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Complete stereocontrol in formation of macrocyclic lanthanide complexes: direct formation of enantiopure systems for circularly polarised luminescence applications†

Nicholas H. Evans, Rachel Carr, Martina Delbianco, Robert Pal, Dmitry S. Yufit and David Parker* 

A single C-substitution of the 1, 4, 7-triazacyclononane ring induces formation of single enantiomers of Eu(III) complexes with nonadentate N$_6$O$_3$ ligands. The absolute configuration of each complex is determined by the stereogenicity of the C-substituent, revealed by comparison of the sign and sequence of CPL transitions for a series of complexes.

Introduction

Complexes of the most emissive lanthanides (Eu, Tb) have been studied extensively for luminescence applications, and now investigations into the circularly polarised luminescence (CPL) of chiral lanthanide complexes are increasingly being reported. Given the omnipresence of chirality, CPL can provide a rich source of information on local asymmetry.1

In working towards the development of well-defined chemical probes that are able to signal changes in the local chiral environment reversibly by CPL, the design and synthesis of highly emissive enantiopure species is key. However, the selective formation of enantiomerically pure metal complexes has been a considerable challenge to the coordination chemist. A highly logical means of achieving this aim is by transmitting the chiral information from one or more enantiopure ligands to the metal centre.2 This approach has been explored in the synthesis of several lanthanide-containing systems, including helicates3 and complexes derived from the cyclen framework.4-6

Ligands based on triazacyclononane macrocycles represent excellent choices for the generation of thermodynamically and kinetically stable metal complexes.7 The ring nitrogens act primarily as donor atoms and are readily elaborated to allow for additional ligation. Six coordinate phosphinate triazacyclononane complexes of In(III) and Ga(III) which exist as RRR/SSS enantiomers have been known for some time.8 Of particular note is control of complex configuration by the incorporation of a single C-substitution into the ring system of a hexadentate copper-containing NOTA-derived complex.9 Nine coordinate tris-carboxylate triazacyclononane complexes of Ln(III) ions have been reported by Mazzanti and co-workers, and were shown in the solid state to exist in tri-capped trigonal prismatic coordination geometry, present as A-(δδδ) and A-(λλλ) enantiomers.10 Very recently, we reported the preparation of the Eu and Tb complexes of trispyridylphosphinate triazacyclononane [LnL$_{1-2}$] (Figure 1).11, 12 These species were prepared as a racemate of their two enantiomers: RRR-A-(δδδ) and SSS-A-(λλλ),13 hence requiring resolution by chiral HPLC to allow for direct CPL analysis. In this work, we have set out to bias formation of a single complex enantiomer, by the inclusion of a stereogenic centre on the triazacyclononane ring.

Results and discussion

Synthesis and characterisation of complexes

The synthesis of the europium complexes [EuL$_{3-9}$] studied is presented in Scheme 1 (see also: ESI†). The substituted 9-N$_3$ macrocycle rings for L$_{4-7}$ were prepared following established methods, in which the substituted chiral centre derives from the alkyl esters of α-amino acids.14, 15 The ethyl esters of ligands L$_{3-7}$ were formed by alkylation of the 9-N$_3$ ring with three
equivalents of the methyl phosphinate mesylate 1a or 1b. Pyridyl bromine substituents have been included to allow for subsequent metal catalysed C-C or C-N functionalization. In addition, the methyl esters of the carboxylate ligands L₈⁻⁹ were prepared to allow for comparison. Basic ester hydrolysis yielded L₃⁻⁹, each of which was complexed with Eu(III).

Complexes [EuL₃⁻⁹] were characterised by ¹H and ³¹P NMR and electrospray MS (Figure 2 and ESI†). The non-equivalence of the P atoms in the substituted phosphinate complexes [EuL₄⁻⁷] is most clearly revealed by the presence of three peaks in the ³¹P NMR spectra (Figure 2d).

Fig. 2 NMR spectra: (a) ¹H [EuL₃], (b) ¹H [EuL₅⁻⁶], (c) ³¹P [EuL₃], (d) ³¹P [EuL₄⁻⁷].

Fluorescence lifetimes for [EuL₃] were recorded in H₂O (τ = 1.23 s) and D₂O (τ = 1.52 s). Using these values, the complex hydration state was calculated to be zero, consistent with the ligand acting as a nonadentate donor for the Eu(III) ion.

Fig. 3 Crystal structure of [EuL₃]. SSS-∆(±±±) enantiomer depicted.

Subsequently, single crystals of [EuL₃] suitable for X-ray crystallographic determination were grown by slow evaporation of a MeOH solution of the racemate of the complex. The structure reveals a nine coordinate complex with C₃ symmetry, in agreement with the solution phase characterisation (Figure 3). The mean bond distances and NCCN and NCCNₚₚ torsional angles are almost identical to those previously reported for a tris(phenyl phosphinate) complex, [EuL⁰] (Table 1).

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Table 1: Selected mean bond distances (Å ± 0.02) and torsional angles (° ± 1.0) for complexes [EuL₃] and [EuL⁰].

<table>
<thead>
<tr>
<th></th>
<th>Eu - O</th>
<th>Eu - N</th>
<th>Eu - Nₚₚ</th>
<th>NCCN</th>
<th>NCCNₚₚ</th>
</tr>
</thead>
<tbody>
<tr>
<td>[EuL₃]</td>
<td>2.33</td>
<td>2.69</td>
<td>2.65</td>
<td>-48</td>
<td>+35.5</td>
</tr>
<tr>
<td>[EuL⁰]</td>
<td>2.33</td>
<td>2.68</td>
<td>2.66</td>
<td>-47</td>
<td>+33</td>
</tr>
</tbody>
</table>

a Signs of torsional angles are reported for the SSS-∆(±±±) enantiomer.

Stereochemistry and CPL of complexes

The racemates of the unsubstituted complexes [EuL₃] and [EuL⁰] were separated by chiral HPLC. For the C-substituted
complexes, chiral HPLC (CHIRALPAK-IC or ID, MeOH) verified an enantiomeric excess > 96% being observed in the case of [EuL^5-R]. The resolved enantiomers of the methyl phosphinate complex [EuL^2] racemise slowly when heated to 60 °C in H_2O, with a half-life of 185 (± 20) h determined by observing the % e.e. change using chiral HPLC (ESI†). The carboxylate complex [EuL^5] racemises in water with a half-life of 240 (± 35) h under the same conditions. These are considerably more stable to racemisation than the frequently studied tris-dipicolinate complexes of the Ln(III) cations, e.g. Eu tris-dipicolinate, [Eu(dpa)_3], has a half-life of 5.1 (± 0.2) ms at 60 °C. Notably, the methyl substituted carboxylate complex [EuL^2], showed no loss in enantiopurity after heating to 60 °C in H_2O for 72 h.

Emission and CPL spectra of enantiopure complexes [EuL^3-R] were recorded (see Figure 4 and ESI†). The CPL spectra of the two enantiomers of the [EuL^1] are mirror images (Fig. 4a, b). The methyl phosphinate complexes derived from the natural stereoisomer (i.e. S enantiomer) of the amino acid have the same spectral sign as for RRR-A-(d/dd) enantiomer of [EuL^2], while for those derived from the unnatural stereoisomer had the opposite sign (see ESI†). Large values for the emission dissymmetry factor, (g_{en} = 2(I_{L}-I_{R})/(I_{L}+I_{R})) were observed in the ΔJ = 1 band (see Fig. 4d), specifically g_{en}(591.5 nm) = ± 0.10 for enantiopure samples of [EuL^3-R], and generally there were no significant differences in the appearance of the CPL spectra for different substituents R, and whether X = Br or H.  

Conclusions

In summary, complete control of the stereochemistry of triazacyclononane based europium complexes has been demonstrated by mono-substitution at a single carbon atom on the 9-N_3 ring, allowing for direct, selective formation of a given enantiomer with e.e. > 96 %. Such behaviour allows the direct preparation of enantiopure emissive complexes, analogues of which can be designed to act as responsive chiral probes for application in CPL spectroscopy and microscopy.

Experimental

General experimental procedures

Commerically available reagents were used as received from suppliers. Solvents were laboratory grade and dried using an appropriate drying agent when required. Reactions requiring anhydrous conditions were carried out under an atmosphere of dry argon. 

1H, 13C and 31P NMR spectra were recorded on spectrometers operating at magnetic inductions corresponding to 1H frequencies at 400, 600 and 700 MHz. Spectra were recorded at 295 K in commercially available deuterated solvents. ESMS was carried out on a TQD mass spectrometer, and accurate masses were recorded on either a LCT Premier or Thermo Finnigan LTQ-FT.

Reverse phase HPLC purification was performed at 295 K on either a Waters or Perkin Elmer system. The Waters system consisted of a Waters 570 pump, Waters “System Fluidics Organizer”, Waters 2545 “Binary Gradient Module”, Waters 2767 “Sample Manager”, Waters Fraction Collector III, Waters 2998 Photodiode Array Detector and Waters 3100 Mass Detector. The Perkin Elmer system consisted of a Perkin Elmer Series 200 pump, Perkin Elmer Series 200 auto-sampler and Perkin Elmer Series 200 UV/Vis detector. XBridge C18...
columns were used with a flow rate of 1 mL/min (analytical) or 4.4 mL/min (semi-prep) or 17 mL/min (prep). Solvent systems of H₂O / CH₃OH with 0.1% HCOOH (gradient elution) were used. Chiral HPLC was performed on the Perkin Elmer system described above using analytical (4.0 mm × 250 mm) and semi-prep (10 mm × 250 mm) CHIRALPAK-IC or ID columns. An isocratic solvent system of CH₃OH was used in all cases.

**Optical spectroscopy**

All samples were contained within quartz cuvettes with a path length of 1 cm and a polished base. Measurements were recorded at 295 K. Absorbance spectra were measured on a Perkin Elmer Lambda 900 UV/Vis/NIR spectrometer using FL Winlab software. Emission spectra were recorded on an ISA Jobin-Yvon Spex-Fluorolog-3 luminescence spectrometer. Lifetime measurements were carried out using a Perkin-Elmer LS55 spectrometer using FL Winlab software. The inner sphere hydration number (q) for [EuL³] was obtained by measuring the excited state lifetime in H₂O and D₂O. The q value was calculated using the equation reported by Clarkson et al.²²

CPL spectra were recorded on a custom built spectrometer consisting of a laser driven light source (Energetiq EQ-99 LDLS, spectral range 170 to 2100 nm) coupled to an Acton SP2150 monochromator (600 g/nm, 300 nm Blaze) that allows excitation wavelengths to be selected with a 6 nm FWHM spectral average sequence in the range of 570-720 nm with 0.5 nm spectral intervals and 500 µs integration time. The recorded CPL spectrum than underwent a 25% Fourier transformation smoothing protocol using Origin 8.0 Software (Origin Labs) to enhance visual appearance (all calculations were carried out using raw spectral data). A schematic figure of the CPL instrumentation is provided in the ESI†.

**Crystal structure determination of [EuL³]**

Crystals of [EuL³] suitable for single crystal structure determination were grown by slow evaporation of a CH₃OH solution. The X-ray single crystal data for [EuL³] were collected at 120 K on an Agilent Gemini S-Ultra diffractometer (graphite monochromator, λMoKα, λ = 0.71073Å) equipped with a Cryostream (Oxford Cryosystems) open-flow nitrogen cryostat. The structure was solved by direct method and refined by full-matrix least squares on F² for all data using Olex2²³ and SHELXL2⁴ software. All non-hydrogen atoms were refined anisotropically, hydrogen atoms were placed in the calculated positions and refined in riding mode.

**Crystal Data for [EuL³]**: C₂₇H₂₅Br₃N₆O₄, x 2 (H₂O), M =1058.23, triclinic, space group P-1, a = 9.8356(4), b = 12.3427(5), c = 17.2609(8) Å, α = 107.259(4), β = 97.936(4), γ = 105.863(4)°, V = 1869.30(14) Å³, Z = 2, µ(Mo Kα) = 5.065 mm⁻¹, Dcalc = 1.880 g/mm³, 21350 reflections measured (5.12 ≤ 2θ ≤ 60.00), 10802 unique (Rint = 0.0439) were used in all calculations. The final R₁ was 0.0429 (8528 >2σ (I)) and wR₂ was 0.0918 (all data). CCDC Number: 948247.

### Synthesis of complexes

The synthesis of phosphinate pyridyl mesylates 1a and 1b have been reported elsewhere.¹¹,²⁵ 1, 4, 7-Triazacyclononane 3 (as its trihydrochloride salt) was purchased from Sigma-Aldrich. Mono-substituted macrocycles 4 - 6 were manufactured following a synthetic route presented in the ESI†. Mono-substituted macrocycle 7 was prepared following an adapted literature method.¹⁴ The unsubstituted carboxylate pyridyl mesylate 2 and carboxylate ligand L⁵ were prepared following adapted literature procedures.¹⁰

### TRI-ETHYL ESTER OF L³

1, 4, 7-Triazacyclononane trihydrochloride (34 mg, 0.14 mmol) and mesylate 1a (160 mg, 0.43 mmol) were dissolved in dry CH₃CN (10 mL) and K₂CO₃ (119 mg, 0.86 mmol) added. The reaction mixture was heated under reflux under Ar (g) until all the mesylate starting material had been consumed (as monitored by TLC). The reaction was then cooled to RT and the solution decanted from excess potassium salts. The solvent was removed under reduced pressure and the crude material purified by repeated column chromatography (alumina, 0 – 2 % CH₃OH : CH₂Cl₂) to give the title compound as a colourless oil (101 mg, 74 %).

## The tri-ethyl ester of L⁴

was prepared in analogous manner to L³, using macrocycle 4 (13 mg, 0.090 mmol). The crude material was purified by column chromatography (alumina, 0 – 2 % CH₃OH : CH₂Cl₂) to give the title compound as a colourless oil (36 mg, 41 %).

## The tri-ethyl ester of L⁵-S

was prepared in analogous manner to L³, using macrocycle 5-S (29 mg, 0.16 mmol). The crude material was purified by column chromatography (alumina, 0 – 2 % CH₃OH : CH₂Cl₂) to give the title compound as a colourless oil (50 mg, 30 %).
The tri-ethyl ester of L₅⁻R was prepared in analogous manner to L⁴, using macrocycle 5⁻R (10 mg, 0.057 mmol). Purification of the crude material by column chromatography (silica, 0 – 12 % CH₃OH : CH₂Cl₂) yielded the *title compound* as a colourless oil (23 mg, 40 %). NMR and MS data were in agreement with the enantiomer tri-ethyl ester of L₅⁻S.

The tri-ethyl ester of L₆⁻S⁻H was prepared in analogous manner to L⁴, using macrocycle 6⁻S (94 mg, 0.68 mmol) and mesylate 1b (199 mg, 0.68 mmol). The crude material was purified by column chromatography (silica, 0 – 9 % CH₃OH : CH₂Cl₂) to give the *title compound* as a yellow oil (66 mg, 35 %).

ΔH (CDCl₃) 6.97-8.07 (14H, br m, ArH), 2.45-4.69 (25 H, br m, ring CH₂, 3 × OCH₂ & 4 × CH₂), 1.50-1.94 (9H, br m, 3 × PCH₃), 0.97-1.35 (9H, br m, 3 × OCH₂CH₃). Δδ (CDCl₃) 39.9. m/z (HRMS⁺) 811.3654 [M + H]+ (C₃₃H₄₅N₆O₆ requires 1138.1926). Rf = 0.25 (silica, CH₂Cl₂ : CH₃OH 90:10:1).

The tri-ethyl ester of L₆⁻S⁻Br was prepared in analogous manner to L⁴, using macrocycle 6⁻S (36 mg, 0.16 mmol). The crude material was purified by column chromatography (silica, 0 – 7 % CH₃OH : CH₂Cl₂) to give the *title compound* as a yellow oil (91 mg, 24 %). Analytical data were in agreement with the enantiomer L₆⁻S⁻H.

The tri-ethyl ester of L₇⁻S⁻Br was prepared in analogous manner to L⁴, using macrocycle 7 (75 mg, 0.24 mmol). The crude material was purified by reverse phase HPLC to give the *title compound* as a yellow oil (65 mg, 25 %).

ΔH (CDCl₃) 7.82-8.20 (6H, m, ArH), 6.45 (1H, br s, CONH), 3.87-4.17 (12H, m, PCH₂ & NCH₂), 2.59-3.23 (13H, m, ring CH₂ & CH₂CONH), 1.76-1.82 (9H, m, PCH₃), 1.26-1.76 (26H, m, PCH₂CH₃, alkyl chain & cyclohexane CH₂/CH₃). Δδ (CDCl₃) 37.8. m/z (HRMS⁺) 1138.1914 [M + H]+ (C₄₄H₆₈Br₃N₇O₇P₃ requires 1138.1926). Rf = 0.32 (silica, CH₂Cl₂ : CH₃OH : NH₃(aq) 90:10:1).

The tri-methyl ester of L⁴ was prepared in analogous manner to L⁴, using macrocycle 4 (50 mg, 0.35 mmol) and mesylate 2 (257 mg, 1.05 mmol). The crude material was purified by repeated column chromatography (silica, 5 – 10 % CH₃OH : CH₂Cl₂) to give the *title compound* as a colourless oil (27 mg, 13 %).

ΔH (CDCl₃) 7.72-8.01 (9H, m, ArH), 3.93-4.21 (15H, m, inc. OCH₂), 2.75-3.21 (14H, m, inc. CH₃). m/z (HRMS⁺) 591.2959 [M + H]+ (C₃₁H₃₉N₆O₆ requires 591.2931). Rf = 0.12 (silica, CH₂Cl₂ : CH₃OH 90:10:1).

Complex [EuL³⁻]. The tri-ethyl ester of L³ (70 mg, 0.073 mmol) was dissolved in CH₃OH (5 mL) and a solution of 0.1 M NaOH(aq) (5 mL) added. The mixture was heated to 60 °C. After verifying the reaction had gone to completion by ³¹P NMR, the solution was cooled to RT, and the pH adjusted to 6 using 0.1 M HBr(aq). Eu(NO₃)₃.5H₂O (34 mg, 0.080 mmol) was added and the mixture heated to 80 °C for 16 h. The pH was raised to 10, precipitated Eu(OH)₃ was removed by centrifugation. The pH was adjusted to 6 using 0.1 M HBr(aq), and the solvent removed under reduced pressure and the product purified by column chromatography (silica, CH₂Cl₂ : CH₃OH : NH₃(aq) 80:20:1) giving the *title compound* as a white solid (74 mg, 98 %).

ΔH (400 MHz, CD₃OD) 8.60 (1H, s, pyH), 7.97 (1H, s, pyCHN), 7.12 (1H, s, pyH), 4.36 (1H, s, NCH₃(eq)), 0.54 (3H, s, CH₃), -0.77 (1H, s, pyCHN), -1.37 (1H, s, NCH₃(eq)), -2.23 (1H, s, NCH₃(eq)), -5.28 (1H, s, NCH₃(eq)). Δδ (162 MHz, CD₃OD) 39.8. m/z (HRMS⁺) 1020.8512 [M + H]+ (C₁₂₇H₁₀₀Br₂N₉O₈P₃⁵¹Eu requires 1020.8491). Rf = 0.31 (silica, CH₂Cl₂ : CH₃OH : NH₃(aq) 82:15:3).

A sample of the complex racemate was separated by chiral HPLC using an analytical CHIRALPAK-ID column. Rₜ = 7.4 min & 14.3 min (4.0 mm × 250 mm, CH₃OH, 1 mL/min, 290 K).

Complex [EuL⁴⁻]. The tri-ethyl ester of L⁴ (24 mg, 0.025 mmol). The crude material was purified by column chromatography (silica, CH₂Cl₂ : CH₃OH : NH₃(aq) 90:10:1), and then reverse phase HPLC to obtain the *title compound* as a white solid (3 mg, 11 %).

ΔH (400 MHz, CD₃OD) 9.57, 8.98, 8.51, 8.15, 7.69, 7.36, 7.14, 6.74, 6.44, 6.04, 4.63, 4.76, 2.76, 1.28, 1.12, 0.65, -0.11, -0.82, -1.02, -1.50, -1.87, -2.40, -2.79, -5.13, -5.68, -5.79. Rₜ (162 MHz, CD₃OD) 41.6, 40.4, 38.8. m/z (HRMS⁺) 1032.8668 [M + H]+ (C₁₂₃H₁ₐBr₂N₉O₈P₃⁵¹Eu requires 1032.8658). Rₜ = 0.49 (silica, CH₂Cl₂ : CH₃OH : NH₃(aq) 84:15:1). Due to the partial racemisation of the chiral centre (see ESI†), a sample of the complex was submitted to chiral HPLC using an analytical CHIRALPAK-ID column to separate the two enantiomers. Rₜ = 6.9 min & 13.4 min (4.0 mm × 250 mm, CH₃OH, 1 mL/min, 290 K).

Complex [EuL⁵⁻S⁻]. The tri-ethyl ester of L⁵ (-S) (25 mg, 0.025 mmol).
The crude material was purified by column chromatography (silica, CH₂Cl₂ : CH₃OH : NH₃(aq) 90:10:1) to obtain the title compound as a white solid (11 mg, 41 %).

δ_H (400 MHz, CD₃OD) 11.67, 9.47, 8.41, 8.28, 7.82, 7.61, 7.23, 7.05, 6.52, 5.14, 4.26, 2.70, 1.97, 1.66, 0.94, 0.83, 0.32, -0.57, -1.15, -2.24, -2.57, -2.82, -3.02, -4.64, -5.96, -6.35.

δ_P (162 MHz, CD₃OD) 44.4, 41.3, 36.1. m/z (HRMS') 1060.8992 [M + H]+ (C₃₀H₄₀N₆O₆P₃Br₃)⁷⁷¹Eu requires 1060.8971. R = 0.10 (silica, CH₂Cl₂ : CH₃OH : NH₃(aq) 90:9:1). Due to the partial racemisation of the chiral centre (see ESIFT), a sample of the complex was submitted to chiral HPLC using an analytical CHIRALPAK-ID column to separate the enantiomers. R = (7.1 min & 10.3 min (4.0 mm × 250 mm, CH₃OH, 1 mL/min, 290 K).

**COMPLEX [EuL⁵-H]** was prepared in an analogous manner to [EuL⁵-H]⁻, using the tri-ethyl ester of L⁵-R (7.0 mg, 7.0 µmol). The crude material was purified by column chromatography (silica, CH₂Cl₂ : CH₃OH : NH₃(aq) 90:10:1) to obtain the title compound as a white solid (3.5 mg, 47 %). NMR and MS data were in agreement with the deprotected ligand as a white solid (as verified by ESMS and ³¹P NMR).

The ligand was dissolved in H₂O : CH₃OH (4 : 1, 1.5 mL) and the pH of the solution adjusted to 5.5 using dilute HBr(aq). Eu(NO₃)₃.5H₂O (12 mg, 0.027 mmol) was added and the reaction mixture was heated at 80 °C for 16 h. After allowing the reaction mixture to cool to RT, the pH was raised to 10.0 by the addition of dilute NaOH(aq). The resulting solution was stirred for 1 h causing excess Eu(III) to precipitate as Eu(OH)₃, which was removed by filtration. The pH of the resulting solution was restored to 5.5 by the addition of dilute HBr(aq) and the solvent lyophilised to give the crude product. The crude product was taken in to CH₂Cl₂ : CH₃OH (8 : 2, 2 mL) and the solution filtered to facilitate the removal of salts. Subsequent removal of solvent under reduced pressure yielded the deprotected solid which was further purified by column chromatography on silica gel (CH₂Cl₂ : CH₃OH : NH₃(aq) 90:20:1) to obtain the title compound (21 mg, 76 %).

δ_H (400 MHz, CD₃OD) 10.87, 9.23, 8.51, 7.89, 7.16, 7.25, 7.48, 7.52, 6.16, 5.09, 4.48, 4.24, 2.85, 2.52, 1.87, 1.30, 1.47, 0.52, -0.34, -0.70, -2.23, -2.38, -2.49, -2.76, -3.11, -4.54, -6.03, -6.46. δ_P (162 MHz, CD₃OD) 43.9, 40.2, 33.5. m/z (HRMS') 1113.9153 [M + H]+ (C₃₀H₃₄N₆O₆P₃Br₃)⁷⁷¹Eu requires 1113.9301. R = 0.56 (silica, CH₂Cl₂ : CH₃OH : NH₃(aq) 80 : 20 : 1). Chiral HPLC (ChiralPAK-ID 4.0 mm × 250 mm, CH₃OH, 1 mL/min, 290 K): R = 11.6 min.

**COMPLEX [EuL⁷]** was prepared in analogous manner to [EuL⁷⁻], using the tri-ethyl ester of L⁷ (10 mg, 8.8 µmol). The crude material was purified by column chromatography on silica gel (CH₂Cl₂ : CH₃OH : NH₃(aq) 90:10:1) to give the title compound as an off-white solid (3 mg, 30 %).

δ_H (400 MHz, CD₃OD) 10.13, 9.08, 8.57, 7.95, 7.85, 7.36, 7.20, 6.66, 6.24, 5.69, 3.10, 2.29, 2.19, 2.03, 1.80, 1.53, 1.37, 1.02, 0.68, -0.28, -0.60, -0.75, -1.71, -2.15, -2.38, -2.61, -4.91, -5.65, -6.01. δ_P (162 MHz, CD₃OD) 43.4, 40.7, 37.5. m/z (HRMS') 1203.9955 [M + H]+ (C₃₄H₆₅N₆O₆P₃Br₃)⁷⁷¹Eu requires 1203.9950. R = 0.32 (silica, CH₂Cl₂ : CH₃OH : NH₃(aq) 90 : 10 : 1). Chiral HPLC (ChiralPAK-ID 4.0 mm × 250 mm, CH₃OH, 1 mL/min, 290 K): R = 14.5 min.
**COMPLEX [EuL³]** (as a racemate) has been prepared within our laboratories previously. A sample of [EuL³] was resolved using a semi-prep CHIRAL-PAK IC column. Chiral HPLC (ChiralPAK-IC 4.0 mm × 250 mm, CH₃OH, 0.5 mL/min, 290 K): Rᵣ = 11.7 min & 19.8 min.

**COMPLEX [EuL⁴]** was prepared in an analogous manner to [EuL³], using the tri-methyl ester of L⁴ (18 mg, 0.031 mmol). The crude material was purified by column chromatography (silica, CH₂Cl₂ : CH₃OH : NH₃ 80 : 20 : 0.1), to obtain the title compound as a white solid (16 mg, 76 %).

δ (400 MHz, D₂O) 7.95, 7.09, 6.79, 6.46, 5.85, 5.61, 5.44, 5.07, 4.65, 4.34, 4.04, 2.77, 2.74, 2.57, 2.35, 1.63, 1.06, -0.53, -0.87, -1.47, -4.58, -5.13, -5.53. m/z (HRMS) 697.1415 [M + H⁺]⁺ (C₂₈H₃₀N₆O₆) Eu requires 697.1425. Rᵣ = 0.23 (silica, CH₂Cl₂ : CH₃OH : NH₃ 72:15:3). Due to the partial racemisation of the chiral centre (see ESI†), a sample of the complex was submitted to chiral HPLC using a semi-prep CHIRALPAK-IC column to separate the two enantiomers. Chiral HPLC (ChiralPAK-IC 4.0 mm × 250 mm, CH₃OH, 0.5 mL/min, 298 K): Rᵣ = (12.3 min &) 19.7 min.

**Acknowledgements**

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**Notes and references**

13. RRR/SSS stereochemical descriptors refer to the stereochemistry at P. A/A refers to the helical arrangement of the pyridylphosphinate arms, associated with negative (A) or positive NCCNₚ torsional angles; similarly, δδδδδδδδδδδδδδδδδδδδδdelta refers to the NCCN ring torsional angle.
16. In some samples, loss of enantiopurity was observed leading to formation of the enantiomers in a ratio of between 2:1 to 9:1. This was confirmed by comparison of the sign of the CPL spectra of the separated species. Racemisation arose during the first step of the ligand synthesis, during reaction of ethylenediamine with the amino acid alkyl ester at 120 °C. The use of the chiral solvating agent R-O-acetyl mandelic acid allowed NMR analysis of the enantiomeric purity of the product. See ESI† for further details. Racemisation can be avoided by running the reaction at lower temperature.
17. In comparison, the half-life of racemisation for [YbL⁷] was longer, t₁/₂ = 680 (± 80) h, consistent with the lanthanide contraction.
19. The enantiomers of [EuL⁴] were assigned by comparison of their CPL spectra with those of [EuL³] (Ref 11 & 12).
20. Large values of gรม were also calculated at wavelengths falling in the ΔJ = 3 and 4 bands, but the low total emission intensity at these wavelengths means that a larger error was associated with the recorded values of gรม.