible on steric grounds for any of the lanthanide-coordinated overhand knot intermediates^{10a,11a}.

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