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

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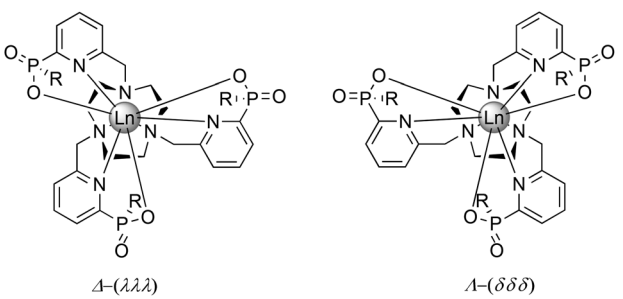
Mono-C-substitution of the 1,4,7-triazacyclononane ring induces formation of single enantiomers of Eu(III) complexes with nonadentate $N_6O_3$ ligands. The absolute configuration of each complex is determined by the stereogenicity of the C-substituent, revealed by comparison of the sign and sequence 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 helicates[3] 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 *Λ*-(*δδδ*) and *Δ*-(*λλλ*) enantiomers.[10] Very recently, we reported the preparation of the Eu and Tb complexes of trispyridylphosphinate triazacyclononane **[LnL$^{1-2}$]** (Fig. 1).[11,12] These species were prepared as a racemate of their two enantiomers: *RRR*-*Λ*-(*δδδ*) and *SSS*-*Δ*-(*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.




*Δ*–(*λλλ*) *Λ*–(*δδδ*)

**Fig. 1** The stereoisomers of trispyridylphosphinate triazacyclononane complexes **[LnL$^{1-2}$]**. R = Ph, Me, where *Δ* and *δ* refer to positive $NCCN_{py}$ and NCCN (ring) torsion angles.

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†Electronic supplementary information (ESI) available: Synthesis of mono-substituted macrocycles **4–6**, spectral characterisation of complexes **[EuL$^{3-9}$]**, plus details of racemisation studies and schematic figure of CPL instrumentation. CCDC 948247. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3dt52425f

## 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$^{4-7,9}$** 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 **L$^{8-9}$** were prepared to allow for comparison. Basic ester hydrolysis yielded **L$^{3-9}$**, each of which was complexed with Eu(III).

Complexes **[EuL$^{3-9}$]** were characterised by $^{1}$H and $^{31}$P NMR and electrospray MS (Fig. 2 and ESI†). The non-equivalence of the P atoms in the substituted phosphinate complexes **[EuL$^{4-7}$]** is most clearly revealed by the presence of three peaks in the $^{31}$P NMR spectra (Fig. 2d).

Fluorescence lifetimes for **[EuL$^{3}$]** were recorded in $H_2O$ ($\tau$ = 1.23 s) and $D_2O$ ($\tau$ = 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.

Subsequently, single crystals of **[EuL$^{3}$]** 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 $C_3$ symmetry, in agreement with the solution phase characterisation (Fig. 3). The mean bond distances and NCCN and $NCCN_{py}$ torsional angles are almost identical to those previously reported for a tris(phenyl phosphinate) complex, **[EuL$^{1}$]** (Table 1).

### Stereochemistry and CPL of complexes

The racemates of the unsubstituted complexes **[EuL$^{3}$]** and **[EuL$^{8}$]** were separated by chiral HPLC. For the C-substituted series of complexes, chiral HPLC (CHIRALPAK-IC or ID, MeOH) verified formation of a single stereoisomer independent of substituent steric bulk, with an enantiomeric excess >96% being observed in the case of **[EuL$^{5\text{-}R}$]**.[16] The resolved enantiomers of the methyl phosphinate complex **[EuL$^{3}$]** racemised slowly when heated to 60 °C in $H_2O$, with a half-life of 185 (±20) h determined by observing the % ee change using chiral HPLC (ESI†). The carboxylate complex **[EuL$^{8}$]** racemised in water with a half-life of 240 (±35) h under the same conditions.[17] These systems are considerably more stable to racemisation than the frequently studied tris-dipicolinate complexes of the Ln(III) cations. The Eu tris-dipicolinate complex, [Eu(dpa)$_3$] for example, has a half-life in water of

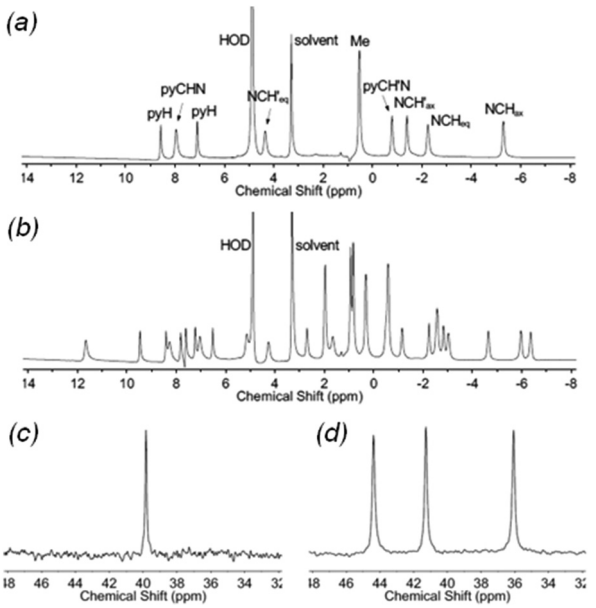
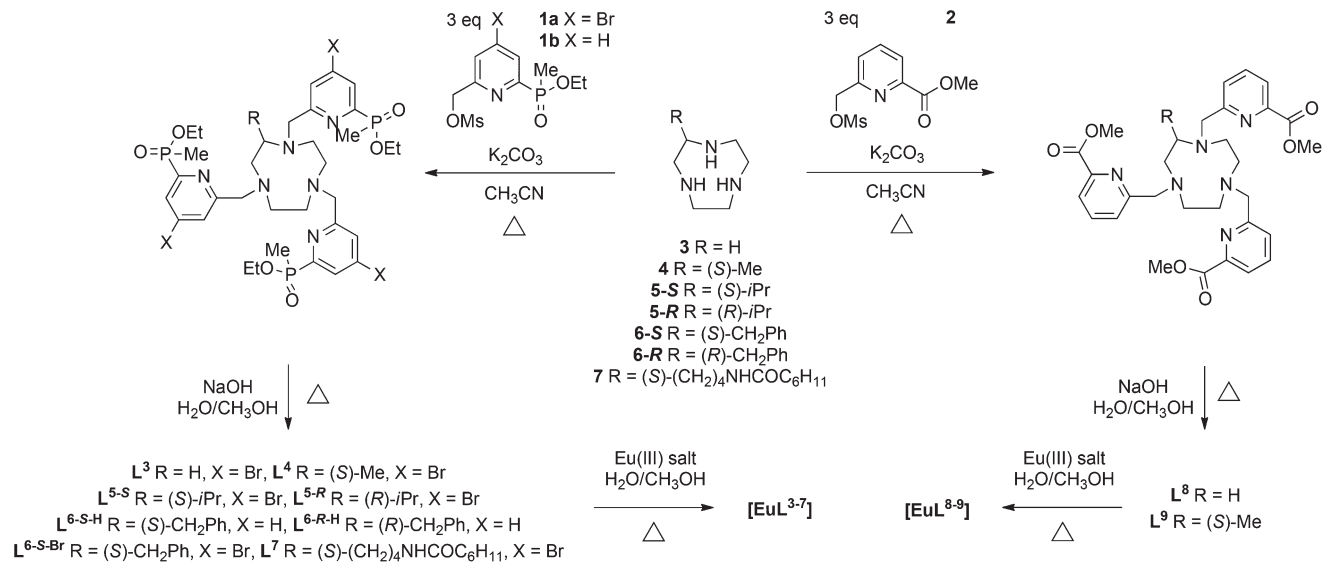



**Fig. 2** NMR spectra: (a) $^{1}$H **[EuL$^{3}$]**, (b) $^{1}$H **[EuL$^{5\text{-}S}$]**, (c) $^{31}$P **[EuL$^{3}$]**, (d) $^{31}$P **[EuL$^{5\text{-}S}$]** (9.4 T, $CD_3OD$, 295 K).




**Scheme 1** Synthesis of **[EuL$^{3-9}$]**. See experimental section for yields.

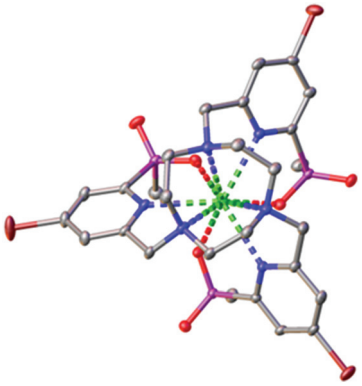


**Fig. 3** Crystal structure of **[EuL$^3$]**. *SSS*-*Δ*-(*λλλ*) enantiomer depicted.

**Table 1** Selected mean bond distances (Å ± 0.02) and torsional angles (° ± 1.0) for complexes **[EuL$^3$]** and **[EuL$^1$]**[11] [a]

| | Eu–O | Eu–N | Eu–$N_{py}$ | NCCN | $NCCN_{py}$ |
|---|---|---|---|---|---|
| **[EuL$^3$]** | 2.33 | 2.69 | 2.65 | −48 | +35.5 |
| **[EuL$^1$]** | 2.33 | 2.68 | 2.66 | −47 | +33 |

[a] Signs of torsional angles are reported for the *SSS*-*Δ*-(*λλλ*) enantiomer.

5.1 (±0.2) ms at 60 °C.[18] Notably, the methyl substituted carboxylate complex **[EuL$^9$]**, showed no loss in enantiopurity after heating to 60 °C in $H_2O$ for 72 h.

Emission and CPL spectra of enantiopure complexes **[EuL$^{3–9}$]** were recorded (see Fig. 4 and ESI†). The CPL spectra of the two enantiomers of the **[EuL$^3$]** are mirror images (Fig. 4). 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*-*Λ*-(*δδδ*) enantiomer of **[EuL$^3$]**, while for those derived from the unnatural stereoisomer had the opposite sign (see ESI†).[19] Large values for the emission dissymmetry factor ($g_{em} = 2(I_L - I_R)/(I_L + I_R)$) were observed in the $\Delta J = 1$ band (see ESI†), specifically $g_{em(591.5\ nm)} = \pm 0.10$ for enantiopure samples of **[EuL$^{3–5}$]**, and generally there were no significant differences in the appearance of the CPL spectra for different substituents R, and whether X = Br or H.[20,21]

The CPL spectra of the two enantiomers of the carboxylate complex **[EuL$^8$]** were also mirror images (ESI†). In comparison

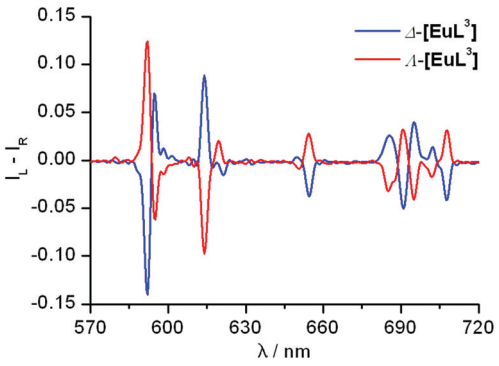



**Fig. 4** CPL spectra of *Δ*-**[EuL$^3$]** and *Λ*-**[EuL$^3$]** ($H_2O$, 295 K).

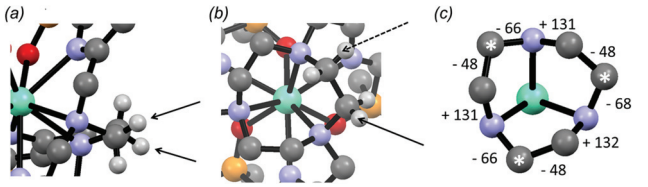



**Fig. 5** Views of the crystal structure of the *SSS*-*Δ*-(*λλλ*) enantiomer of **[EuL$^3$]** illustrating (a) the pseudo-equatorial positions of the pro-*R* hydrogens on the ring, (b) the corner position of the pro-*R* hydrogen (filled arrow), *versus* the side position of the pro-*R* hydrogen (dashed arrow) and (c) the ring torsional angles; 'corner' carbons – those that fall between two gauche bonds – are marked with asterisks.

to the phosphinate complexes there are significant changes in sign of the CPL spectra, but with maximum values of $g_{em}$ being of the same magnitude in the $\Delta J = 1$ band. As for the methyl phosphinate series, C-substitution (*e.g.* for **[EuL$^9$]**, ESI†) had negligible impact on the form and nature of the CPL spectra.

Rationalisation of the observed stereoselectivity in complex formation is provided by consideration of the solid state structure of **[EuL$^3$]**. The enantiomer depicted in Fig. 5 is *SSS*-*Δ*-(*λλλ*), *i.e.* the configuration observed from complexes derived from the unnatural *R*-amino acid, *e.g.* **[EuL$^{5\text{-}R}$]**. Inspection reveals that the pro-*R* hydrogen atom, where the ring substituent would reside, is in one of two pseudo-equatorial positions (Fig. 5a), the most likely of which (on steric grounds) is the one directed away from the three pyridyl arms (Fig. 5b), consistent with it occupying a corner (rather than a side) carbon atom (Fig. 5c).

## Conclusions

In summary, complete control of the stereochemistry of triazacyclononane based europium complexes has been demonstrated by mono-substitution at a carbon atom on the 9-$N_3$ ring. The direct and selective formation of a chiral complex was observed with >96% isomeric purity. Such behaviour simplifies 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

Commercially 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.

$^1$H, $^{13}$C and $^{31}$P NMR spectra were recorded on spectrometers operating at magnetic inductions corresponding to $^1$H 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 575 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 $min^{-1}$ (analytical) or 4.4 mL $min^{-1}$ (semi-prep) or 17 mL $min^{-1}$ (prep). Solvent systems of $H_2O$–$CH_3OH$ 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 $CH_3OH$ 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 **[EuL$^3$]** was obtained by measuring the excited state lifetime in $H_2O$ and $D_2O$. 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 $nm^{-1}$, 300 nm Blaze) that allows excitation wavelengths to be selected with a 6 nm FWHM band-pass. The collection of the emitted light was facilitated (90° angle set up, 1 cm path length quartz cuvette) by a Lock-In Amplifier (Hinds Instruments Signaloc 2100) and Photoelastic Modulator (Hinds Instruments PEM-90). The differentiated light was focused onto an Acton SP2150 monochromator (1200 g $nm^{-1}$, 500 nm Blaze) equipped with a high sensitivity cooled Photo Multiplier Tube (Hamamatsu 7155-01 red corrected). Spectra were recorded using a 5 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 smoothening 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 [EuL$^3$]

Crystals of **[EuL$^3$]** suitable for single crystal structure determination were grown by slow evaporation of a $CH_3OH$ solution. The X-ray single crystal data for **[EuL$^3$]** were collected at 120 K on an Agilent Gemini S-Ultra diffractometer (graphite monochromator, $\lambda$MoKα, $\lambda$ = 0.71073 Å) 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 $F^2$ for all data using Olex2[23] and SHELXTL[24] software. All non-hydrogen atoms were refined anisotropically, hydrogen atoms were placed in the calculated positions and refined in riding mode.

Crystal data for **[EuL$^3$]**: $C_{27}H_{33}Br_3N_6O_6{\cdot}2(H_2O)$, $M$ = 1058.23, triclinic, space group $P\bar{1}$, $a$ = 9.8356(4), $b$ = 12.3427(5), $c$ = 17.2609(8) Å, $\alpha$ = 107.259(4), $\beta$ = 97.936(4), $\gamma$ = 105.863(4)°, $V$ = 1869.30(14) Å$^3$, $Z$ = 2, $\mu$(Mo Kα) = 5.065 $mm^{-1}$, $D_{calc}$ = 1.880 g $mm^{-3}$, 21 350 reflections measured ($5.12 \leq 2\Theta \leq 60.00$), 10 802 unique ($R_{int}$ = 0.0439) were used in all calculations. The final $R_1$ was 0.0429 ($8528 > 2\sigma(I)$) and w$R_2$ 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 **L$^8$** were prepared following adapted literature procedures.[10]

Tri-ethyl ester of **L$^3$**. 1,4,7-Triazacyclononane trihydrochloride (34 mg, 0.14 mmol) and mesylate **1a** (160 mg, 0.43 mmol) were dissolved in dry $CH_3CN$ (10 mL) and $K_2CO_3$ (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% $CH_3OH$–$CH_2Cl_2$) to give the *title compound* as a colourless oil (101 mg, 74%).

$\delta_H$ ($CDCl_3$) 8.08 (3H, dd, $^3J_{H-P}$ 5.8 Hz $^4J_{H-H}$ 1.8 Hz, Ar*H*), 7.87 (3H, s, Ar*H*), 3.80–4.10 (12H, m, $CH_2$), 2.94 (12H, br s, ring *H*), 1.74 (9H, d, $^2J_{H-P}$ 15 Hz, PC$H_3$), 1.25 (9H, t, $^3J_{H-H}$ 7.1 Hz, C$H_3$). $\delta_C$ ($CDCl_3$) 163.2 (*para*-Ar*C*), 155.5 (d, $^1J_{C-P}$ 153 Hz, *ortho*-Ar*C*), 134.2 (*ortho*-Ar*C*), 129.2 (d, $^2J_{C-P}$ 22 Hz, *meta*-Ar*C*), 128.6 (*meta*-Ar*C*), 63.7 (*C*$H_2$), 61.3 (d, $^3J_{C-P}$ 6 Hz, *C*$H_2$CH$_3$), 56.0 (ring *C*), 16.6 (d, $^4J_{C-P}$ 6 Hz, $CH_2$*C*H$_3$), 13.5 (d, $^1J_{C-P}$ 104 Hz, P*C*H$_3$). $\delta_P$ ($CDCl_3$) 38.4. $m/z$ (HRMS$^+$) 955.0486 $[M + H]^+$ ($C_{33}H_{49}{}^{79}Br_3N_6O_6P_3$ requires 905.0477). $R_f$ = 0.44 (alumina, $CH_2Cl_2$–$CH_3OH$ 98 : 2).

The tri-ethyl ester of **L$^4$** was prepared in analogous manner to **L$^3$**, using macrocycle **4** (13 mg, 0.090 mmol). The crude material was purified by column chromatography (alumina, 0–2% $CH_3OH$–$CH_2Cl_2$) to give the *title compound* as a colourless oil (36 mg, 41%).

$\delta_H$ ($CDCl_3$) 8.05–8.09 (4H, m, Ar*H*), 7.85 (1H, s, Ar*H*), 7.79 (1H, s, Ar*H*), 2.51–4.14 (23H, multiple C$H_2$ and C*H*) 1.73–1.78

(9H, m, PC$H_3$), 1.24–1.29 (9H, m, $CH_2CH_3$), 0.95 (3H, d, $^3J$ = 5.7 Hz, C$H_3$). $\delta_P$ ($CDCl_3$) 38.0. *m/z* (HRMS$^+$) 969.0625 $[M + H]^+$ ($C_{34}H_{51}{}^{79}Br_3N_6O_6P_3$ requires 969.0633). $R_f$ = 0.48 (alumina, $CH_2Cl_2$–$CH_3OH$ 98 : 2).

The tri-ethyl ester of $\mathbf{L^{5\text{-}S}}$ was prepared in analogous manner to $\mathbf{L^3}$, using macrocycle **5-*S*** (29 mg, 0.16 mmol). The crude material was purified by column chromatography (alumina, 0–2% $CH_3OH$–$CH_2Cl_2$) to give the *title compound* as a colourless oil (50 mg, 30%).

$\delta_H$ ($CDCl_3$) 8.04–8.11 (4H, m, Ar*H* & Ar*H*), 7.77 (2H, app s, Ar*H*), 2.67–4.11 (23H, multiple C$H_2$ and C*H*), 1.73–1.80 (10H, m, PC$H_3$ & C$H(CH_3)_2$), 1.24–1.29 (9H, m, $CH_2CH_3$), 0.95 (6H, app t, C$H_3$). $\delta_P$ ($CDCl_3$) 38.1. *m/z* (HRMS$^+$) 997.0955 $[M + H]^+$ ($C_{36}H_{55}N_6O_6P_3{}^{79}Br_3$ requires 997.0946). $R_f$ = 0.53 (alumina, $CH_2Cl_2$–$CH_3OH$ 98 : 2).

The tri-ethyl ester of $\mathbf{L^{5\text{-}R}}$ was prepared in analogous manner to $\mathbf{L^3}$, using macrocycle **5-*R*** (10 mg, 0.057 mmol). Purification of the crude material by column chromatography (silica, 0–12% $CH_3OH$–$CH_2Cl_2$) 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 $\mathbf{L^{5\text{-}S}}$.

The tri-ethyl ester of $\mathbf{L^{6\text{-}S\text{-}H}}$ was prepared in analogous manner to $\mathbf{L^3}$, 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% $CH_3OH$–$CH_2Cl_2$) to give the *title compound* as a yellow oil (66 mg, 35%).

$\delta_H$ ($CDCl_3$) 6.97–8.07 (14H, br m, Ar*H*), 2.45–4.69 (25 H, br m, ring C$H_2$, 3 × OC$H_2$ & 4 × C$H_2$), 1.50–1.94 (9H, br m, 3 × PC$H_3$), 0.97–1.35 (9H, br m, 3 × $OCH_2CH_3$). $\delta_P$ ($CDCl_3$) 39.9. *m/z* (HRMS$^+$) 811.3654 $[M + H]^+$ ($C_{40}H_{58}N_6O_6P_3$ requires 811.3631). $R_f$ = 0.25 (silica, $CH_2Cl_2$–$CH_3OH$ 90 : 10).

The tri-ethyl ester of $\mathbf{L^{6\text{-}R\text{-}H}}$ was prepared in analogous manner to $\mathbf{L^{6\text{-}S\text{-}H}}$, using macrocycle **6-*R*** (102 mg, 0.47 mmol). The crude material was purified by column chromatography (silica, 0–25% $CH_3OH$–$CH_2Cl_2$) to give the *title compound* as a yellow oil (91 mg, 24%). Analytical data were in agreement with the enantiomer $\mathbf{L^{6\text{-}S\text{-}H}}$.

The tri-ethyl ester of $\mathbf{L^{6\text{-}S\text{-}Br}}$ was prepared in analogous manner to $\mathbf{L^3}$, using macrocycle **6-*S*** (36 mg, 0.16 mmol). The crude material was purified by column chromatography (silica, 0–7% $CH_3OH$–$CH_2Cl_2$) to give the *title compound* as a yellow oil (65 mg, 38%).

$\delta_H$ ($CDCl_3$) 7.07–8.22 (11H, br m, Ar*H*), 2.36–4.89 (25H, br m, ring C$H_2$, 3 × OC$H_2$, 4 × C$H_2$), 1.54–1.93 (9H, br m, 3 × PC$H_3$), 1.12–1.43 (9H, br m, 3 × $OCH_2CH_3$). $\delta_P$ ($CDCl_3$) 36.1. *m/z* (HRMS$^+$) 1045.0978 $[M + H]^+$ ($C_{40}H_{55}N_6O_6P_3{}^{79}Br_3$ requires 1045.0946). $R_f$ = 0.27 (silica, $CH_2Cl_2$–$CH_3OH$ 95 : 5).

The tri-ethyl ester of $\mathbf{L^7}$ was prepared in analogous manner to $\mathbf{L^3}$, 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%).

$\delta_H$ ($CDCl_3$) 7.82–8.20 (6H, m, Ar*H*), 6.45 (1H, br s, CON*H*), 3.87–4.17 (12H, m, PC$H_2$ & NC$H_2$), 2.59–3.23 (13H, m, ring C$H_2$ & C$H_2$CONH), 1.76–1.82 (9H, m, PC$H_3$), 1.26–1.76 (26H, m, $PCH_2CH_3$, alkyl chain & cyclohexane C$H_2$/C*H*). $\delta_P$ ($CDCl_3$) 37.8. *m/z* (HRMS$^+$) 1138.1914 $[M + H]^+$ ($C_{44}H_{68}{}^{79}Br_3N_7O_7P_3$ requires 1138.1926). $R_f$ = 0.32 (silica, $CH_2Cl_2$–$CH_3OH$–$NH_{3(aq)}$ 90 : 10 : 1).

The tri-methyl ester of $\mathbf{L^9}$ was prepared in analogous manner to $\mathbf{L^3}$, 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% $CH_3OH$–$CH_2Cl_2$) to give the *title compound* as a colourless oil (27 mg, 13%).

$\delta_H$ ($CDCl_3$) 7.72–8.01 (9H, m, Ar*H*), 3.93–4.21 (15H, m, inc. OC$H_3$), 2.75–3.21 (14H, m inc. C$H_3$). *m/z* (HRMS$^+$) 591.2959 $[M + H]^+$ ($C_{31}H_{39}N_6O_6$ requires 591.2931). $R_f$ = 0.12 (silica, $CH_2Cl_2$–$CH_3OH$ 90 : 10).

Complex $\mathbf{[EuL^3]}$. The tri-ethyl ester of $\mathbf{L^3}$ (70 mg, 0.073 mmol) was dissolved in $CH_3OH$ (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 $^{31}P$ NMR, the solution was cooled to RT, and the pH adjusted to 6 using 0.1 M $HBr_{(aq)}$. $Eu(NO_3)_3{\cdot}5H_2O$ (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 centrifuge. 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, $CH_2Cl_2$–$CH_3OH$–$NH_{3(aq)}$ 80 : 20 : 1) giving the *title compound* as a white solid (74 mg, 98%).

$\delta_H$ (400 MHz, $CD_3OD$) 8.60 (1H, s, py*H*), 7.97 (1H, s, pyC*H*N), 7.12 (1H, s, py*H*), 4.36 (1H, s, NC$H'_{eq}$), 0.54 (3H, s, C$H_3$), −0.77 (1H, s, pyC*H'*N), −1.37 (1H, s, NC$H'_{ax}$), −2.23 (1H, s, NC$H_{eq}$), −5.28 (1H, s, NC$H_{ax}$). $\delta_P$ (162 MHz, $CD_3OD$) 39.8. *m/z* (HRMS$^+$) 1020.8512 $[M + H]^+$ ($C_{27}H_{34}{}^{79}Br_3N_6O_6P_3{}^{151}Eu$ requires 1020.8491). $R_f$ = 0.31 (silica, $CH_2Cl_2$–$CH_3OH$–$NH_{3(aq)}$ 82 : 15 : 3).

A sample of the complex racemate was separated by chiral HPLC using an analytical CHIRALPAK-ID column. $R_t$ = 7.4 min & 14.3 min (4.0 mm × 250 mm, $CH_3OH$, 1 mL $min^{-1}$, 290 K).

Complex $\mathbf{[EuL^4]}$ was prepared in an analogous manner to $\mathbf{[EuL^3]}$, using the tri-ethyl ester of $\mathbf{L^4}$ (24 mg, 0.025 mmol). The crude material was purified by column chromatography (silica, $CH_2Cl_2$–$CH_3OH$–$NH_{3(aq)}$ 90 : 10 : 1), and then reverse phase HPLC to obtain the *title compound* as a white solid (3 mg, 11%).

$\delta_H$ (400 MHz, $CD_3OD$) 9.57, 8.98, 8.51, 8.15, 7.69, 7.36, 7.14, 6.74, 6.44, 6.04, 4.63, 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. $\delta_P$ (162 MHz, $CD_3OD$) 41.6, 40.4, 38.8. *m/z* (HRMS$^+$) 1032.8668 $[M + H]^+$ ($C_{28}H_{36}{}^{79}Br_3N_6O_6P_3{}^{151}Eu$ requires 1032.8658). $R_f$ = 0.49 (silica, $CH_2Cl_2$–$CH_3OH$–$NH_{3(aq)}$ 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. $R_t$ = 6.9 min & 13.4 min (4.0 mm × 250 mm, $CH_3OH$, 1 mL $min^{-1}$, 290 K).

Complex $\mathbf{[EuL^{5\text{-}S}]}$ was prepared in an analogous manner to $\mathbf{[EuL^3]}$, using the tri-ethyl ester of $\mathbf{L^{5\text{-}S}}$ (25 mg, 0.025 mmol). The crude material was purified by column chromatography (silica, $CH_2Cl_2$–$CH_3OH$–$NH_{3(aq)}$ 90 : 10 : 1) to obtain the *title compound* as a white solid (11 mg, 41%).

$\delta_H$ (400 MHz, $CD_3OD$) 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. $\delta_P$ (162 MHz, $CD_3OD$) 44.4, 41.3, 36.1. *m/z* (HRMS$^+$) 1060.8992 $[M + H]^+$ ($C_{30}H_{40}N_6O_6P_3{}^{79}Br_3{}^{151}Eu$ requires 1060.8971). $R_f$ = 0.10 (silica, $CH_2Cl_2$–$CH_3OH$–$NH_{3(aq)}$ 90 : 9 : 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. $R_t$ = 7.1 min & 10.3 min (4.0 mm × 250 mm, $CH_3OH$, 1 mL min$^{-1}$, 290 K).

Complex **[EuL$^{5\text{-}R}$]** was prepared in an analogous manner to **[EuL$^3$]**, using the tri-ethyl ester of **L$^{5\text{-}R}$** (7.0 mg, 7.0 μmol). The crude material was purified by column chromatography (silica, $CH_2Cl_2$–$CH_3OH$–$NH_{3(aq)}$ 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 enantiomer **[EuL$^{5\text{-}S}$]**. Chiral HPLC (ChiralPAK-ID 4.0 mm × 250 mm, $CH_3OH$, 1 mL min$^{-1}$, 290 K): $R_t$ = 7.0 min.

Complex **[EuL$^{6\text{-}S\text{-}H}$]**. The tri-ethyl ester of **L$^{6\text{-}S\text{-}H}$** (32 mg, 0.04 mmol) was dissolved in $CD_3OD$ (3.5 mL) and a solution of 0.1 M NaOH in $D_2O$ (3.5 mL) was added. The reaction mixture was heated for 16 h at 90 °C with stirring. Subsequent removal of the solvent under reduced pressure yielded the deprotected ligand as a white solid (as verified by ESMS).

The ligand was dissolved in $H_2O$–$CH_3OH$ (4 : 1, 2.5 mL) and the pH of the solution adjusted to 5.5 using dilute $HCl_{(aq)}$. $EuCl_3{\cdot}6H_2O$ (15.9 mg, 0.04 mmol) was added and the reaction mixture was heated at 80 °C for 16 h. After allowing the reaction mixture to cool to room temperature, 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 $HCl_{(aq)}$ and the solvent lyophilised to give the crude product. The crude product was taken in to $CH_2Cl_2$–$CH_3OH$ (8 : 2, 2 mL) and the solution filtered to facilitate the removal of salts. Subsequent removal of solvent under reduced pressure yielded an off-white solid which was further purified by column chromatography on silica gel ($CH_2Cl_2$–$CH_3OH$–$NH_{3(aq)}$, 80 : 20 : 1) to give the title compound as an off-white solid (17 mg, 50%).

$\delta_H$ (400 MHz, $CD_3OD$) 10.56, 8.50, 7.76, 7.61, 7.38, 7.28, 7.17, 7.07, 6.68, 6.29, 5.33, 4.60, 4.30, 2.98, 2.17, 1.44, 1.31, 0.82, 0.42, −0.11, −0.37, −1.75, −1.88, −2.33, −2.87, −4.18, −5.82, −6.20. $\delta_P$ (162 MHz, $CD_3OD$) 44.5, 40.2, 34.9. *m/z* (HRMS$^+$) 875.1659 $[M + H]^+$ ($C_{34}H_{43}N_6O_6P_3{}^{151}Eu$ requires 875.1656). $R_f$ = 0.16 (silica, $CH_2Cl_2$–$CH_3OH$–$NH_{3(aq)}$ 80 : 20 : 1). Chiral HPLC (ChiralPAK-ID 4.0 mm × 250 mm, $CH_3OH$, 1 mL min$^{-1}$, 290 K): $R_t$ = 6.1 min.

Complex **[EuL$^{6\text{-}R\text{-}H}$]** was prepared in analogous manner to **[EuL$^{6\text{-}S\text{-}H}$]**, using the tri-ethyl ester of **L$^{6\text{-}R\text{-}H}$** (34 mg, 0.04 mmol). The crude material was purified by column chromatography on silica gel ($CH_2Cl_2$–$CH_3OH$–$NH_3$, 80 : 20 : 1) to give the title compound as an off-white solid (27 mg, 73%). NMR and MS data were in agreement with the enantiomer **[EuL$^{6\text{-}S\text{-}H}$]**. Chiral HPLC (ChiralPAK-ID 4.0 mm × 250 mm, $CH_3OH$, 1 mL min$^{-1}$, 290 K): $R_t$ = 10.9 min.

Complex **[EuL$^{6\text{-}S\text{-}Br}$]**. The tri-ethyl ester of **L$^{6\text{-}S\text{-}Br}$** (26 mg, 0.025 mmol) was dissolved in $CD_3OD$ (2.4 mL) and a solution of 0.1 M NaOH in $D_2O$ (2.2 mL) was added. The reaction mixture was heated for 5 h at 90 °C with stirring. Subsequent removal of the solvent under reduced pressure yielded the deprotected ligand as a white solid (as verified by ESMS and $^{31}$P NMR).

The ligand was dissolved in $H_2O$–$CH_3OH$ (4 : 1, 1.5 mL) and the pH of the solution adjusted to 5.5 using dilute $HBr_{(aq)}$. $Eu(NO_3)_3{\cdot}5H_2O$ (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 $CH_2Cl_2$–$CH_3OH$ (8 : 2, 2 mL) and the solution filtered to facilitate the removal of salts. Subsequent removal of solvent under reduced pressure yielded an off-white solid which was further purified by column chromatography on silica gel ($CH_2Cl_2$–$CH_3OH$–$NH_{3(aq)}$, 80 : 20 : 1) to give the *title compound* as an off-white solid (21 mg, 76%).

$\delta_H$ (400 MHz, $CD_3OD$) 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. $\delta_P$ (162 MHz, $CD_3OD$) 43.9, 40.2, 33.5. *m/z* (HRMS$^+$) 1113.9153 $[M + H]^+$ ($C_{34}H_{40}N_6O_6P_3{}^{79}Br_3{}^{151}Eu$ requires 1113.9031). $R_f$ = 0.56 (silica, $CH_2Cl_2$–$CH_3OH$–$NH_{3(aq)}$ 80 : 20 : 1). Chiral HPLC (ChiralPAK-ID 4.0 mm × 250 mm, $CH_3OH$, 1 mL min$^{-1}$, 290 K): $R_t$ = 11.6 min.

Complex **[EuL$^7$]** was prepared in analogous manner to **[EuL$^3$]**, using the tri-ethyl ester of **L$^7$** (10 mg, 8.8 μmol). The crude material was purified by column chromatography (silica, $CH_2Cl_2$–$CH_3OH$–$NH_{3(aq)}$ 90 : 10 : 1) to give the *title compound* as a white solid (3 mg, 30%).

$\delta_H$ (400 MHz, $CD_3OD$) 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. $\delta_P$ (162 MHz, $CD_3OD$) 43.4, 40.7, 37.5. *m/z* (HRMS$^+$) 1203.9955 $[M + H]^+$ ($C_{38}H_{53}N_7O_7P_3{}^{79}Br_3{}^{151}Eu$ requires 1203.9950). $R_f$ = 0.32 (silica, $CH_2Cl_2$–$CH_3OH$–$NH_{3(aq)}$ 90 : 10 : 1). Chiral HPLC (ChiralPAK-ID 4.0 mm × 250 mm, $CH_3OH$, 1 mL min$^{-1}$, 290 K): $R_t$ = 14.5 min.

Complex **[EuL$^8$]** (as a racemate) has been prepared within our laboratories previously.[12] A sample of **[EuL$^8$]** was resolved using a semi-prep CHIRAL-PAK IC column. Chiral HPLC (ChiralPAK-IC 4.0 mm × 250 mm, $CH_3OH$, 0.5 mL min$^{-1}$, 290 K): $R_t$ = 11.7 min & 19.8 min.

Complex **[EuL$^9$]** was prepared in an analogous manner to **[EuL$^3$]**, using the tri-methyl ester of **L$^9$** (18 mg, 0.031 mmol). The crude material was purified by column chromatography (silica, $CH_2Cl_2$–$CH_3OH$–$NH_3$ 80 : 20 : 0.1), to obtain the *title compound* as a white solid (16 mg, 76%).

$\delta_H$ (400 MHz, $D_2O$) 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

$[M + H]^+$ ($C_{28}H_{30}N_6O_6{}^{151}Eu$ requires 697.1425). $R_f$ = 0.23 (silica, $CH_2Cl_2$–$CH_3OH$–$NH_3$ 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, $CH_3OH$, 0.5 mL $min^{-1}$, 298 K): $R_t$ = 12.3 min & 19.7 min.

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