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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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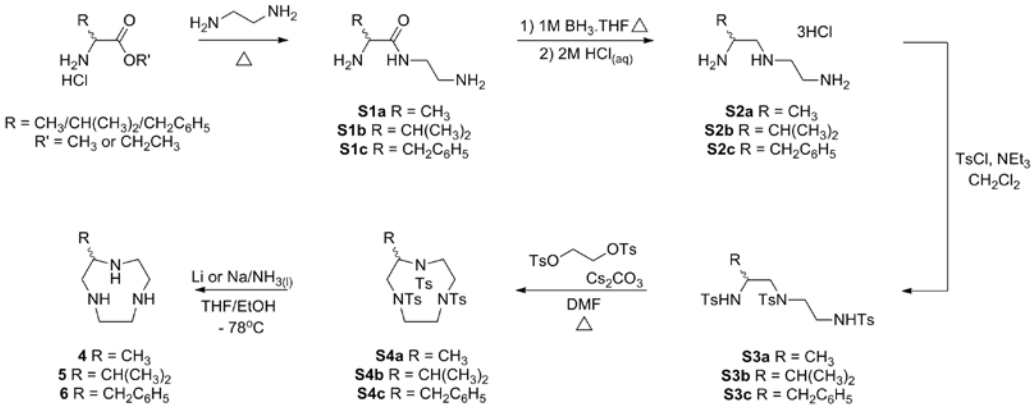
Synthesis of the substituted triazacyclononane macrocycles 4-6

Mono-substituted macrocycles **4 - 6** were manufactured following the synthetic route presented in *Scheme S1*. [a]



Scheme S1: Preparation of mono-substituted macrocycles.

Bis-amine, amide **S1**

N-(2-Aminoethyl)-*S*-alaninamide, S1a

L-alanine methyl ester hydrochloride (5.00 g, 36.0 mmol) was added in small portions over 1 h to stirring ethylenediamine at 90 ºC under an atmosphere of $Ar_{(g)}$. The reaction mixture was then heated at 120 ºC for 3 h, during which time the reaction mixture went yellow. Excess ethylenediamine was removed by distillation under reduced pressure. The orange oil was taken into $NaOH_{(aq)}$ (4 M, 10 mL), the solvent removed *in vacuo*, and the residue redissolved in CH_3OH (25 mL). This solution was filtered under vacuum, with the resulting filtrate added to CH_2Cl_2 (50 mL), and filtered through Celite®. The filtrate was evaporated to give the *title compound* as a yellow oil (3.65 g, 78 %). NMR spectroscopic analysis revealed the presence of very small amounts of unidentified contaminant. The material was taken on as isolated, with no adjustments for the contamination being made.

δ_H ($CDCl_3$) 7.54 (1H, br s, N*H*), 3.50 (1H, quart, ^3J = 7.0 Hz, C*H*), 3.28-3.33 (2H, m, CH_2CH_2NH_2), 2.83 (2H, t, ^3J = 6.0 Hz, CH_2NH_2), 1.34 (3H, d, ^3J = 7.0 Hz, CH_3).

δ_C ($CDCl_3$) 176.1 (*C*O), 50.9, 41.9, 41.6, 21.9.

m/z (MS^+) 132.1137 $[M + H]^+$ ($C_5H_{14}N_3O$ requires 132.1137).

N*-(2-Aminoethyl)-*S*-valinamide, S1b-*S was prepared in analogous manner to **S1a**, using *L*-valine methyl ester hydrochloride (5.00 g, 29.8 mmol), being isolated as a yellow oil (4.62 g, 97 %). NMR spectroscopic analysis revealed the presence of very small amounts of unidentified contaminant. The material was taken on as isolated, with no adjustments for the contamination being made.

δ_H ($CDCl_3$) 7.55 (1H, br s, N*H*), 3.27-3.36 (2H, m, CH_2CH_2NH_2), 3.23 (1H, d, ^3J = 3.8 Hz, C*H*NH_2), 2.82 (2H, t, ^3J = 6.0 Hz, CH_2NH_2), 2.24-2.35 (1H, m, C*H*), 0.98 (3H, d, ^3J = 7.0 Hz, CH_3), 0.82 (3H, d, ^3J = 7.0 Hz, CH_3).

δ_C ($CDCl_3$) 174.8 (*C*O), 60.3, 41.9, 41.7, 30.9, 19.7, 16.1.

m/z ($HRMS^+$) 160.1454 $[M + H]^+$ ($C_7H_{18}N_3O$ requires 160.1450).

[a] The synthesis of the *iso*-propyl substituted macrocycle **6-*S*** by the route in Scheme S1, has previously been reported not to be possible (see: G. Stones, G. Argouarch, A. R. Kennedy, D. C. Sherrington and C. L. Gibson, *Org. Biomol. Chem.* 2003, **1**, 2357). No such difficulties were found in our hands.

N*-(2-Aminoethyl)-*R*-valinamide, S1b-*R was prepared in analogous manner to **S1a**, using *D*-valine methyl ester hydrochloride (2.50 g, 14.9 mmol), the product being isolated as a yellow oil (2.11 g, 89 %). NMR spectroscopic analysis revealed the presence of very small amounts of unidentified contaminant. The material was taken on as isolated, with no adjustments for the contamination being made. NMR and MS data were in agreement with the enantiomer **S1b-*S***.

N*-(2-Aminoethyl)-*S*-phenylalaninamide, S1c-*S was prepared in analogous manner to **S1a**, using *L*-phenylalanine ethyl ester hydrochloride (3.30 g, 14.4 mmol), the product being isolated as a yellow oil (2.42 g, 81 %). NMR spectroscopic analysis revealed the presence of very small amounts of unidentified contaminant. The material was taken on as isolated, with no adjustments for the contamination being made.
δ_H ($CDCl_3$) 7.47 (1H, br s, N*H*), 7.17-7.34 (5H, m, Ar*H*), 3.61 (1H, dd, ^3J = 4.5, 9.0 Hz, C*H*NH_2), 3.25-3.33 (2H, m, CH_2C$H_2$$NH_2$), 3.23 (1H, dd, ^2J = 13.5 Hz, ^3J = 4.5 Hz, CH_2Ar), 2.79 (2H, t, ^3J = 6.0 Hz, CH_2C$H_2$$NH_2$), 2.74 (1H, dd, ^2J = 13.5 Hz, ^3J = 9.0 Hz, CH_2Ar).
δ_C ($CDCl_3$) 174.5 (*C*O), 137.8, 129.2, 128.6, 126.7, 56.5, 41.8, 41.4, 41.1.
m/z ($HRMS^+$) 208.1442 $[M + H]^+$ ($C_{11}H_{18}N_3O$ requires 208.1450).

N*-(2-Aminoethyl)-*R*-phenylalaninamide, S1c-*R was prepared in analogous manner to **S1a**, using *D*-phenylalanine methyl ester hydrochloride (4.10 g, 19.0 mmol), the product being isolated as a yellow oil (3.52 g, 89 %). NMR spectroscopic analysis revealed the presence of very small amounts of unidentified contaminant. The material was taken on as isolated, with no adjustments for the contamination being made. NMR and MS data were in agreement with the enantiomer **S1c-*S***.

Tris-amine **S2**

(*S*)-*N*-(2-Aminoethyl)-1-methylethane-1, 2-diamine, S2a
BH_3.THF (1 M, 100 mL) was added to compound **S1a** (1.82 g, 13.9 mmol) in a flask under a flowing stream of $Ar_{(g)}$ (CARE! Immediate exothermic reaction). The resulting reaction mixture was heated to 70 ºC under an atmosphere of $Ar_{(g)}$ for 24 h. After verifying reduction was complete (quenching sample of mixture, and recording an IR spectrum checking for the absence of the C=O stretch at ~ 1600 cm^{-1}) the reaction mixture was fully quenched by dropwise addition of CH_3OH (15 mL) at 0 ºC (CARE! Exothermic reaction). The solvents were removed *in vacuo*, and the residue was boiled under reflux in $HCl_{(aq)}$ (2 M, 60 mL). The solvent was removed by co-evaporation with CH_3OH, to yield the *title compound* (as the trihydrochloride salt) (3.15 g, quantitative). NMR spectroscopic analysis revealed the presence of small amounts of unidentified contaminant. The material was taken on immediately, with no adjustments for the contaminants being made.
δ_H (D_2O) 3.38-3.89 (7H, m, 3 × CH_2 & C*H*), 1.47 (3H, d, ^3J = 6.8 Hz, CH_3).
m/z (MS^+) 118.4 $[M + H]^+$ ($C_5H_{16}N_3$ requires 118.1).

(*S*)-*N*-(2-Aminoethyl)-1-*iso*-propylethane-1, 2-diamine, S2b-*S* was prepared in analogous manner to **S2a**, using **S1b-*S*** (2.28 g, 14.3 mmol), the product (as the trihydrochloride salt) being isolated as an off-white highly hygroscopic solid (3.64 g, quantitative). NMR spectroscopic analysis revealed the presence of small amounts of unidentified contaminant. The material was taken on immediately, with no adjustments for the contaminants being made.

δ_H (D_2O) 3.41-3.61 (6H, m, 3 × C*H*$_2$ & C*H*), 2.12-2.17 (1H, m, C*H*(CH_3)$_2$), 1.04-1.07 (6H, m, 2 × C*H*$_3$).
m/z (MS^+) 146.1 $[M + H]^+$ ($C_7H_{20}N_3$ requires 146.2).

(*R*)-*N*-(2-Aminoethyl)-1-*iso*-propylethane-1, 2-diamine, S2b-*R* was prepared in analogous manner to **S2a**, using **S1b-*R*** (1.04 g, 6.53 mmol). Upon removal of solvent, the product (as the trihydrochloride salt) was isolated as an off-white highly hygroscopic solid). NMR spectroscopic analysis revealed the presence of unidentified contaminant. All the material was taken on immediately, with no adjustments for the contaminants being made. NMR and MS data were in agreement with the enantiomer **S2b-*S***.

(*S*)-*N*-(2-Aminoethyl)-1-benzylethane-1, 2-diamine, S2c-*S* was prepared in analogous manner to **S2a**, using **S1c-*S*** (2.40 g, 11.6 mmol), the product (as the trihydrochloride salt) being isolated as an off-white highly hygroscopic solid (2.20 g, 63 %). NMR spectroscopic analysis revealed the presence of small amounts of unidentified contaminant. The material was taken on immediately, with no adjustments for the contaminants being made.
δ_H (D_2O) 7.32-7.34 (2H, m, Ar*H*), 7.27-7.29 (1H, m, Ar*H*), 7.23-7.24 (2H, m, Ar*H*), 3.85-3.90 (1H, m, C*H*NH_2), 3.25-3.47 (6H, m, 3 × C*H*$_2$N), 3.09 (1H, dd, ^2J = 14.0 Hz, ^3J = 6.0 Hz, C*H*$_2$Ar), 2.92 (1H, dd, ^2J = 14.0 Hz, ^3J = 8.5 Hz, C*H*$_2$Ar).
m/z (MS^+) 194.2 $[M + H]^+$ ($C_{11}H_{20}N_3$ requires 194.2).

(*R*)-*N*-(2-Aminoethyl)-1-benzylethane-1, 2-diamine, S2c-*R* was prepared in analogous manner to **S2a**, using **S1c-*R*** (2.26 g, 10.9 mmol), the product (as the trihydrochloride salt) being isolated as an off-white highly hygroscopic solid (3.22 g, 98 %). NMR spectroscopic analysis revealed the presence of small amounts of unidentified contaminant. The material was taken on immediately, with no adjustments for the contaminants being made. NMR and MS data were in agreement with the enantiomer **S2c-*S***.

Acyclic *tris*-tosylamide **S3**

(*S*)-2-*N*-2, 6-Bistoluene-*p*-sulfonamido-4-toluene-*p*-sulphonyl-4-azahexane, S3a
A solution of 4-methylbenzenesulfonyl chloride (8.41 g, 44.1 mmol) in dry CH_2Cl_2 (50 mL) was added dropwise to a solution of tri-amine **S2a** (3.33 g, '14.7 mmol') and NEt_3 (13.4 g, ~ 18 mL, 132 mmol) in dry CH_2Cl_2 (125 mL) over 1 h under an atmosphere of $Ar_{(g)}$. The reaction mixture was stirred under $Ar_{(g)}$ for 16 h. The resulting organic phase was washed with H_2O (125 mL), dried over $MgSO_4$, and the solvent removed *in vacuo* to give an off-white foaming solid. This crude reaction material was purified by silica gel chromatography (CH_2Cl_2 : EtOAc 100:0 to 90:10) to give the *title compound* as a foaming white solid (1.84 g, 22 % from **S1a**).
δ_H ($CDCl_3$) 7.79 (2H, d, ^3J = 8.3 Hz, Ar*H*), 7.73 (2H, d, ^3J = 8.3 Hz, Ar*H*), 7.62 (2H, d, ^3J = 8.3 Hz, Ar*H*), 7.29-7.32 (6H, m, Ar*H*), 5.26 (1H, t, ^3J = 8.3 Hz, N*H*CH_2), 5.13 (1H, d, ^3J = 6.7 Hz, N*H*$CHCH_3$), 3.46-3.56 (1H, m, C*H*), 3.19-3.25 (2H, m, C*H*$_2$), 2.99-3.08 (3H, m, 1.5 × C*H*$_2$), 2.88 (1H, dd, ^2J = 14.7 Hz, ^3J = 5.3 Hz, 0.5 × C*H*$_2$), 2.41-2.43 (9H, m, ArC*H*$_3$), 0.97 (3H, d, ^3J = 6.6 Hz, C*H*$_3$).
δ_C ($CDCl_3$) 144.2, 143.7, 143.6, 137.6, 136.9, 134.9, 130.1, 129.9, 127.5, 127.3, 127.2 (11 × Ar*C* - 1 missing), 56.1, 51.0, 49.3, 42.6 (4 × *C*N), 21.7 (Ar*C*H_3 coincidental), 19.1 (*C*H_3).
m/z ($HRMS^+$) 602.1425 $[M + Na]^+$ ($C_{26}H_{33}N_3O_6S_3Na$ requires 602.1429).
Mt Pt = 78 °C.
R_f = 0.44 (silica, CH_2Cl_2 : EtOAc 90:10).

(*S*)-1-*N*-1-*iso*-Propyl-1, 5-bistoluene-*p*-sulfonamido-3-toluene-*p*-sulphonyl-3-azapentane, S3b-*S* was prepared in analogous manner to **S3a**, using **S2b-*S*** (1.00 g, '3.93 mmol'). The crude reaction material was purified by silica gel chromatography (CH_2Cl_2 : EtOAc 100:0 to 96:4) to give the product as a white solid (0.45 g, '19 %').
δ_H ($CDCl_3$) 7.80 (2H, d, ^3J = 8.3 Hz, Ar*H*), 7.73 (2H, d, ^3J = 8.3 Hz, Ar*H*), 7.62 (2H, d, ^3J = 8.3 Hz, Ar*H*), 7.28-7.33 (6H, m, Ar*H*), 5.22 (1H, t, ^3J = 5.8 Hz, N*H*CH_2), 4.90 (1H, d, ^3J = 7.3 Hz, N*H*CH), 3.32-3.39 (1H, m, NHC*H*), 3.02-3.21 (6H, m, 3 × CH_2), 2.43 (6H, app s, 2 × ArCH_3), 2.40 (3H, s, ArCH_3), 1.86-1.94 (1H, m, C*H*$(CH_3)_2$), 0.77 (3H, d, ^3J = 6.9 Hz, CH_3), 0.63 (3H, d, ^3J = 6.9 Hz, CH_3).
δ_C ($CDCl_3$) 144.3, 143.6, 137.5, 136.9, 134.7, 130.1, 129.9, 129.8, 127.5, 127.5 (sic), 127.2 (11 × Ar*C* - 1 coincidental), 57.5, 52.1, 50.9, 42.6 (4 × *C*N), 28.8 (*C*H$(CH_3)_2$), 21.7 (Ar*C*H_3 coincidental), 18.3, 16.5 (2 × CH_3).
m/z (HRMS$^+$) 608.1945 $[M + H]^+$ ($C_{26}H_{38}N_3O_6S_3$ requires 608.1923).
Mt Pt = 86 °C.
R_f = 0.56 (silica, CH_2Cl_2 : EtOAc 90:10).

(*R*)-1-*N*-1-*iso*-Propyl-1, 5-bistoluene-*p*-sulfonamido-3-toluene-*p*-sulphonyl-3-azapentane, S3b-*R* was prepared in analogous manner to **S3a**, using **S2b-*R*** (1.66 g, '6.53 mmol'). The crude reaction material was purified by silica gel chromatography (CH_2Cl_2 : EtOAc 100:0 to 96:4) to give the product as a white solid (1.43 g, 36 % from **S1b-*R***). Analytical data were in agreement with the enantiomer **S3b-*S***.

(*S*)-1-*N*-1-Benzyl-1, 5-bistoluene-*p*-sulfonamido-3-toluene-*p*-sulphonyl-3-azapentane, S3c-*S* was prepared in analogous manner to **S3a**, using **S2c-*S*** (1.14 g, 3.80 mmol). The crude reaction material was purified by silica gel chromatography (CH_2Cl_2 : EtOAc 100:0 to 95:5) to give the product as a white solid (0.78 g, 31 %).
δ_H ($CDCl_3$) 7.71 (2H, d, ^3J = 8.0 Hz, tosyl Ar*H*), 7.52 (4H, d, ^3J = 8.0 Hz, tosyl Ar*H*), 7.21-7.25 (4H, m, tosyl Ar*H*), 7.05-7.10 (5H, m, tosyl Ar*H* & Ar*H*), 6.88 (2H, d, ^3J = 7.0 Hz, Ar*H*), 5.58 (1H, t, ^3J = 6.0 Hz, N*H*CH_2), 5.33 (1H, d, ^3J = 6.5 Hz, N*H*), 3.59-3.64 (1H, m, C*H*), 3.22 (1H, dd, ^2J = 14.5 Hz, ^3J = 6.5 Hz, CHCH_2NTs), 3.12 (1H, dd, ^2J = 13.5 Hz, ^3J = 6.5 Hz, CH_2CH_2NTs), 2.97-3.08 (4H, m, CHCH_2NTs, CH_2CH_2NTs & CH_2CH_2NTs), 2.79 (1H, dd, ^2J = 14.0 Hz, ^3J = 6.0 Hz, CH_2Ar), 2.52 (1H, dd, ^2J = 14.0 Hz, ^3J = 8.0 Hz, CH_2Ar), 2.33-2.36 (9H, m, 3 × CH_3).
δ_C ($CDCl_3$) 144.0, 143.4, 143.2, 136.8, 136.5, 134.4, 129.9, 129.8, 129.7, 129.1, 128.5, 127.4, 127.1, 127.0, 126.5 (15 × tosyl Ar*C* & Ar*C* – 1 coincidental), 54.6, 50.9, 42.3 (3 × *C*N – 1 coincidental), 38.7 (*C*H_2Ar), 21.5 (Ar*C*H_3 coincidental).
m/z (HRMS$^+$) 678.1744 $[M + Na]^+$ ($C_{32}H_{37}N_3O_6S_3Na$ requires 678.1742).
Mt Pt = 101 °C.
R_f = 0.35 (silica, CH_2Cl_2 : EtOAc 95 : 5).

(*R*)-1-*N*-1-Benzyl-1, 5-bistoluene-*p*-sulfonamido-3-toluene-*p*-sulphonyl-3-azapentane, S3c-*R* was prepared in analogous manner to **S3c-*S***, using **S2c-*R*** (1.44 g, 4.80 mmol). The crude reaction material was purified by silica gel chromatography (CH_2Cl_2 : EtOAc 100:0 to 95:5) to give the product as a white solid (1.24 g, 40 %). Analytical data were in agreement with the enantiomer **S3c-*S***.

Cyclic *tris*-tosylamide **S4**

(*S*)-2-Methyl-1, 4, 7-tris(toluene-*p*-sulphonyl)-1, 4, 7-triazacyclononane, S4a
Cs_2CO_3 (3.30 g, 10.1 mmol) was added to a solution of compound **S3a** (1.78 g, 3.07 mmol) dissolved in dry DMF (100 mL) under an atmosphere of $Ar_{(g)}$. To this well-stirred suspension, ethylene di(*p*-toluenesulfonate) (1.25 g, 3.38 mmol) dissolved in dry DMF (50 mL) was added dropwise over 2 h. The resulting reaction mixture was heated at 65 ºC for 16 h, then stirred at RT for 48 h under an atmosphere of $Ar_{(g)}$. The solvent was removed *in vacuo*, and the residue dissolved in $CHCl_3$ (150 mL), and washed with H_2O (2 × 150 mL). The organic phase was dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude material was purified by silica gel chromatography (CH_2Cl_2 : EtOAc 100:0 to 99:1), to yield the *title compound* as a white solid (1.40 g, 75 %).
δ_H ($CDCl_3$) 7.73-7.76 (4H, m, Ar*H*), 7.62 (2H, t, ^3J = 8.3 Hz, Ar*H*), 7.30-7.33 (6H, m, Ar*H*), 4.45 (1H, br s, ring *H*), 3.06-3.65 (10H, m, multiple ring *H*), 2.42-2.44 (9H, m, 3 × ArCH_3), 0.77 (3H, s, CH_3).
δ_C ($CDCl_3$) 144.2, 143.8, 143.8 (sic), 136.7, 135.1, 134.4, 130.0, 129.9, 127.8, 127.6, 127.4 (11 × Ar*C* – 1 coincidental), 55.2, 54.2, 53.9, 53.3, 50.8 45.7 (6 × *C*N), 21.6 (3 × ArCH_3 coincidental), 14.5 (CH_3).
m/z (HRMS$^+$) 628.1594 $[M + Na]^+$ ($C_{28}H_{35}N_3O_6S_3Na$ requires 628.1586).
Mt Pt = 114 °C
R_f = 0.16 (silica, CH_2Cl_2 : EtOAc 98:2).

(*S*)-2-*iso*-Propyl-1, 4, 7-tris(toluene-*p*-sulphonyl)-1, 4, 7-triazacyclononane, S4b-*S* was prepared in analogous manner to **S4a**, using **S3b-*S*** (0.40 g, 0.66 mmol). The crude reaction material was purified by silica gel chromatography (CH_2Cl_2 : EtOAc 100:0 to 99:1) to give the product as a white solid (0.31 g, 74 %).
δ_H ($CDCl_3$) 7.84 (2H, d, ^3J = 8.3 Hz, Ar*H*), 7.70 (2H, d, ^3J = 8.0 Hz, Ar*H*), 7.58 (2H, d, ^3J = 7.8 Hz, Ar*H*), 7.27-7.35 (6H, m, 3 × Ar*H*), 4.32 (1H, br s, ring *H*), 3.80-3.85 (1H, br s, ring *H*), 2.95-3.62 (9H, m, multiple ring *H*), 2.43 (3H, s, ArCH_3), 2.42 (3H, s, ArCH_3), 2.40 (3H, s, ArCH_3), 1.53 (1H, br s, C*H*$(CH_3)_2$), 1.06 (3H, br s, CH(C$H_3)_2$), 0.68 (3H, d, ^3J = 6.7 Hz, CH(C$H_3)_2$).
δ_C ($CDCl_3$) 144.2, 143.9, 143.4, 138.6, 134.5, 134.1, 130.1, 130.0, 129.7, 128.0, 127.9, 127.4 (12 × Ar*C*), 66.1, 53.9, 52.0, 51.3, 46.7 (5 × *C*N – 1 missing), 29.2 (*C*H$(CH_3)_2$), 21.7 (3 × ArCH_3 coincidental), 20.9, 20.6 (2 × CH_3).
m/z (HRMS$^+$) 656.1904 $[M + Na]^+$ ($C_{30}H_{39}N_3O_6S_3Na$ requires 656.1899).
Mt Pt = 120 °C
R_f = 0.28 (silica, CH_2Cl_2 : EtOAc 98:2).

(*R*)-2-*iso*-Propyl-1, 4, 7-tris(toluene-*p*-sulphonyl)-1, 4, 7-triazacyclononane, S4b-*R* was prepared in analogous manner to **S4a**, using **S3b-*R*** (1.38 g, 2.27 mmol). The crude reaction material was purified by silica gel chromatography (CH_2Cl_2 : EtOAc 100:0 to 99:1) to give the product as a white solid (0.917 g, 64 %). Analytical data were in agreement with the enantiomer **S4b-*S***.

(*S*)-2-Benzyl-1, 4, 7-tris(toluene-*p*-sulphonyl)-1, 4, 7-triazacyclononane, S4c-*S* was prepared in analogous manner to **S4a**, using **S3c-*S*** (396 mg, 0.60 mmol). The crude reaction material was purified by silica gel chromatography (CH_2Cl_2 : EtOAc 100:0 to 98:2) to give the product as a white solid (340 mg, 82 %).

δ_H ($CDCl_3$) 7.84 (2H, d, ^3J = 8.0 Hz, tosyl Ar*H*), 7.62 (2H, d, ^3J = 8.0 Hz, tosyl Ar*H*), 7.34 (2H, t, ^3J = 7.5 Hz, Ar*H*), 7.29-7.33 (5H, m, tosyl Ar*H* & Ar*H*), 7.15 (2H, d, ^3J = 7.5 Hz, Ar*H*), 7.04-7.13 (4H, m, tosyl Ar*H*), 4.73 (1H, br s, C*H*), 3.56-3.84 (4H, m, ring CH_2), 2.88-3.32 (6H, m, ring CH_2), 2.54 (1H, br s, CH_2Ar), 2.41 (3H, s, ArCH_3), 2.38 (3H, s, ArCH_3), 2.35 (3H, s, ArCH_3) - second CH_2Ar proton obscured under ArCH_3 singlets.
δ_C ($CDCl_3$) 144.2, 143.8, 143.4, 137.1, 137.0, 134.2, 133.6, 130.0, 129.9, 129.6, 129.3, 128.7, 127.5, 127.3, 126.7 (15 × tosyl Ar*C* & Ar*C*), 60.2, 54.7, 53.6, 53.5, 50.9, 46.1 (6 × N*C*), 36.4 (*C*H_2Ar), 21.5, 21.4 (2 × tosyl *C*H_3 – 1 coincidental).
m/z (HRMS$^+$) 704.1926 $[M + Na]^+$ ($C_{34}H_{39}N_3O_6S_3Na$ requires 704.1899).
Mt Pt = 120 °C.
R_f = 0.13 (silica, CH_2Cl_2).

(*R*)-2-Benzyl-1, 4, 7-tris(toluene-*p*-sulphonyl)-1, 4, 7-triazacyclononane, S4c-*R* was prepared in analogous manner to **S4c-*S***, using **S3c-*R*** (0.93 g, 1.40 mmol). The crude reaction material was purified by silica gel chromatography (CH_2Cl_2 : EtOAc 100:0 to 99:1) to give the product as a white solid (0.65 g, 70 %). Analytical data were in agreement with the enantiomer **S4c-*S***.

Deprotected macrocycles **4 - 6**

Macrocycle 4
Ammonia (30 mL) was condensed into a solution of **S4a** (400 mg, 0.66 mmol) dissolved in dry THF (15 mL) and dry EtOH (1 mL) whilst stirring under $Ar_{(g)}$ at -78 °C. Li metal (300 mg, excess) was added in small portions to the solution and a strong blue colour developed. The solution was allowed to warm to RT overnight, during which time the solution turned colourless and $NH_{3(g)}$ evaporated through an anti-suck back apparatus. H_2O (15 mL) was added to the solution (CARE! Metallic Li may be present in excess) and all solvent removed. The residue was dissolved in $HCl_{(aq)}$ (2 M, 15 mL) and washed with Et_2O (2 × 15 mL). The aqueous layer was concentrated, and the residue dissolved in $KOH_{(aq)}$ (6 M, 15 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The organic layer was concentrated to give a yellow oil (54 mg, ’57 %’) containing the *title compound* contaminated by small quantities of tosylate containing species. The material was taken on with no adjustments for the contaminants being made.
δ_H ($CDCl_3$) 2.43-2.92 (11H, m, ring *H*), 1.05 (3H, s, d, ^3J = 6.6 Hz, CH_3).
m/z (ESMS$^+$) 144.1 $[M + H]^+$ ($C_7H_{18}N_3$ requires 144.1).

Macrocycle 5-*S* was prepared in analogous manner to **4**, using **S4b-*S*** (250 mg, 0.39 mmol). The organic layer was concentrated to give a yellow oil (34 mg, ’50 %’) containing the *title compound* contaminated by small quantities of tosylate containing species. The material was taken on with no adjustments for the contaminants being made.
δ_H ($CDCl_3$) 2.38-2.86 (11H, m, ring *H*), 1.49-1.57 (1H, m, C*H*$(CH_3)_2$), 0.94 (3H, d, ^3J = 6.8 Hz, CH(CH_3)$_2$), 0.89 (3H, d, ^3J = 6.8 Hz, CH(CH_3)$_2$).
m/z (ESMS$^+$) 172.1 $[M + H]^+$ ($C_9H_{22}N_3$ requires 172.2).

Macrocycle 5-*R* was prepared in analogous manner to **4**, using **S4b-*R*** (300 mg, 0.47 mmol). The organic layer was concentrated to give a yellow oil (56 mg, ’69 %’) containing the *title compound* contaminated by small quantities of tosylate containing species. The material was taken on with no adjustments for the contaminants being made. NMR and MS data were in agreement with the enantiomer **5-*S***.

Macrocycle 6-*S*

Ammonia (30 mL) was condensed into a solution of **S4c-*S*** (0.35 g, 0.51 mmol) dissolved in dry THF (15 mL) and dry EtOH (1 mL) whilst stirring under $Ar_{(g)}$ at -78 °C. Na metal (0.58 g, excess) was added in small portions to the solution and a strong blue colour developed. The solution was allowed to warm to RT overnight, during which time the solution turned colourless and $NH_{3(g)}$ evaporated through an anti-suck back apparatus. H_2O (15 mL) was added to the solution (CARE! Metallic Na may be present in excess) and all solvent removed. The residue was dissolved in $HCl_{(aq)}$ (2 M, 15 mL) and washed with Et_2O (2 × 15 mL). The aqueous layer was concentrated, and the residue dissolved in $KOH_{(aq)}$ (6 M, 15 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The organic layer was concentrated to give a yellow oil (0.10 g, '91 %') containing the *title compound* contaminated by unidentified species. The material was taken on with no adjustments for the contaminants being made.

δ_H ($CDCl_3$) 7.09-7.25 (5H, m, Ar*H*), 2.86-2.96 (1H, m, C*H*), 2.50-2.81 (10H, br m, ring CH_2), 2.37-2.47 (2H, m, CH_2).

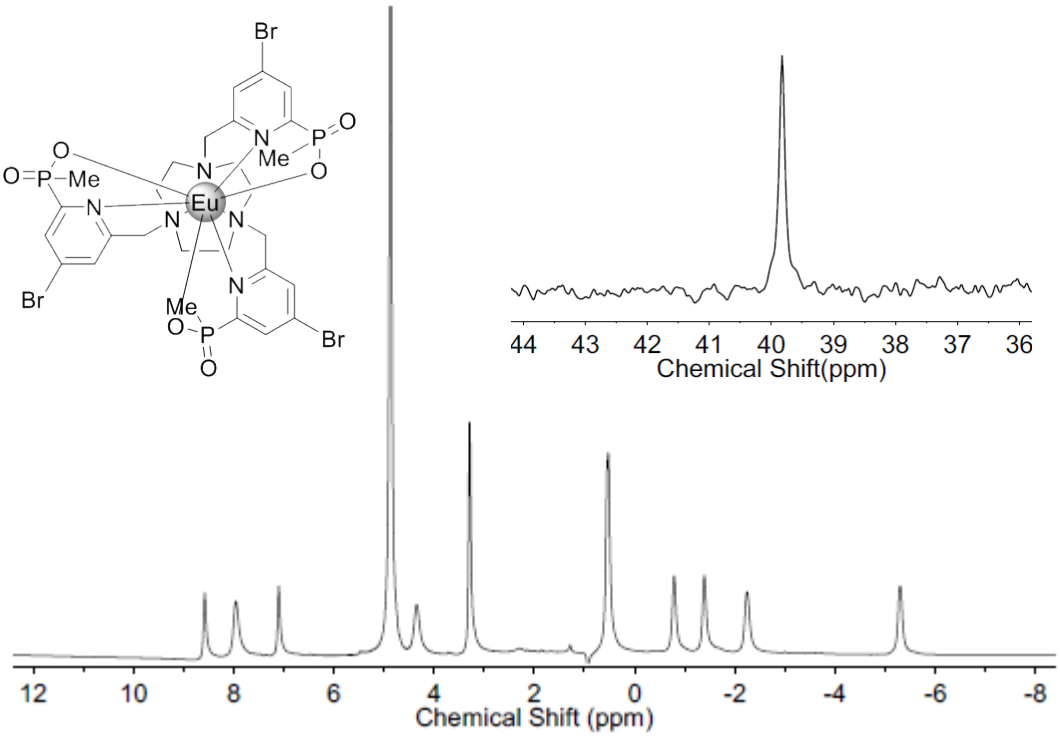
m/z ($HRMS^+$) 220.1811 $[M + H]^+$ ($C_{13}H_{22}N_3$ requires 220.1814).

Macrocycle 6-*R* was prepared in analogous manner to **6-*S***, using **S4c-*R*** (0.66 g, 1.00 mmol). The organic layer was concentrated to give a yellow oil (0.20 g, '96 %') containing the *title compound* contaminated by unidentified species. The material was taken on with no adjustments for the contaminants being made. NMR and MS data were in agreement with the enantiomer **6-*S***.

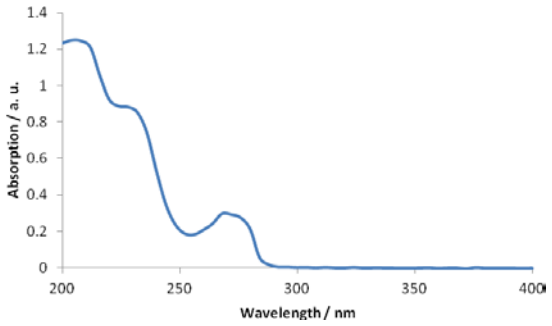
Spectral characterisation of complexes

[EuL^3]

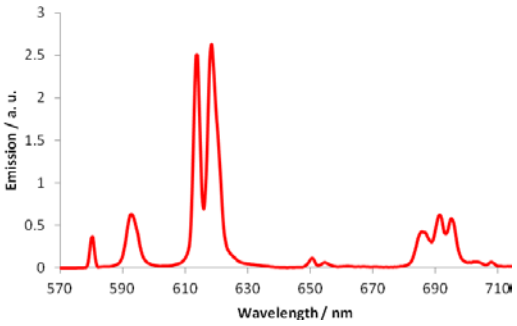
^{1}H and ^{31}P NMR (9.4 T, CD_3OD, 295 K)



Absorption (H_2O, 295 K)



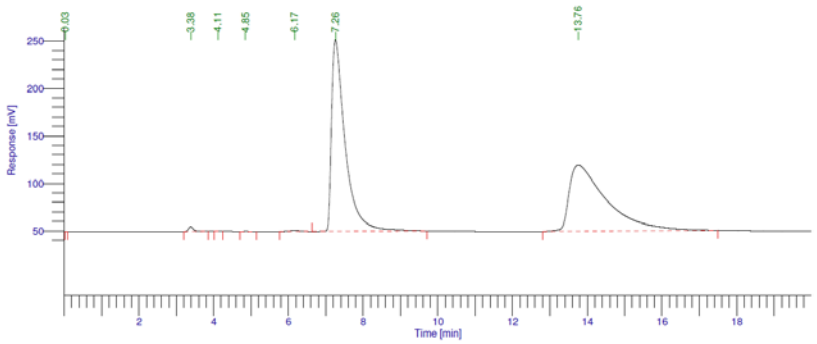
Emission (λ_{exc} = 268 nm, H_2O, 295 K)



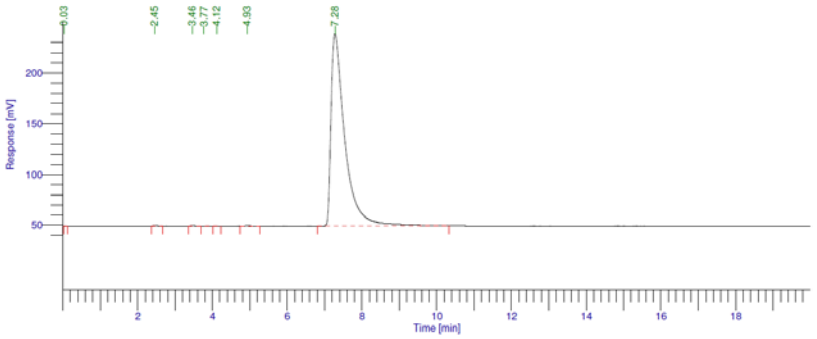
[EuL^3] (cont.)

Chiral HPLC (CHIRALPAK-ID 4.0 mm × 250 mm, MeOH, 1 mL/min, λ = 268 nm, 290 K)

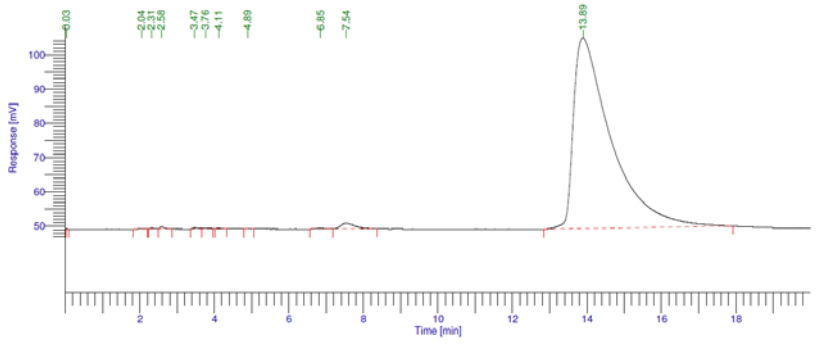
Racemate



Enantiomer 1



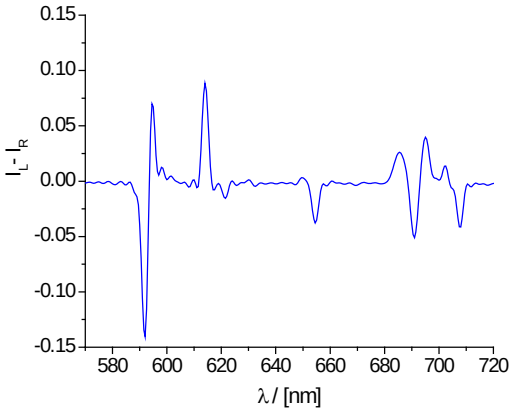
Enantiomer 2

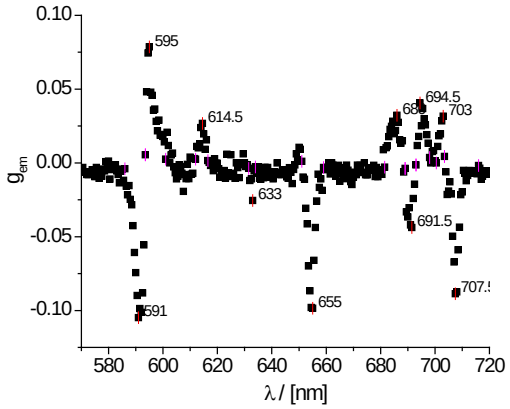


[EuL^3] (cont.)

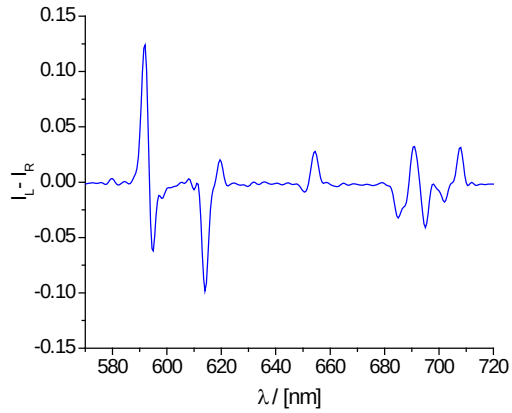
CPL (λ_{exc} = 268 nm, H_2O, 295 K)

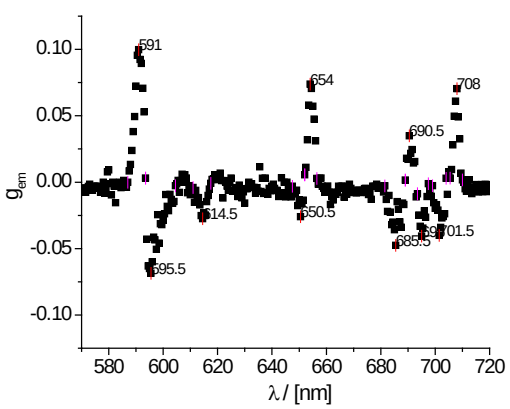
Enantiomer 1: *SSS*-Λ-($\lambda\lambda\lambda$)





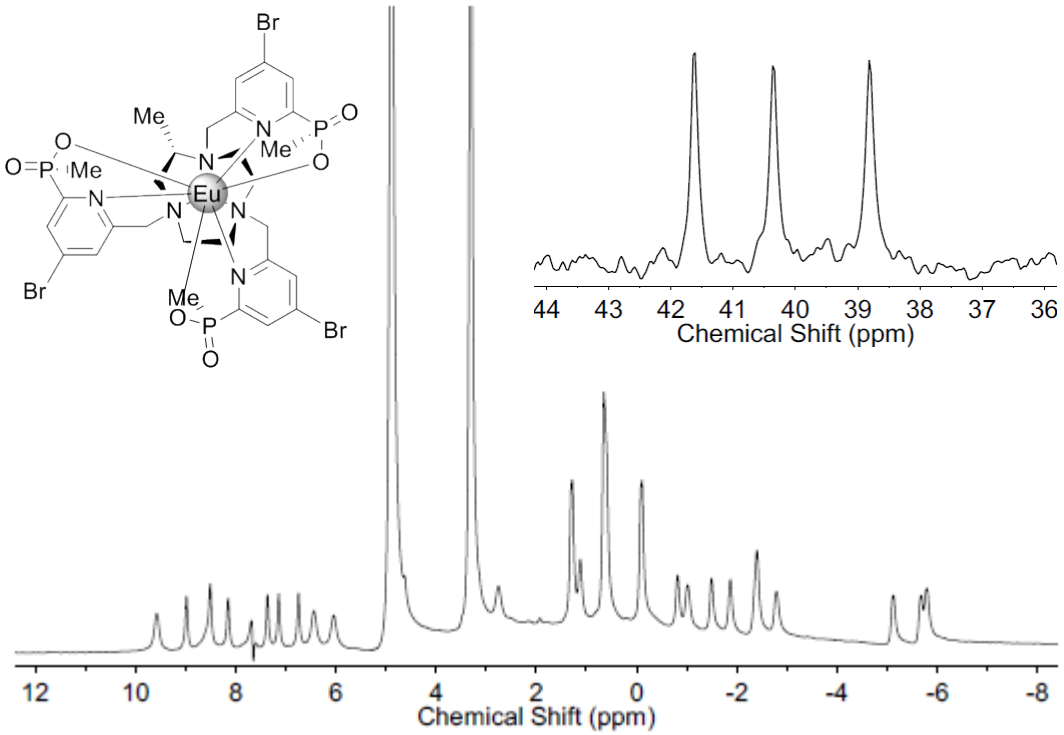
Enantiomer 2: *RRR*-Λ-($\delta\delta\delta$)



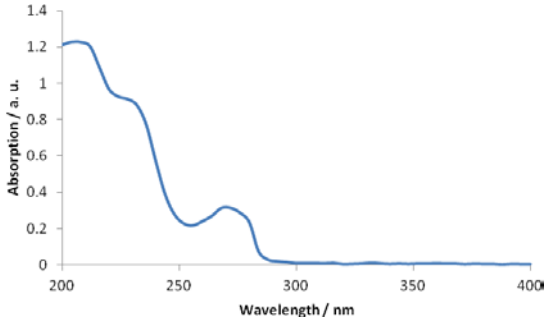


[EuL^4]

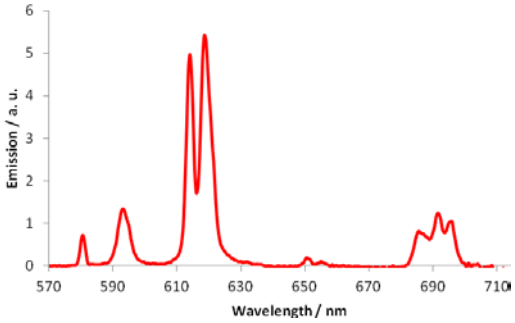
^{1}H and ^{31}P NMR (9.4 T, CD_3OD, 295 K)



Absorption (H_2O, 295 K)



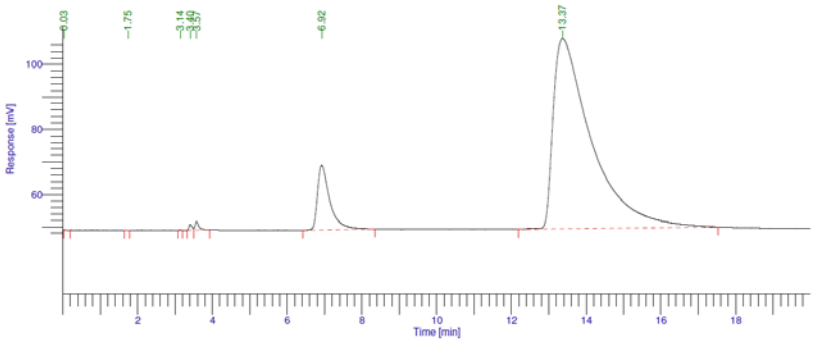
Emission (λ_{exc} = 268 nm, H_2O, 295 K)



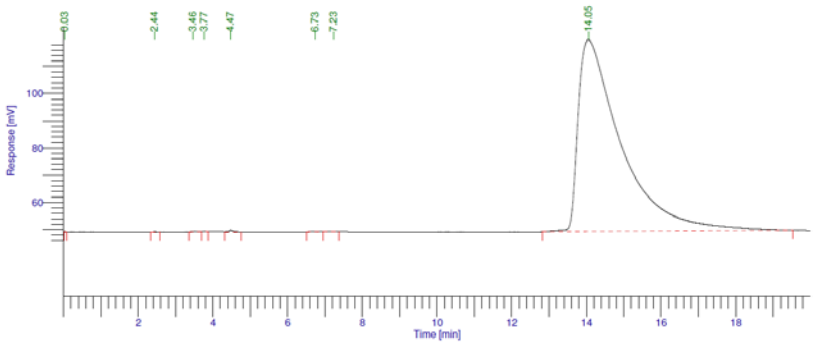
[EuL^4] (cont.)

Chiral HPLC (CHIRALPAK-ID 4.0 mm × 250 mm, MeOH, 1 mL/min, λ = 268 nm, 290 K)

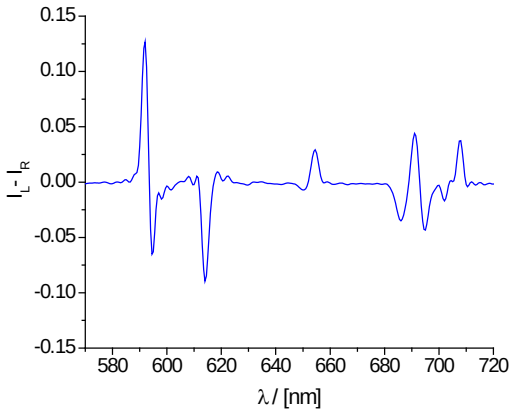
Pre-purification

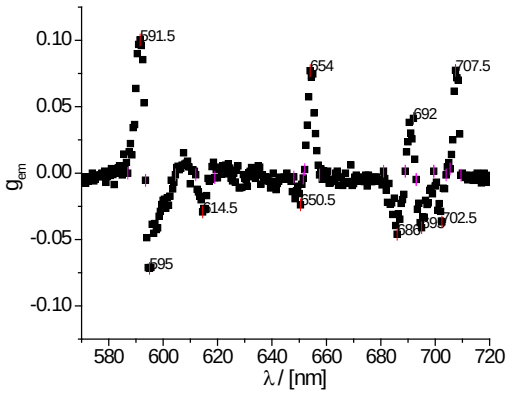


Pure



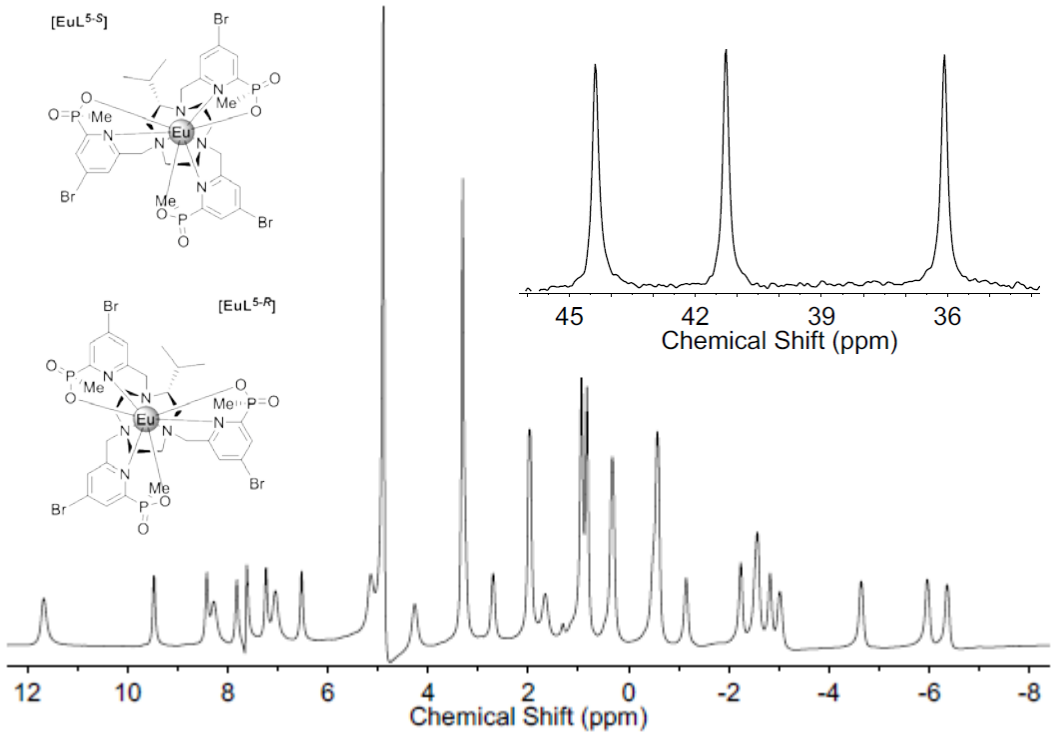
CPL (λ_{exc} = 268 nm, H_2O, 295 K)



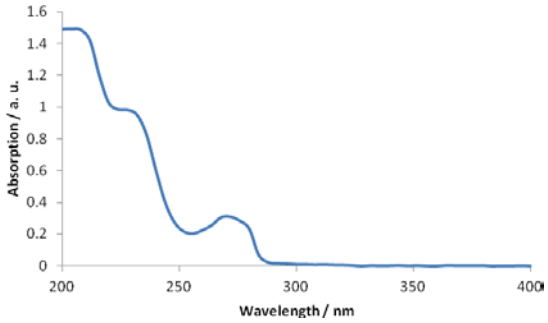


[EuL$^{5\text{-}S}$] & [EuL$^{5\text{-}R}$]

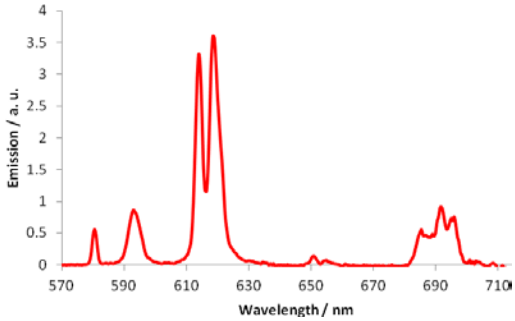
^{1}H and ^{31}P NMR (9.4 T, CD_3OD, 295 K)



Absorption (H_2O, 295 K)



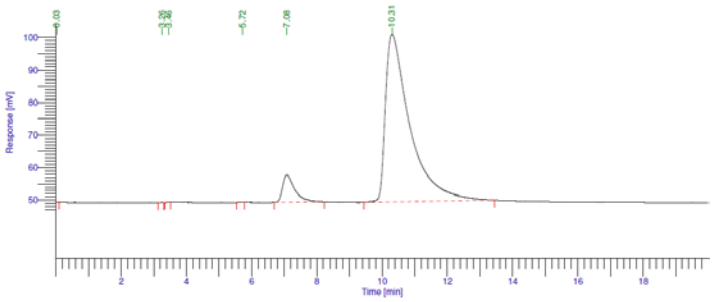
Emission (λ_{exc} = 268 nm, H_2O, 295 K)



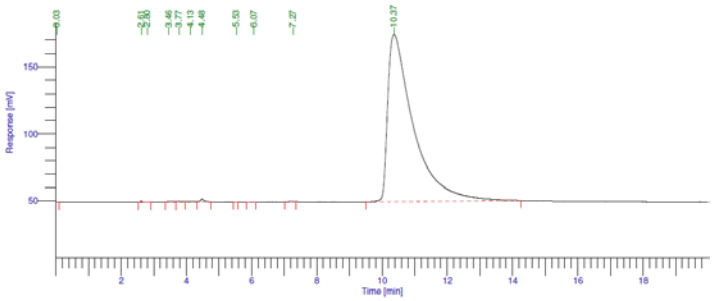
[EuL$^{5\text{-}S}$] & [EuL$^{5\text{-}R}$] (cont.)

Chiral HPLC (CHIRALPAK-ID 4.0 mm × 250 mm, MeOH, 1 mL/min, λ = 268 nm, 290 K)

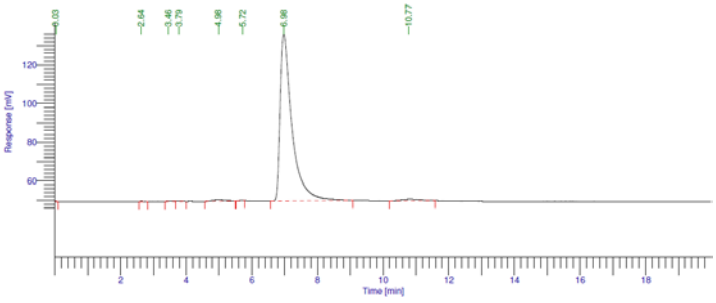
[EuL$^{5\text{-}S}$] pre-purification



[EuL$^{5\text{-}S}$] pure



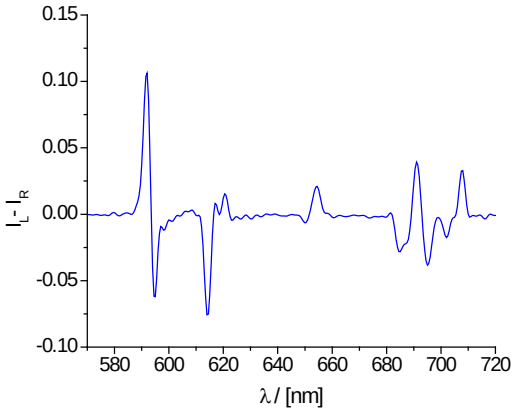
[EuL$^{5\text{-}R}$]

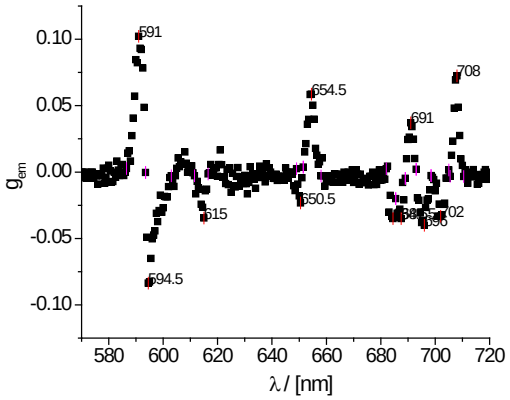


[EuL$^{5\text{-}S}$] & [EuL$^{5\text{-}R}$] (cont.)

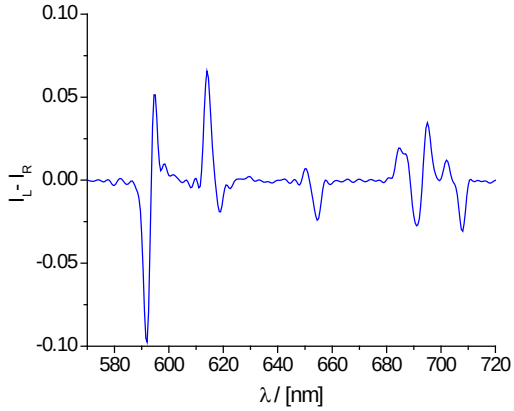
CPL (λ_{exc} = 268 nm, H_2O, 295 K)

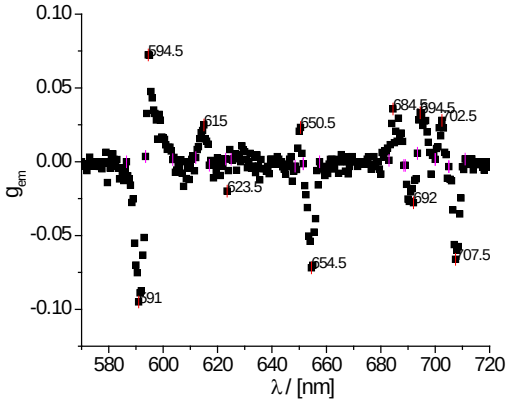
[EuL$^{5\text{-}S}$]





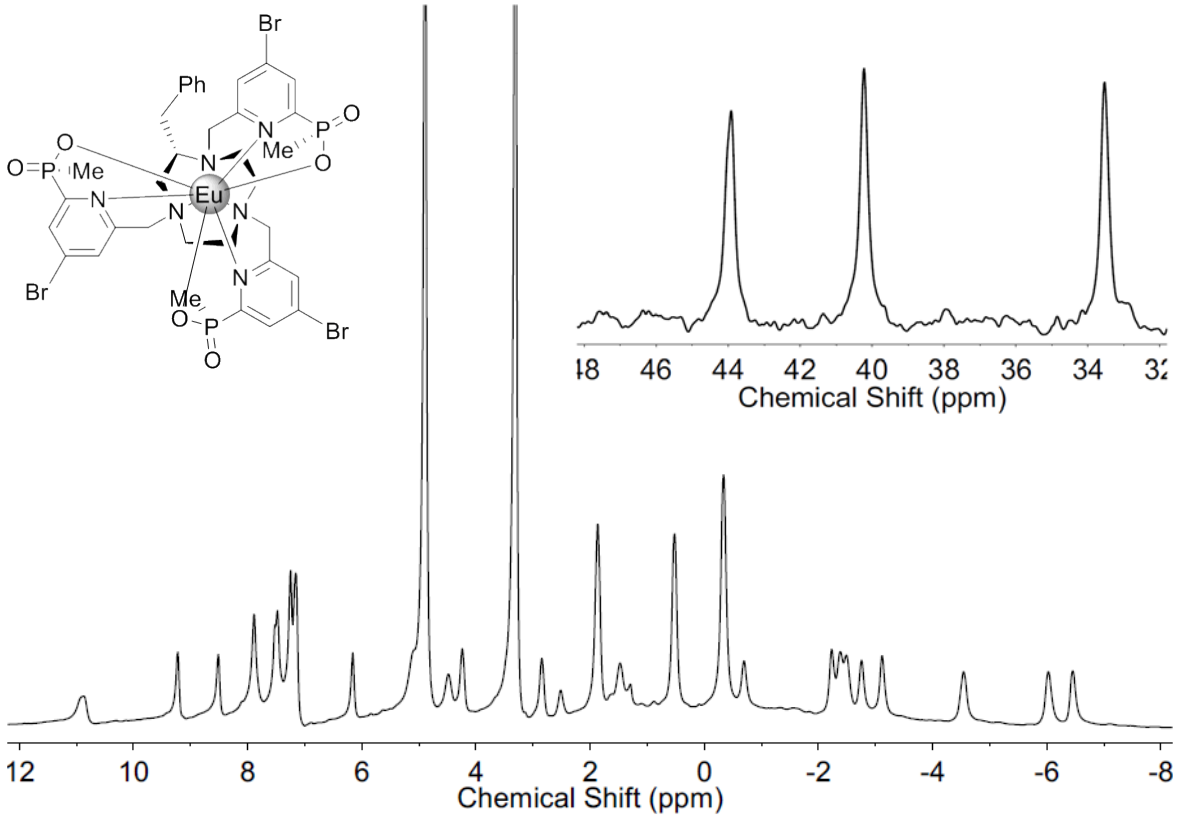
[EuL$^{5\text{-}R}$]



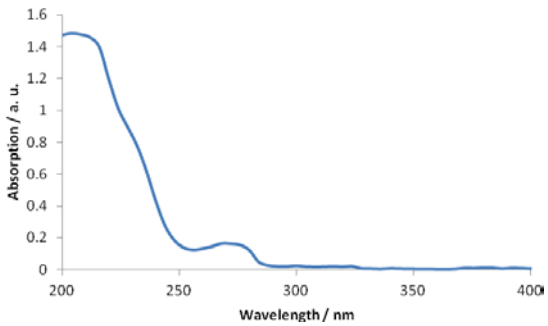


[EuL$^{6\text{-Br-}S}$]

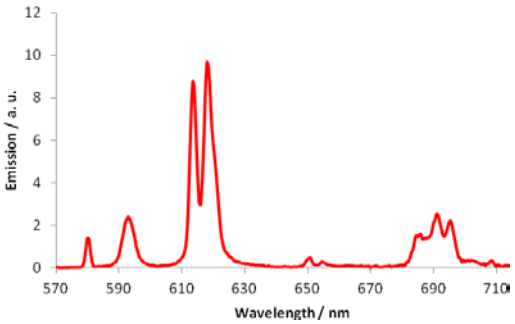
^{1}H and ^{31}P NMR (9.4 T, CD_3OD, 295 K)



Absorption (H_2O, 295 K)

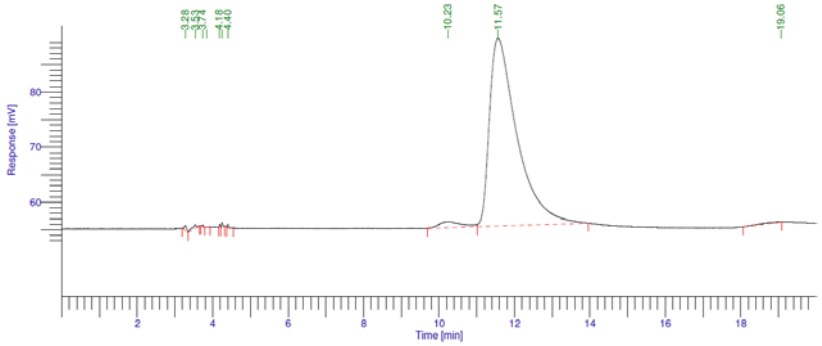


Emission (λ_{exc} = 268 nm, H_2O, 295 K)

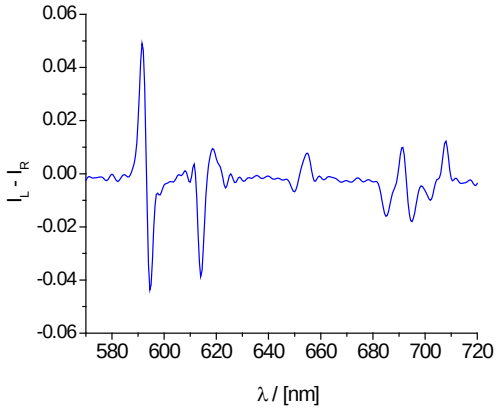


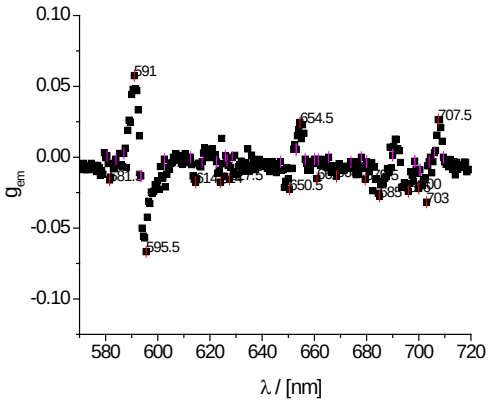
[EuL$^{6\text{-Br-}S}$] (cont.)

Chiral HPLC (CHIRALPAK-ID 4.0 mm × 250 mm, MeOH, 1 mL/min, λ = 268 nm, 290 K)



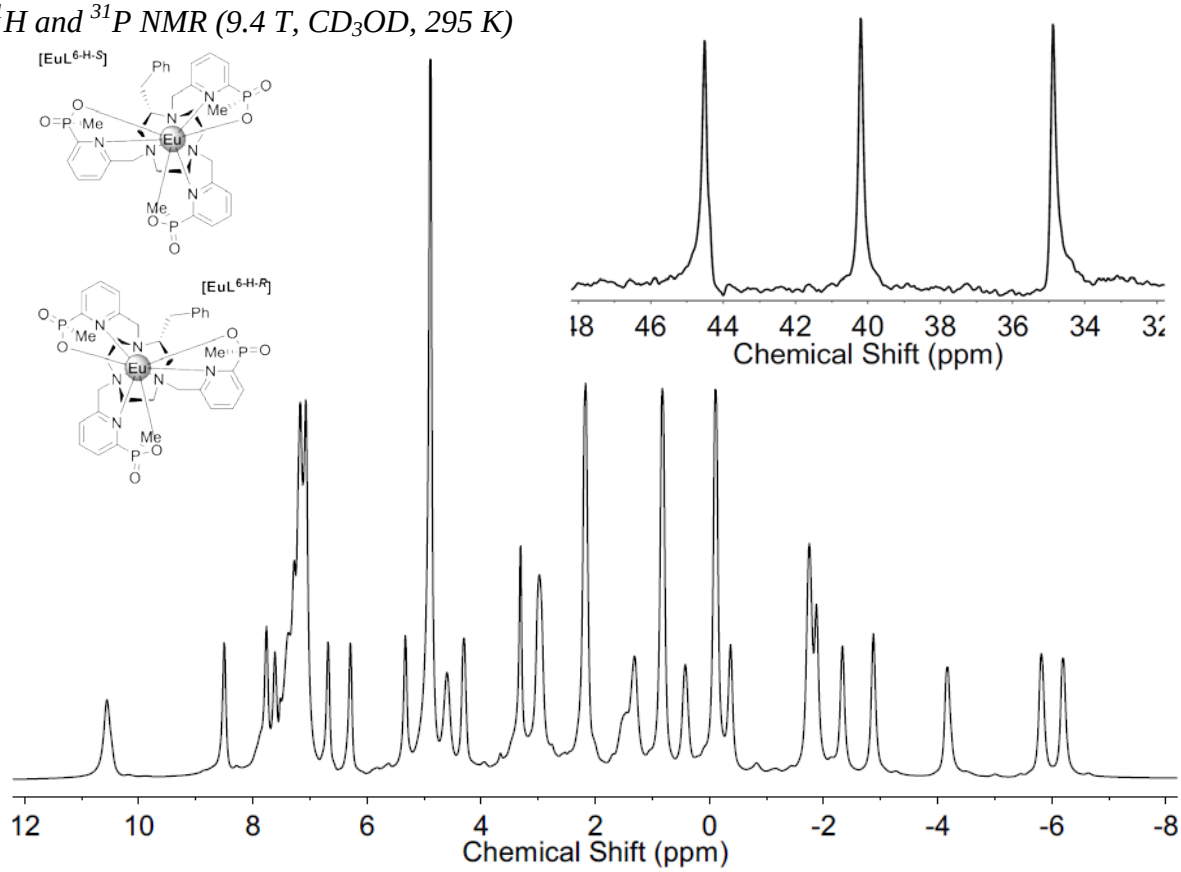
CPL (λ_{exc} = 268 nm, D_2O, 295 K)



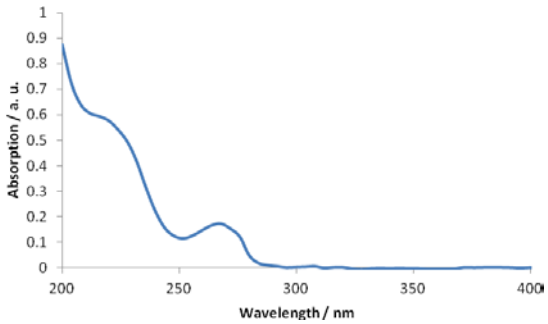


[EuL$^{6\text{-H-}S}$] & [EuL$^{6\text{-H-}R}$]

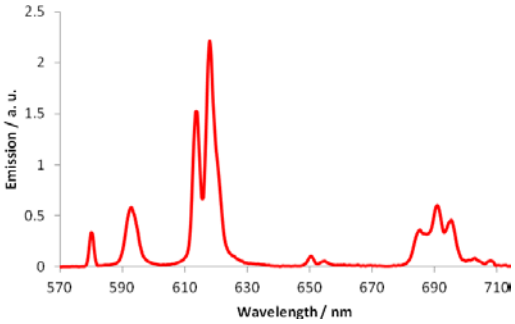
^{1}H and ^{31}P NMR (9.4 T, CD_3OD, 295 K)



Absorption (H_2O, 295 K)



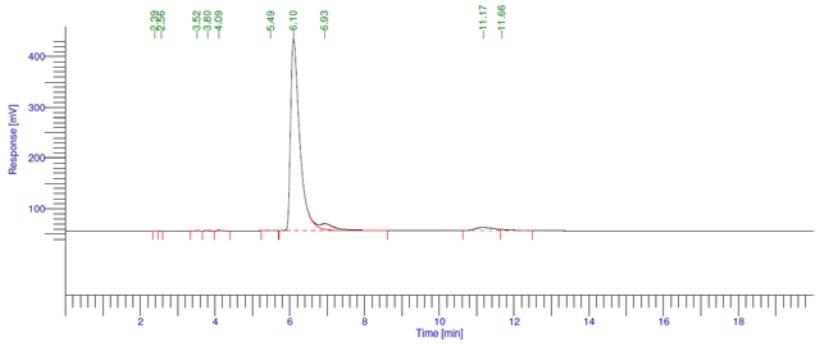
Emission (λ_{exc} = 268 nm, H_2O, 295 K)



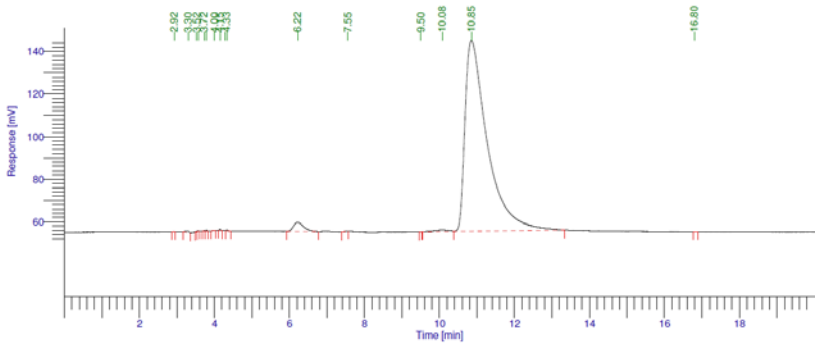
[EuL$^{6\text{-H-}S}$] & [EuL$^{6\text{-H-}R}$] (cont.)

Chiral HPLC (CHIRALPAK-ID 4.0 mm × 250 mm, MeOH, 1 mL/min, λ = 268 nm, 290 K)

[EuL$^{6\text{-H-}S}$]



[EuL$^{6\text{-H-}R}$]

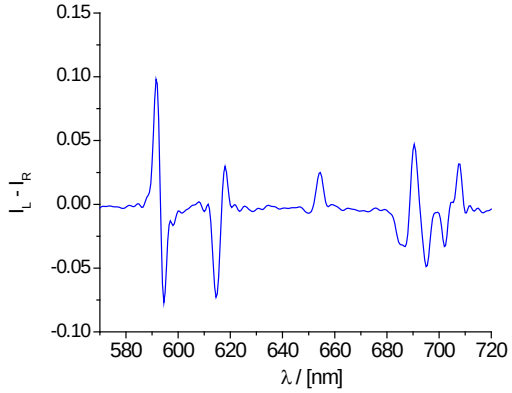


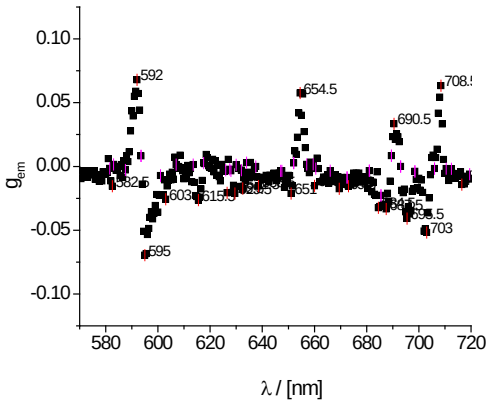
The order of elution of enantiomers from the chiral column (ChiralPak ID) was reversed in the case of the protic enantiomers **[EuL$^{6\text{-H-}S}$]/[EuL$^{6\text{-H-}R}$]**, in comparison to the bromo enantiomeric pairs, e.g. **[EuL$^{5\text{-}S}$]/[EuL$^{5\text{-}R}$]**.

[EuL$^{6\text{-H-}S}$] & [EuL$^{6\text{-H-}R}$] (cont.)

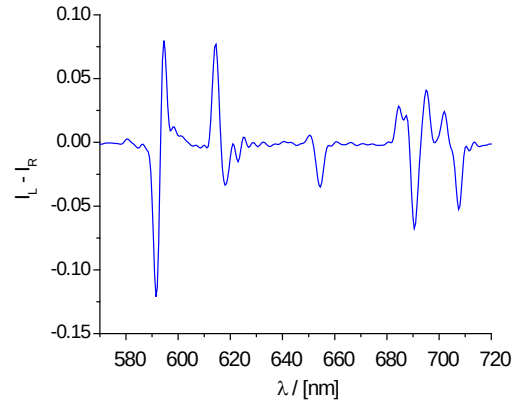
CPL (λ_{exc} = 268 nm, D_2O, 295 K)

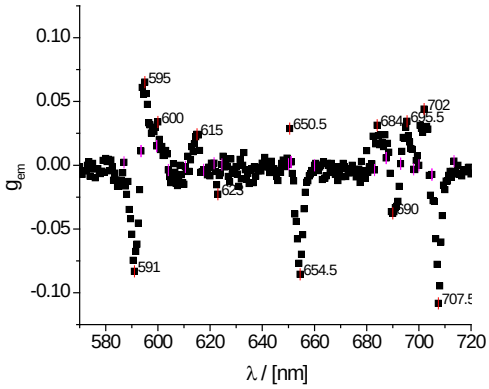
[EuL$^{6\text{-H-}S}$]





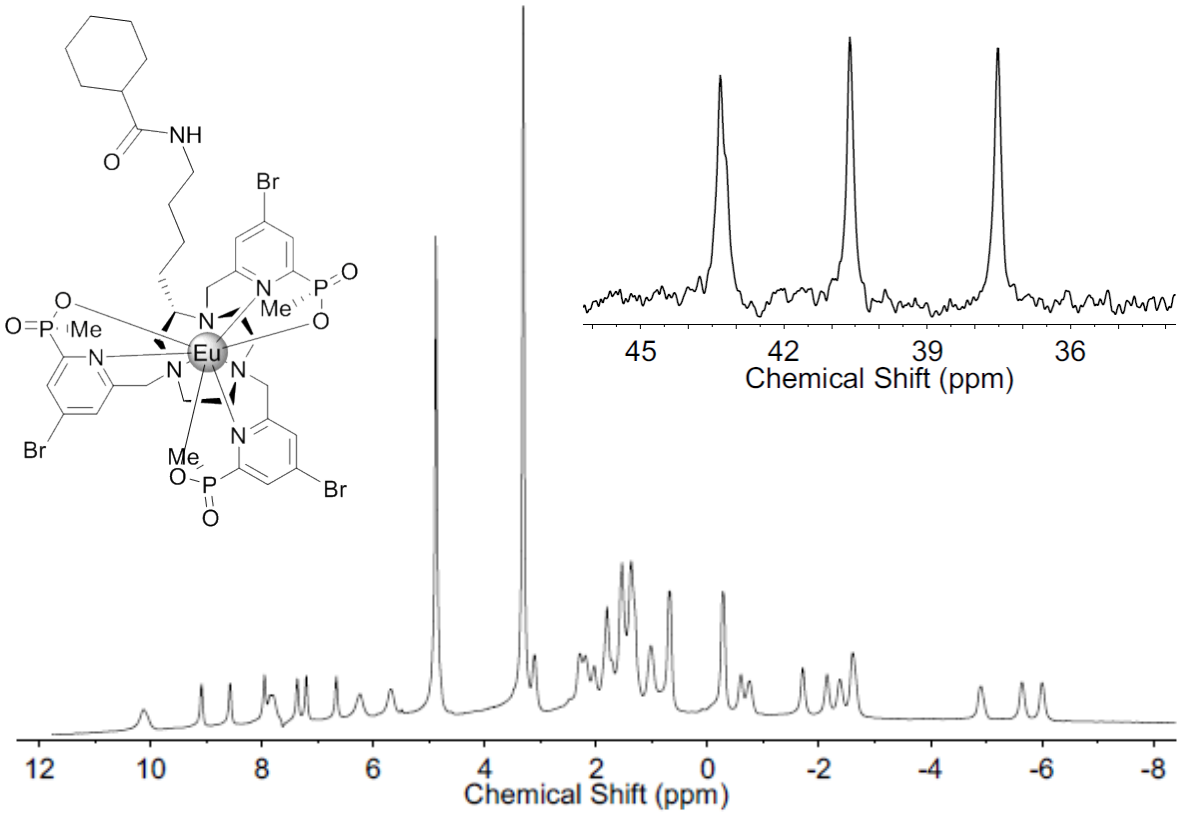
[EuL$^{6\text{-H-}R}$]



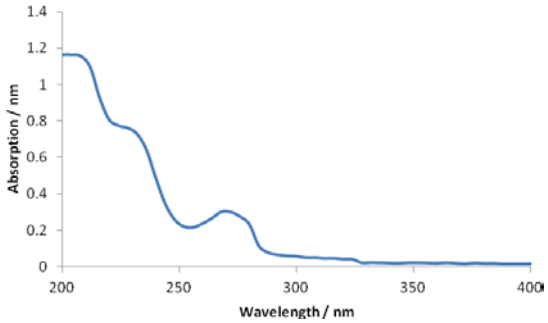


[EuL^7]

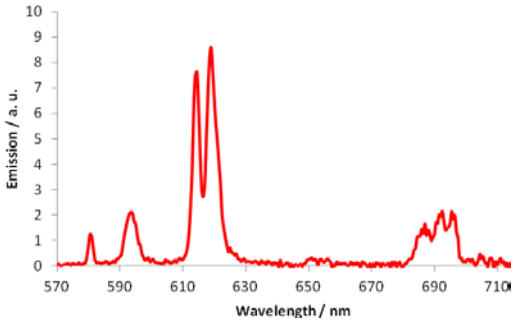
^{1}H and ^{31}P NMR (9.4 T, CD_3OD, 295 K)



Absorption (H_2O, 295 K)

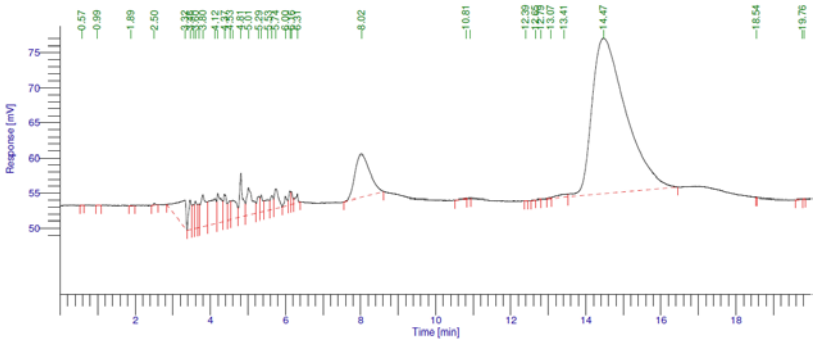


Emission (λ_{exc} = 268 nm, H_2O, 295 K)

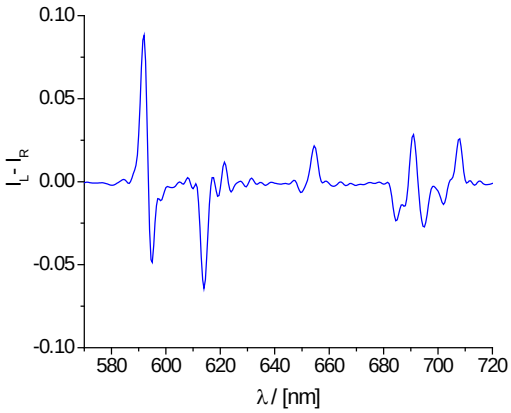


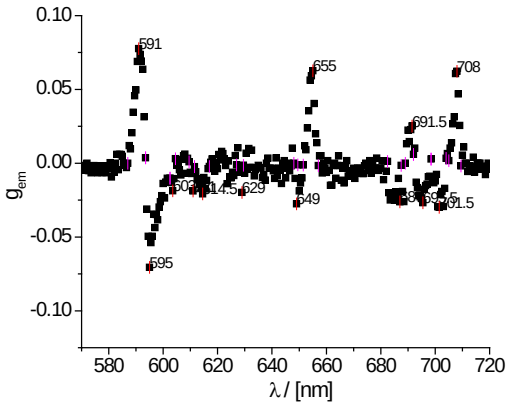
[EuL^7] (cont.)

Chiral HPLC (CHIRALPAK-ID 4.0 mm × 250 mm, MeOH, 1 mL/min, λ = 268 nm, 290 K)



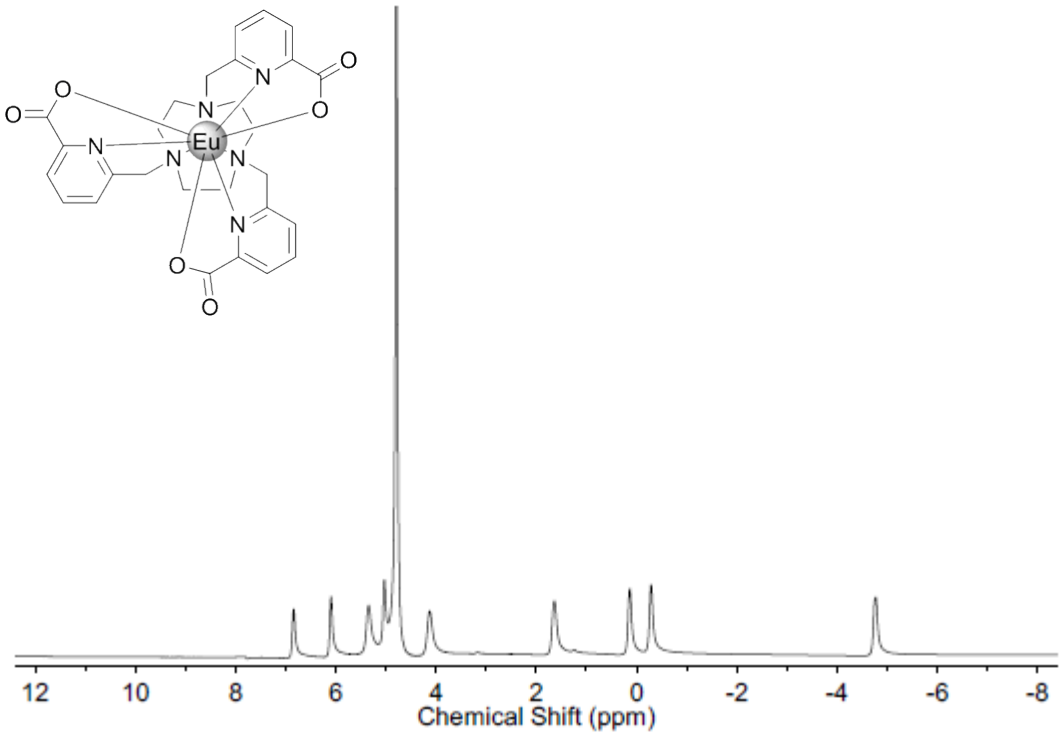
CPL (λ_{exc} = 268 nm, H_2O, 295 K)



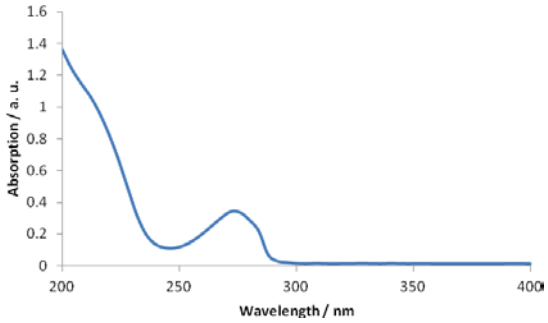


[EuL^{8}]

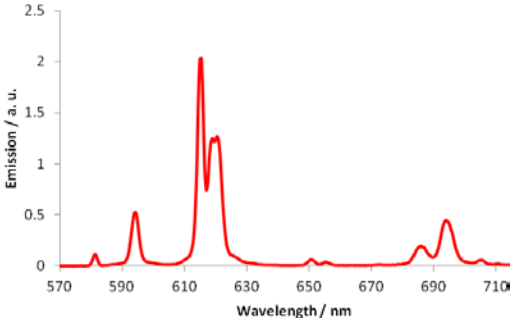
^{1}H NMR (9.4 T, D_2O, 295 K)



Absorption (H_2O, 295 K)



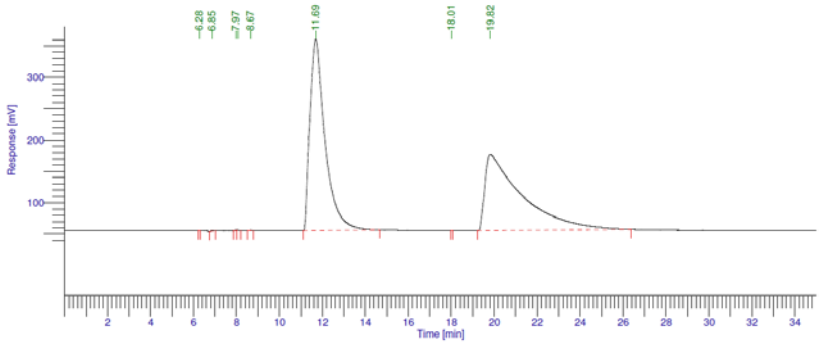
Emission (λ_{exc} = 272 nm, H_2O, 295 K)



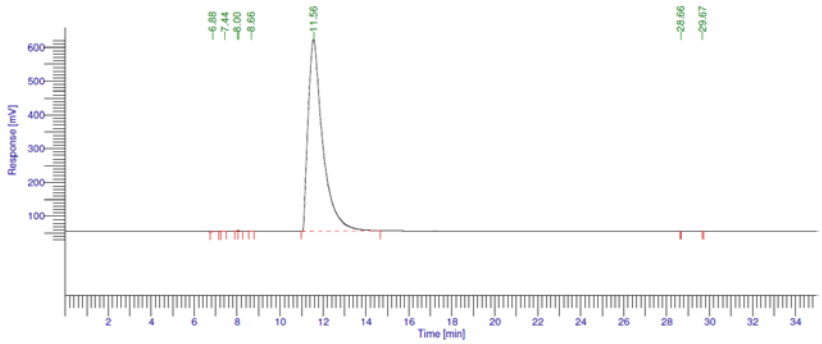
[EuL^8] (cont.)

Chiral HPLC (CHIRALPAK-IC 4.0 mm × 250 mm, MeOH, 0.5 mL/min, λ = 274 nm, 290 K)

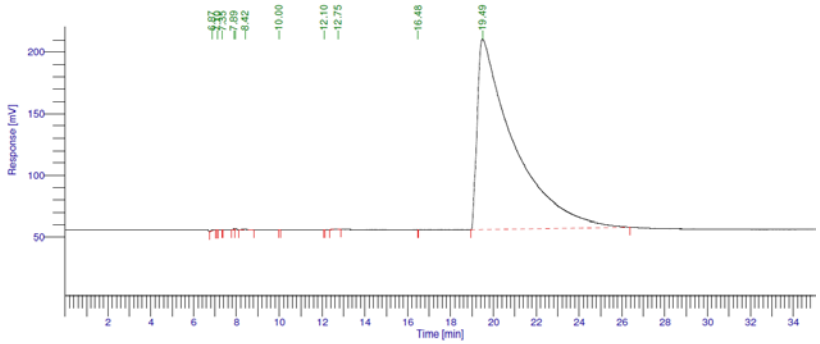
Racemate



Enantiomer 1



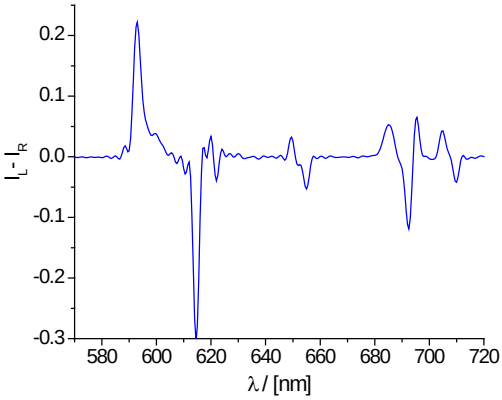
Enantiomer 2

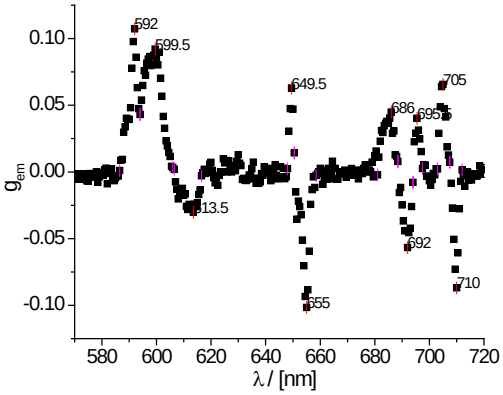


[EuL^8] (cont.)

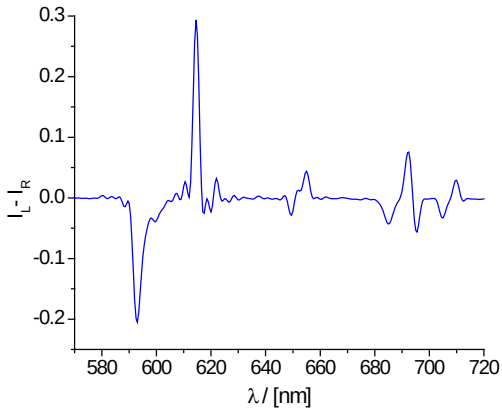
CPL (λ_{exc} = 272 nm, H_2O, 295 K)

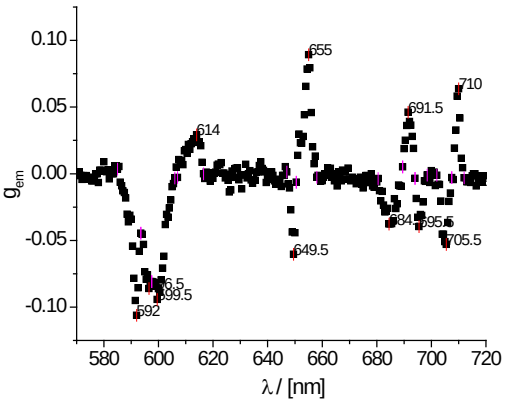
Enantiomer 1





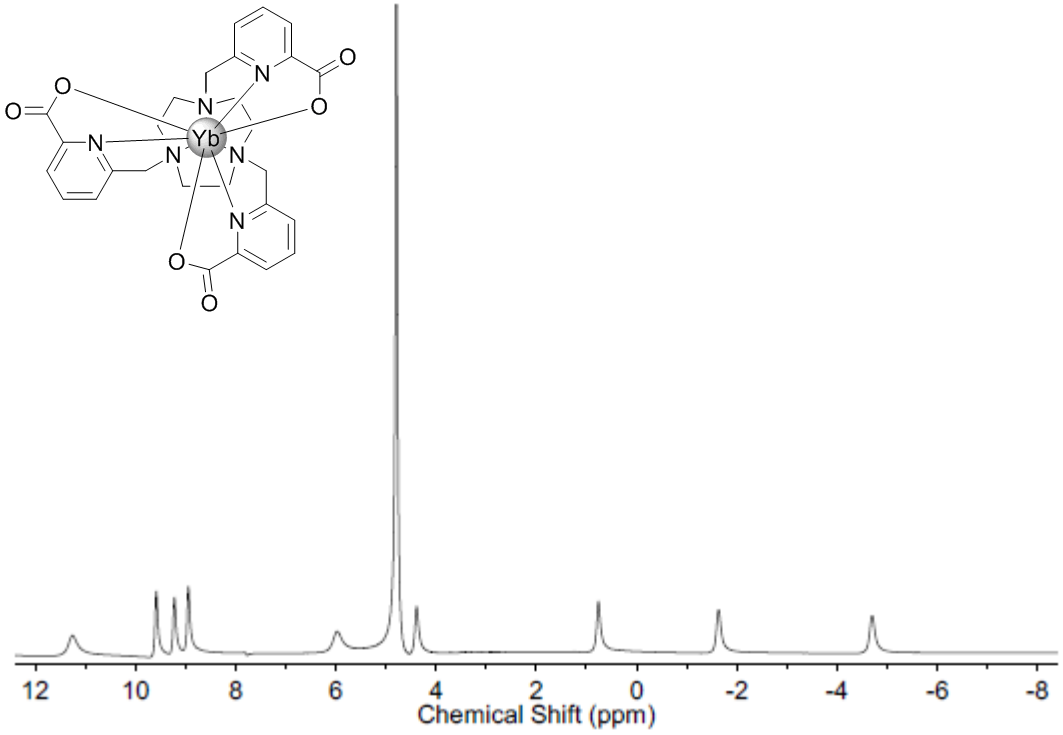
Enantiomer 2



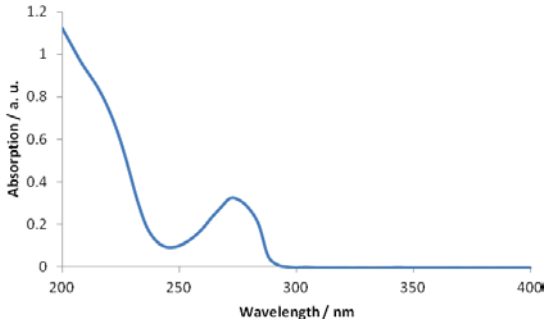


[YbL^{8}] [b]

^{1}H NMR (9.4 T, D_2O, 295 K)



Absorption (H_2O, 295 K)

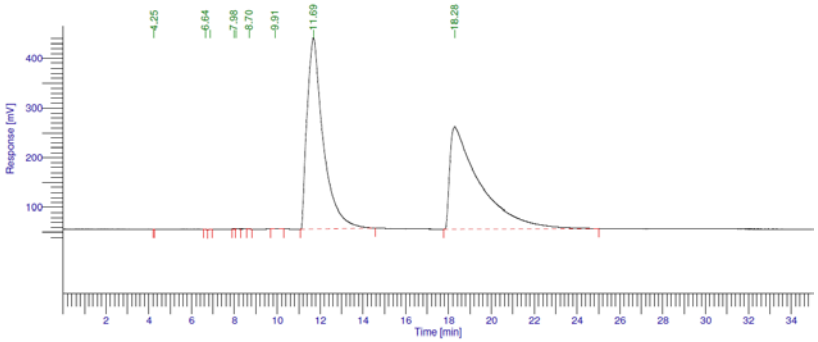


[b] The sample of **[YbL^{8}]** was prepared in an analogous fashion to [**EuL^{8}**]. δ_H (400 MHz, D_2O) 11.25, 9.58, 9.22, 8.94, 5.97, 4.39, 0.76, -1.64, -4.70. *m/z* (HRMS^{+}) 703.1453 $[M + H]^{+}$ ($C_{27}H_{28}N_6O_6Yb$ requires 703.1434). R_f = 0.33 (silica, CH_2Cl_2 : CH_3OH : NH_3 75:25:3). The racemate was resolved using resolved using a semi-prep CHIRAL-PAK IC column Chiral HPLC (ChiralPAK-IC 4.0 mm × 250 mm, CH_3OH, 0.5 mL/min, 290 K): R_t = 11.7 min & 18.2 min.

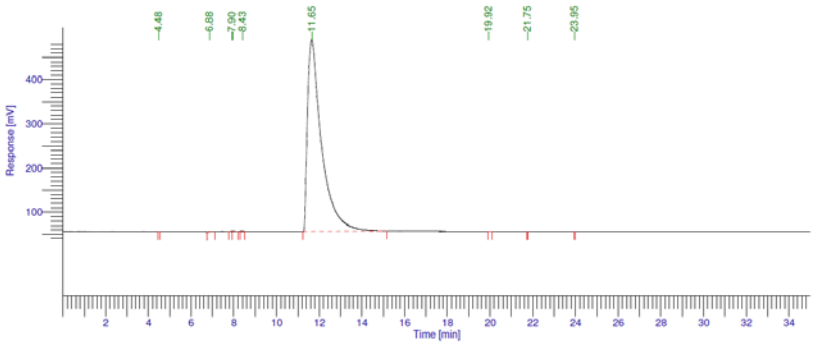
[YbL^8] (cont.)

Chiral HPLC (CHIRALPAK-IC 4.0 mm × 250 mm, MeOH, 0.5 mL/min, λ = 274 nm, 290 K)

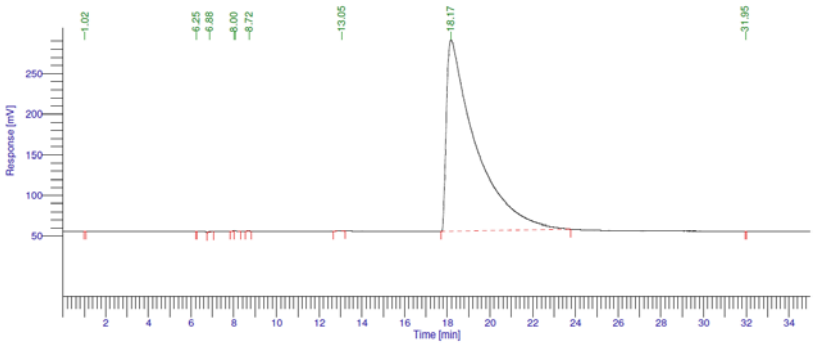
Racemate



Enantiomer 1

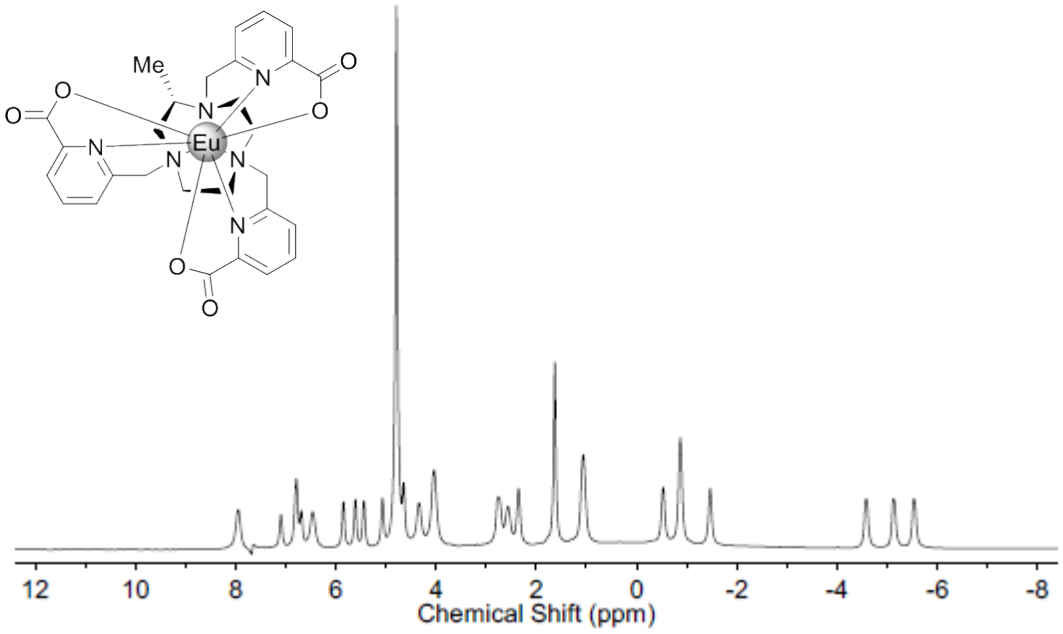


Enantiomer 2

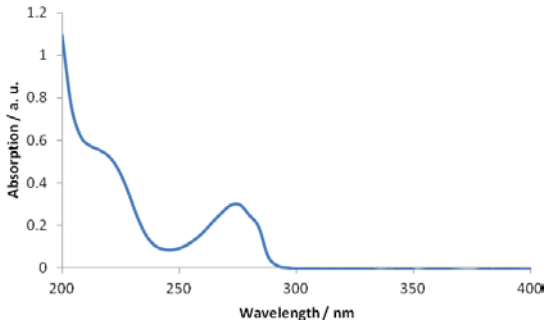


[EuL^9]

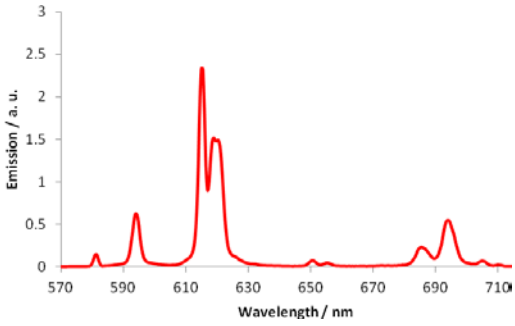
^{1}H NMR (9.4 T, D_2O, 295 K)



Absorption (H_2O, 295 K)



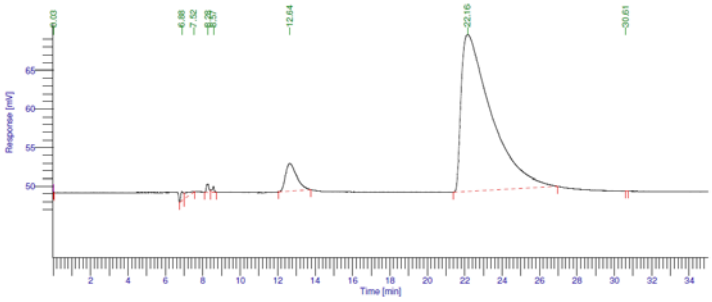
Emission (λ_{exc} = 272 nm, H_2O, 295 K)



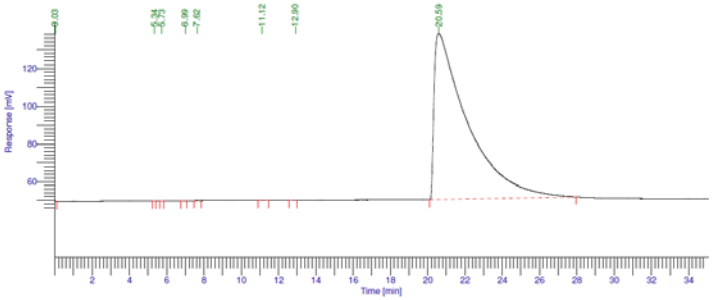
[EuL^9] (cont.)

Chiral HPLC (CHIRALPAK-IC 4.0 mm × 250 mm, MeOH, 0.5 mL/min, λ = 274 nm, 290 K)

Pre-purification



Purified sample



CPL (λ_{exc} = 272 nm, H_2O, 295 K)

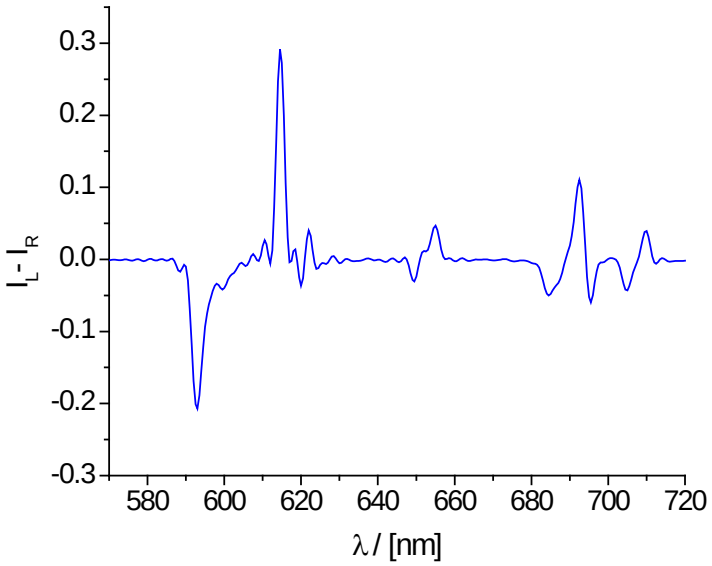


Diagram of CPL instrumentation

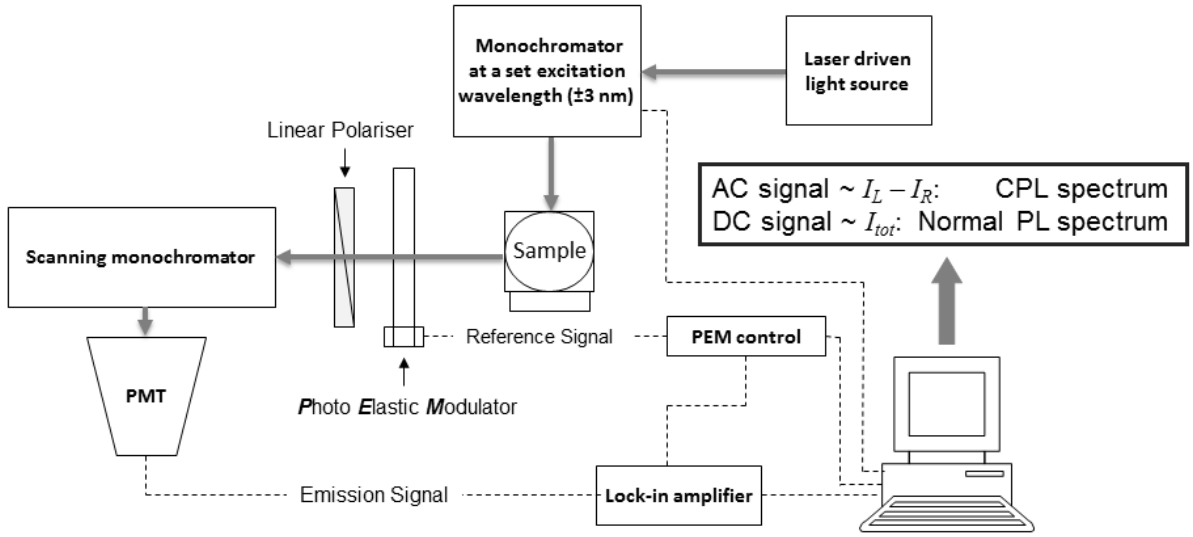


Figure S1: Schematic diagram of CPL instrumentation.

Racemisation studies

Samples of enantiopure (or enantio-enriched) **[EuL^3]**, **[EuL^8]** and **[YbL^8]** in H_2O were heated to 60 °C. Periodically the samples were analysed by chiral HPLC to determine the rate of racemisation. The natural logarithm of the proportion of the starting enantiomer was plotted against time, with the fitted trend line revealing half-lives for the complexes of: **[EuL^3]** 185 (± 20) h, **[EuL^8]** 240 (± 35) h and **[YbL^8]** 680 (± 80) h (see below).

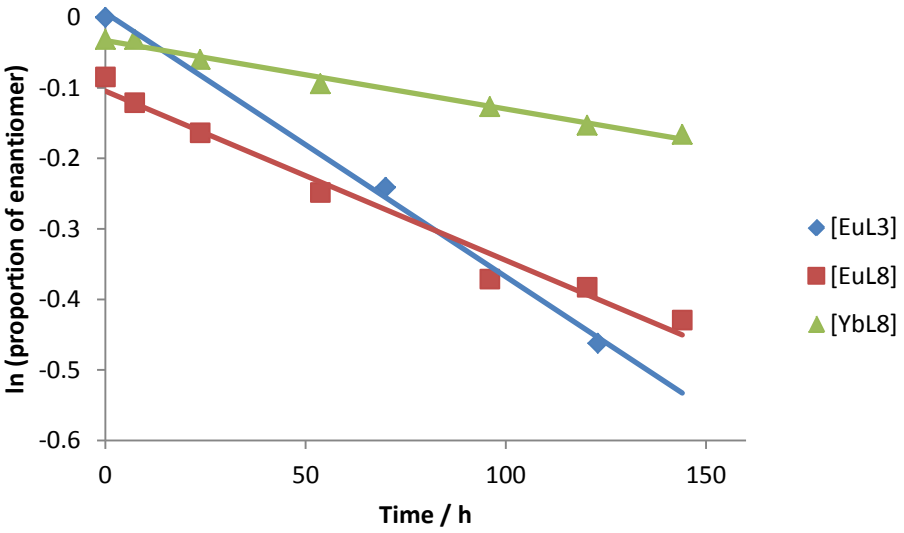


*Figure S2: Plot of ln(proportion of enantiomer) vs time for samples of **[EuL^3]**, **[EuL^8]** and **[YbL^8]** heated to 333 K. Solvent: H_2O.*

Further details on Reference 16 (*caveat:* origins of the reduction in enantiopurity)

In the cases of **[EuL^{4}]**, **[EuL$^{5\text{-}S}$]** and **[EuL^{9}]**, significant loss in enantiopurity was observed for some samples by chiral HPLC, which led to the formation of both enantiomeric complexes. This was confirmed by comparison of the CPL spectra of the two observed species in the cases of **[EuL^{4}]** and **[EuL^{9}]**, and the retention time of the minor isomer of **[EuL$^{5\text{-}S}$]** with that of (enantiopure) **[EuL$^{5\text{-}R}$]**.

The origin of this racemisation was identified by adding the chiral solvating agent *R-O*-acetyl mandelic acid (1.2 eq) to samples of bis-amine, amide **S1a** and **S1b** dissolved in $CDCl_3$.[c] The amide peak shifted downfield and split; with the integral ratios in agreement with the ratio of complex enantiomers observed in the chiral HPLC. Thus racemisation may occur in the first step of the ligand synthesis, but it can be suppressed by lowering the temperature of the reaction between the amino-acid ester and ethylenediamine and the subsequent distillation.

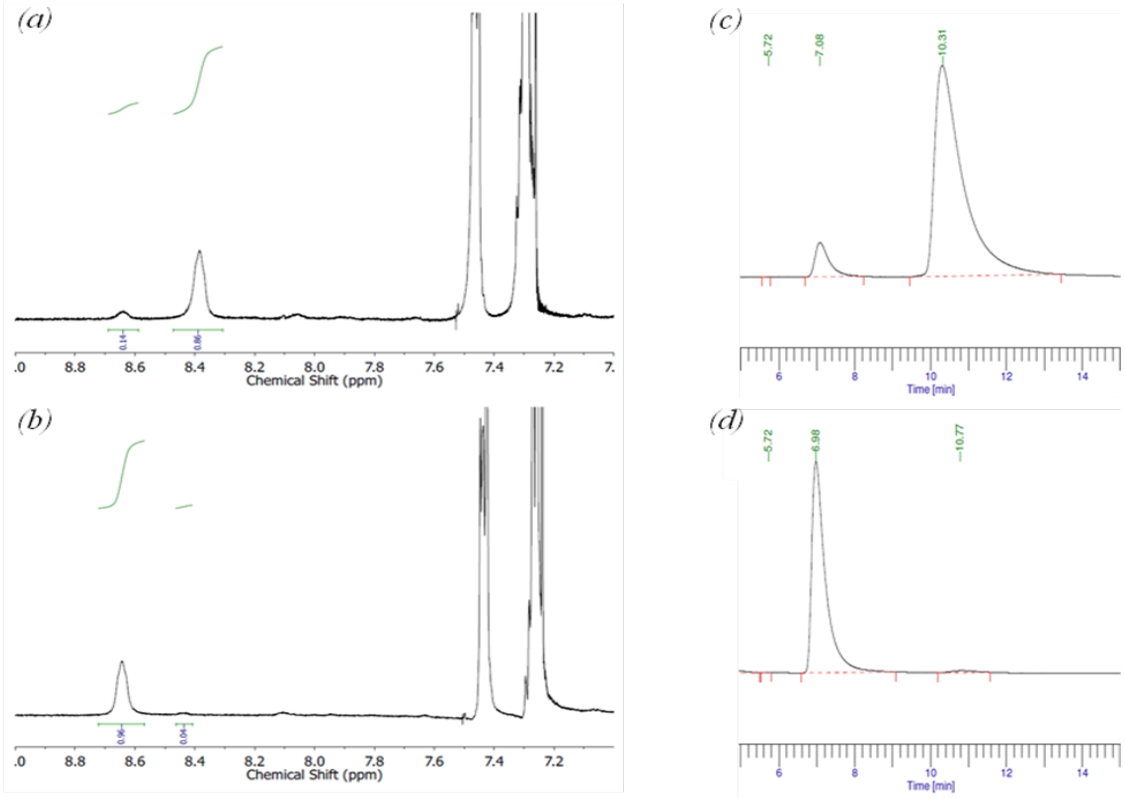


*Figure S3: Amide region of ^{1}H NMR spectra ($CDCl_3$) of R-O-acetyl mandelic acid (1.2 eq) added to (a) **S1b-S** and (b) **S1b-R**. (c) & (d) are the chiral HPLC traces of **[EuL$^{5\text{-}S}$]** and **[EuL$^{5\text{-}R}$]** derived from these samples.*

[c] D. Parker and R. J. Taylor, *Tetrahedron*, 1987, **43**, 5451.