Supplementary Information: Using the Ugi multicomponent condensation reaction to prepare families of chromophore appended azamacrocycles and their complexes

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Synthesis of ligands and complexes

General:

NMR spectroscopy

^{1}H (300.13 MHz) and ^{13}C (75.47 MHz) NMR spectra of the ligands were acquired on Bruker AV 300 and AC 300 spectrometers respectively; the ^{13}C NMR were run using a **pendant** pulse sequence. ^{1}H (500.0 MHz) NMR spectra of the lanthanide complexes were acquired on a Varian Inova NMR spectrometer. VT NMR were acquired on a Bruker AV 500 spectrometer. Multiplicities of the spectroscopic data are recorded as follows: s = singlet; d = doublet; dd = double doublet; t = triplet; q = quartet; m = multiplet; br = broad. Coupling constants are given in Hz.

Mass spectrometry

Electron impact (EI) mass spectra were recorded on a Zabspec spectrometer with an Opus data system. Electrospray (ES) spectra were measured on a Micromass LCT spectrometer using a methanol mobile phase. High Resolution (HRMS) ES spectra were obtained using a suitable lockmass on the same machine. Matrix-assisted laser desorption (MALDI) spectra were obtained using a Bruker Biflex IV spectrometer with Flex software and an appropriate matrix.

Chromatography

Thin layer chromatography (TLC) was carried out on pre-coated, glass-backed silica gel plates: (silica gel 60, F_{254}, thickness 0.25 mm, supplied by E.Merck A.G., Darmstadt, Germany) and visualisation was achieved using UV light (254 / 365 nm) or basic $KMnO_4$ solution. Column chromatography was performed using laboratory grade solvents on silica gel (43 – 63u) 60A supplied by Fluorochem, Glossop, UK) under gravity or with gentle pressure applied using hand bellows.

High performance liquid chromatography

All HPLC analyses were performed on a Dionex Summit HPLC system with Chromeleon software. Analytical HPLCs were run with the aid of a Summit P580 quarternary low pressure gradient pump with built in vacuum degasser. The detector was a Summit UVD 170s UV/VIS multi-channel detector with analytical flow cell. Similarly, for the preparative HPLC, a high pressure binary gradient pump was employed with the same multi-channel detector but with a preparative flow cell. Helium degassed HPLC grade solvents were used throughout.
Method A: Solvents: MeCN + 0.05% TFA and H_2O + 0.05% TFA. 0-100% MeCN + 0.05% TFA on a continuous gradient over 40 minutes.

Method B: Solvents: MeOH + 0.05% TFA and H_2O + 0.05% TFA. 0-100% MeOH +0.05% TFA on a continuous gradient over 40 minutes.

The wavelengths measured in both methods were 210, 230, 254 & 280 nm.
Retention times (t_r) as reported.

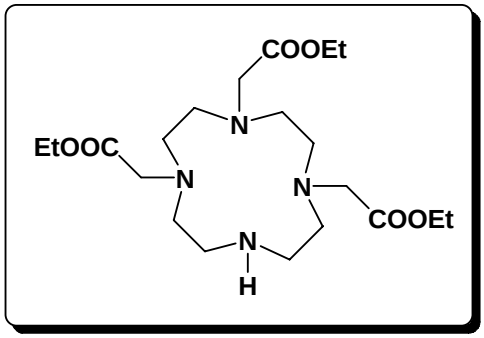
Melting Points

Melting points were determined in open ended glass capillaries using a Stuart Scientific SMP1 apparatus. Melting points are reported in degrees Celsius, °C.

Infra-red spectra
Infra-red spectra were recorded on a Perkin Elmer Paragon 1600 FTIR spectrophotometer and are reported in wavenumbers (ν) cm^{-1}.

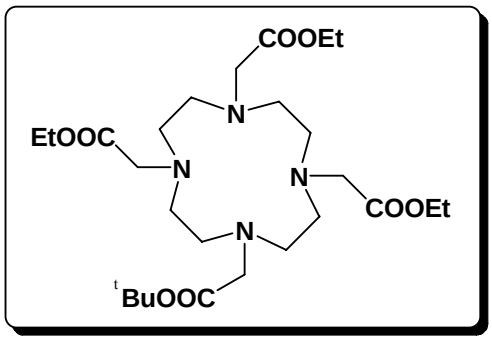
Reactions
All reactions were carried out under a nitrogen or argon atmosphere in flame- or oven-dried glassware unless otherwise stated. Evaporation and concentration under reduced pressure were carried out at pressures of 30-350 mmHg and residual solvent was removed under high vacuum (0.1-1 mmHg).

Preparation of 1,4,7-tris(ethoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane 2



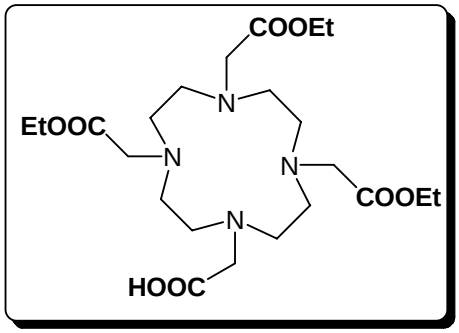
Ethyl bromoacetate (6.08 mL, 54.85 mmol, 3.5 eq.), dissolved in dry $CHCl_3$ (20 mL), was added dropwise to a mixture of 1,4,7,10-tetraazacyclododecane (cyclen) (2.70 g, 15.7 mmol, 1 eq.) and sodium hydrogen carbonate (13.17 g, 0.157 mol, 10 eq.) in dry $CHCl_3$ (40 mL). The resulting mixture was stirred at room temperature for 72 hours.
The thick white precipitate was removed by gravity filtration, washed with chloroform (3 x 10 mL) and the solvent evaporated under reduced pressure to leave the product as a viscous pale brown oil.
Purification by gradient flash column chromatography (silica, CH_2Cl_2 to CH_2Cl_2 / MeOH / $NH_{3(aq)}$ 9 / 1 / 0.05, R_f = 0.59 in CH_2Cl_2 / MeOH / $NH_{3(aq)}$ system) yielded the pure product as a pale brown oil (4.77 g, 71%); υ_{max} ($CHCl_3$) / cm^{-1} 1732, 1735 (2 x C=O); δ_H (300 MHz, $CDCl_3$) 0.96 (9H, t, J 7.1, 3 x OCH_2CH_3), 2.59, 2.62, 2.71, 2.81 (16H, 4 x s, 8 x CH_2 from cyclen), 3.11 (2H, s, NCH_2COOEt), 3.22 (4H, s, 2 x NCH_2COOEt), 3.86 (6H, q, J 7.1, 3 x OCH_2CH_3), 9.55 (1H, s, NH); δ_C (300 MHz $CDCl_3$) 12.1 (OCH_2CH_3), 45.2, 46.1, 47.1, 49.2 (4 x cyclen CH_2 envir.), 55.0 (NCH_2COOEt), 58.5 (OCH_2CH_3), 168.2, 169.1 (2 x C=O envir.); m/z (ES) 431 ($[M+H]^+$, 100%); HRMS (ES^+) Found: 453.2689, required for $C_{20}H_{38}N_4O_6Na$: 453.2686.

Preparation of 1,4,7-tris(ethoxycarbonylmethyl)-10-(tert butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane 3



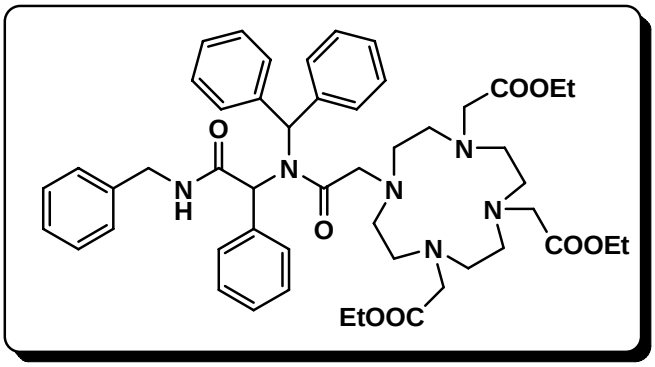
Triethyl ester **2** (4.77 g, 11.1 mmol, 1 eq.) was combined with dry Et_3N (7.79 mL, 55.4 mmol, 5 eq.) in dry THF (20 mL). Tert-butyl bromoacetate (2.13 mL, 14.4 mmol, 1.3 eq.) in dry THF (20 mL) was then added dropwise and the resulting mixture stirred at room temperature under N_2 for 72hr.
The thick white precipitate was removed by gravity filtration, washed with THF (3 x 10 mL), the solvent evaporated under reduced pressure and the flask subjected to high vacuum drying for 24 hr to leave the product as a viscous pale brown oil (5.42 g, 89%); υ_{max} ($CHCl_3$) / cm^{-1} 1725, 1736, 1738 (3 x C=O); δ_H (300MHz, $CDCl_3$) 1.20 (9H, t, J 7.1, 3 x OCH_2CH_3), 1.39 (9H, s, $(CH_3)_3C$), 2.77 (16H, s, 8 x cyclen CH_2 envir.), 3.22 (2H, s, NCH_2COO^tBu), 3.34 (6H, s, 3 x NCH_2COOEt), 4.08 (6H, q, J 7.1, 3 x OCH_2CH_3); δ_C (300 MHz $CDCl_3$) 12.7 ($(CH_3)_3C$), 26.5 (OCH_2CH_3), 53.6, 53.9, 54.4 (3 x cyclen CH_2 envir.), 59.9 (OCH_2CH_3), 80.8 ($(CH_3)_3C$), 171.7, 172.2 (2 x C=O envir.); m/z (ES) 545 ($[M+H]^+$ 100%), 567 ($[M+Na]^+$ 11%).

Preparation of 1,4,7-tris(ethoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecyl acetic acid 4



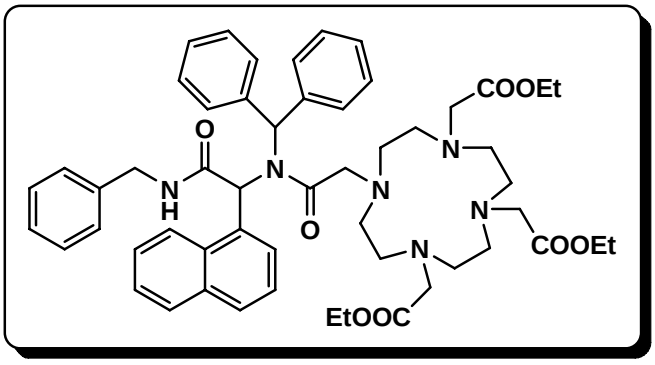
To the tetra ester **3** (0.20 g, 0.37 mmol) was added TFA (3 mL) and CH_2Cl_2 (3 mL) at 0°C. The mixture was then allowed to warm to ambient temperature and stirred for 16 hours. The solvent and excess TFA were then removed under reduced pressure and the viscous light brown oil dissolved in CH_2Cl_2 (3 x 10 mL) and re-evaporated to remove excess TFA. The crude product was then purified by preparative HPLC method B (t_r = 16.6 minutes), and lyophilised to afford the product as a fine white powder (0.17 g, 95%); υ_{max} ($CHCl_3$) / cm^{-1} 1715, 1736, 1746 (C=O), 2875 (OH br); δ_H (300 MHz, CD_3OD) 1.25-1.34 (9H, m, 3 x OCH_2CH_3), 3.13 (8H, s, 4 x cyclen CH_2 envir.), 3.46 (8H, s, 4 x cyclen CH_2 envir.), 3.74 (6H, s, 3 x NCH_2COOEt), 3.89 (2H, s, NCH_2COOH), 4.19 (6H, q, J 7.2, 3 x OCH_2CH_3), 4.91 (1H, br s, COOH); δ_C (300 MHz CD_3OD) 11.9 (OCH_2CH_3), 48.2 (NCH_2COOEt), 51.1, 51.4, 53.2, 53.6 (4 x cyclen CH_2 envir.), 54.6 (NCH_2COOH), 59.4, 59.6 (2 x OCH_2CH_3), 167.9, 170.1 (2 x C=O envir.); m/z (ES) 489 ($[M+H]^+$, 100%), 511 ($[M+Na]^+$, 22%); HRMS (ES^+) Found: 489.2924, required for $C_{22}H_{41}N_4O_8$: 489.2918.

Preparation of (4-{[Benzhydryl(benzylcarbamoylphenylmethyl)carbamoyl] methyl}-7,10-bis(ethoxycarbonylmethyl)-1,4,7,10-tetraaza-cyclododec-1-yl) acetic acid ethyl ester 5



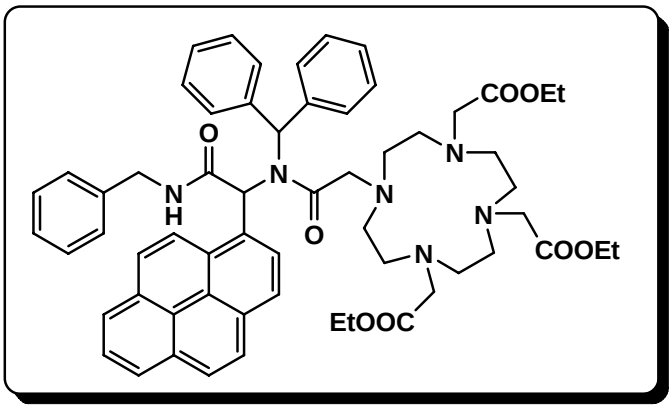
1,4,7-Tris(ethoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecyl ethanoic acid **4** (0.14 g, 0.29 mmol, 1eq.) was dissolved in dry EtOH (5 mL) under $N_{2(g)}$. Benzaldehyde (0.029 mL, 0.29 mmol, 1 eq.), aminodiphenylmethane (0.049 mL, 0.29 mmol, 1 eq.) and benzyl isocyanide (0.035 mL, 0.29 mmol, 1 eq.) were then added simultaneously, and the mixture stirred at 65 °C for 72 hours. The solvent was then removed under reduced pressure and the crude product purified using gradient flash column chromatography (silica, CH_2Cl_2 (100%) to CH_2Cl_2 / MeOH / $NH_{3(aq)}$ (9 / 1 / 0.05, v/v), R_f = 0.43 in CH_2Cl_2 / MeOH / $NH_{3(aq)}$ system). The product was then further purified by preparative HPLC method A (t_r = 28.70 minutes), and lyophilised to afford the title compound as a fine white powder (0.17 g, 68%); Mp = 60-62 ºC; υ_{max} ($CHCl_3$) / cm^{-1} 1658, 1679, 1730, 1741 (4 x C=O), 3249, 3300 (NH); *m/z* (ES) 877 ($[M+H]^+$,100%), 899 ($[M+Na]^+$, 36); HRMS (ES^+) Found: 899.4683, required for $C_{50}H_{64}N_6O_8Na$: 899.4695.
Due to the conformational flexibility of the molecule the NMR spectra were too complex to assign.

Preparation of (4-{[Benzhydryl(benzylcarbamoylnaphthalen-1-ylmethyl) carbamoyl]methyl}-7,10-bis(ethoxycarbonylmethyl)-1,4,7,10-tetraaza-cyclododec-1-yl) acetic acid ethyl ester 6



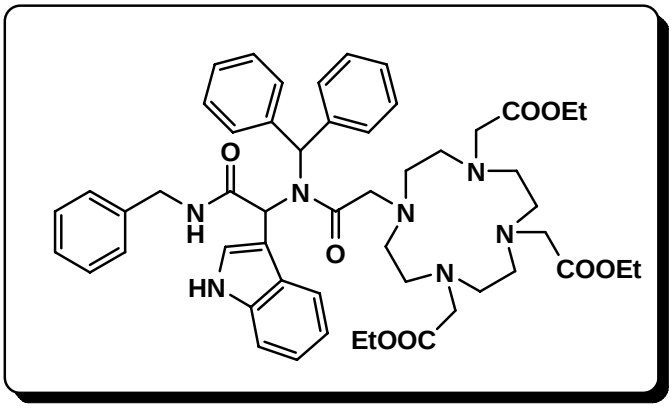
1,4,7-Tris(ethoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecyl ethanoic acid **4** (0.165 g, 0.34 mmol, 1 eq.) was dissolved in dry EtOH (5 mL) under $N_{2(g)}$. 2-Naphthaldehyde (0.053 g, 0.34 mmol, 1 eq.), aminodiphenylmethane (0.058 mL, 0.34 mmol, 1 eq.) and benzyl isocyanide (0.041 mL, 0.34 mmol, 1 eq.) were then added simultaneously, and the mixture stirred at 65 °C for 72 hours. The solvent was then removed under reduced pressure and the crude product purified using gradient flash column chromatography (silica, CH_2Cl_2 (100%) to CH_2Cl_2 / MeOH / $NH_{3(aq)}$ (9 / 1 / 0.05, v/v), R_f = 0.41 in CH_2Cl_2 / MeOH / $NH_{3(aq)}$ system). The product was then further purified by preparative HPLC method A (t_r = 29.36 minutes), and lyophilised to afford the product as a fine white powder (0.22g, 70%); m.p. = 66 – 69 ºC, υ_{max} ($CHCl_3$) / cm^{-1} 1668, 1683, 1736, 1748 (4 x C=O), 3246, 3296 (NH); *m/z* (ES) 927 ($[M+H]^+$,100%), 949 ($[M+Na]^+$, 7); HRMS (ES^+) Found: 927.5020, required for $C_{54}H_{67}N_6O_8$: 927.5001.
Due to the conformational flexibility of the molecule the NMR spectra were too complex to assign.

Preparation of (4-{[Benzhydryl(benzylcarbamoylpyren-1-ylmethyl) carbamoyl]methyl}-7,10-bis(ethoxycarbonylmethyl)-1,4,7,10-tetraaza-cyclododec-1-yl) acetic acid ethyl ester 7



1,4,7-Tris(ethoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecyl ethanoic acid **4** (0.15 g, 0.31 mmol, 1 eq.) was dissolved in dry EtOH (5 mL) under $N_{2(g)}$. 1-pyrenecarboxaldehyde (0.071 g, 0.31 mmol, 1 eq.), aminodiphenylmethane (0.053 mL, 0.31 mmol, 1 eq.) and benzyl isocyanide (0.037 mL, 0.31 mmol, 1 eq.) were then added simultaneously, and the mixture stirred at 65 °C for 72 hours. The solvent was then removed under reduced pressure and the crude product purified using gradient flash column chromatography (silica, CH_2Cl_2 (100%) to CH_2Cl_2 / MeOH / $NH_{3(aq)}$ (9 / 1 / 0.05, v/v), R_f = 0.49 in CH_2Cl_2 / MeOH / $NH_{3(aq)}$ system). The product was then further purified by preparative HPLC method A (t_r = 30.33 minutes), and lyophilised to afford the product as a fine white powder (0.11g, 36%); m.p. = 165 – 168 ºC; υ_{max} ($CHCl_3$) / cm^{-1} 1664, 1678, 1738, 1745 (4 x C=O), 3258, 3310 (NH); *m/z* (ES) 1023 ($[M+Na]^+$, 100%); HRMS (ES^+) Found: 1023.4996, required for $C_{60}H_{68}N_6O_8Na$: 1023.5010.
Due to the conformational flexibility of the molecule the NMR spectra were too complex to assign.

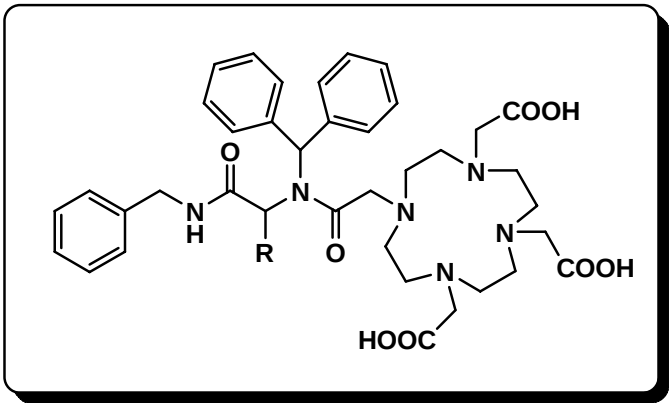
Preparation of (4-{[Benzhydryl(benzylcarbamoylindolylmethyl)carbamoyl] methyl}-7,10-bis(ethoxycarbonylmethyl)-1,4,7,10-tetraaza-cyclododec-1-yl) acetic acid ethyl ester 8



1,4,7-Tris(ethoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecyl ethanoic acid **4** (0.70 g, 1.43 mmol, 1 eq.) was dissolved in dry EtOH (5 mL) under $N_{2(g)}$. Indole-3-carboxaldehyde (0.21 g, 1.43 mmol, 1 eq.), aminodiphenylmethane (0.25 mL, 1.43 mmol, 1 eq.) and benzyl isocyanide (0.17 mL, 1.43 mmol, 1 eq.) were then added simultaneously, and the mixture stirred at 65 °C for 72 hours. The solvent was then removed under reduced pressure and the crude product purified using gradient flash column chromatography (silica, CH_2Cl_2 (100%) to CH_2Cl_2 / MeOH / $NH_{3(aq)}$ (9 / 1 / 0.05, v/v), R_f = 0.48 in CH_2Cl_2 / MeOH / $NH_{3(aq)}$ system). The product was then further purified by preparative HPLC method A (t_r = 30.60 minutes), and lyophilised to afford the title compound as a fine white powder (0.86 g, 66%); m.p. = 160 –

162 ºC; υ_{max} ($CHCl_3$) / cm^{-1} 1664, 1678, 1738, 1745 (4 x C=O), 3258, 3310 (NH); *m/z* (ES) 916 ($[M+H]^+$, 30%); 938 ($[M+Na]^+$, 100%); HRMS (ES^+) Found: 938.4792, required for $C_{52}H_{65}N_7O_8Na$: 938.4769. Due to the conformational flexibility of the molecule the NMR spectra were too complex to assign.

General procedure for ethyl ester hydrolysis of 5-8

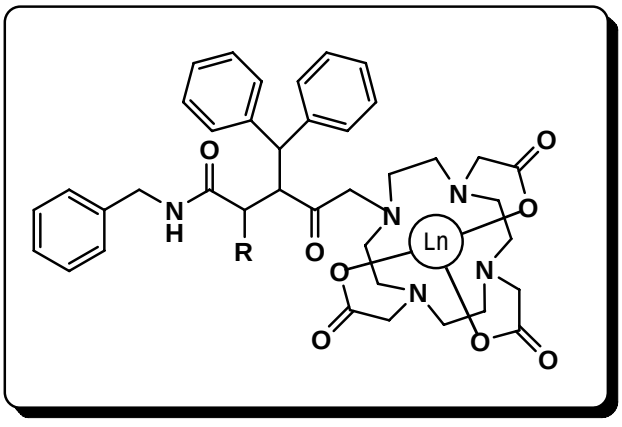


The Ugi products **5-8** were dissolved in a 1:1 mix of THF / H_2O. LiOH (3.5 eq.) in H_2O (2 mL) was then added and the reaction mixture stirred for 24 hours at ambient temperature. The excess THF was then removed under reduced pressure and the mixture neutralised with 1M HCl. The product was purified using preparative HPLC, method B.

Ester	**R**	**Acid**	**Yield**$^+$ (%)	**HPLC Retention Time** (minutes)	**M/z** (ES+)
5	Benzyl	**9**	85	23.3	815 M+Na
6	Naphthyl	**10**	88	32.8	865 M+Na
7	Pyrenyl	**11**	87	22.7	975 M+Na
8	Indolyl	**12**	83	23.9	854 M+Na

$^+$ Post HPLC

General procedure for lanthanide complexation of tris acids 9-12.



The tricarboxylic acid was dissolved in dry MeOH and $Ln(OTf)_3$ (1.1 eq.) added. The mixture was stirred at 40 ºC under $N_{2(g)}$ for 72 hours. The MeOH was then removed under reduced pressure and the product purified using HPLC method B.

Acid	**Lanthanide**	**Yield**[+] **(%)**	**HPLC Retention Times** (minutes)	**M/z** (ES+)
9 (Benzyl)	**Eu**	86	37.5, 40.7*	963-966 M+Na
	Tb	96	37.2, 40.5*	971 M+Na
	Yb	83	36.6, 40.3*	983-988 M+Na
10 (Naphthyl)	**Eu**	84	35.0, 37.8 *	1013-1016 M+Na
	Tb	88	38.7, 41.6 *	1021 M+Na
	Yb	84	35.5, 39.6*	1033-1038 M+Na
11 (Pyrenyl)	**Eu**	90	41.6	1087-1090 M+Na
	Tb	89	41.7	1095 M+Na
	Yb	92	41.7	1085-1090 M+H
12 (Indolyl)	**Eu**	96	38.0, 41.0*	1002-1005 M+Na
	Tb	95	38.2, 41.1*	1010 M+Na
	Yb	84	38.1, 40.8*	1022-1027 M+Na

[+] Post HPLC
***** Mixture of diastereoisomers

Luminescence spectroscopy
For the europium and terbium complexes, luminescence spectra were obtained using a Perkin-Elmer LS55 spectrometer. This was also used to determine the luminescence lifetimes by observing the intensity of emission at a variety of delay times while keeping the gate time constant.
In the case of the ytterbium complexes, the sample was excited using a pulsed nitrogen laser (PTI-3301, 337nm) operating at 10Hz. Light emitted at right angles to the excitation beam was focused onto the slits of a monochromator (PTI120), which was used to select the appropriate wavelength. The growth and decay of the luminescence at selected wavelengths was detected using a germanium photodiode (Edinburgh Instruments, EI-P) and recorded using a digital oscilloscope (Tektronix TDS220) before being transferred to a PC for analysis. Luminescence lifetimes were obtained by iterative reconvolution of the detector response (obtained by using a scatterer) with exponential components for growth and decay of the metal centred luminescence, using a spreadsheet running in Microsoft Excel. The details of this approach have been discussed elsewhere (A. Beeby and S. Faulkner, *Chem. Phys. Lett*., (1997), **266**, 116).

Isomerism in DOTA monoamide complexes

The square antiprism and twisted square antiprism forms of a DOTA monoamide complex are shown below. It should be noted that chirality in the side arm (as obtained in these Ugi products) gives rise to further isomerism, which would make the figure too complicated to depict effectively. This has been discussed at length by other authors (see, for example, S. Aime, M. Botta, G. Ermondi, Inorg. Chem., **1992**, *31*, 4291, and D. Parker, R.S. Dickins, H. Puschmann, C. Crossland & J.A.K. Howard, *Chem. Rev.* **2002**, *102*, 1977-2010).