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Tetrahedron
Tetrahedron 60 (2004) 105–113

Three step vs one pot synthesis and X-ray crystallographic investigation of heptadentate triamide cyclen (1,4,7,10-tetraazacyclododecane) based ligands and some of their lanthanide ion complexes

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Received 14 August 2003; revised 7 October 2003; accepted 30 October 2003

Abstract—The synthesis of several lanthanide complexes from the tris alkylated cyclen (1,4,7,10-tetraazacyclododecane) ligands **1** and **2** is described. The syntheses of **1** and **2** were investigated by means of two different synthetic routes (Method 1 and Method 2). The first of these involves the mono protection of cyclen using 4-methoxyphenylsulfonyl chloride, followed by alkylation of the remaining three secondary amines of cyclen, and deprotection using solvated Na(s). Using this approach only **1** was successfully formed. The X-ray crystal structure of the intermediate, **9** and the corresponding La(III) complex, **9.La** is presented. The second method involved the direct synthesis of the two ligands in a single step. The X-ray crystallography of the Eu(III) complex of one of these ligands is presented. Whereas, Method 1 yielded the product **1** in high purity, but in low overall yield, Method 2 gave higher yields for both ligands (~50% for both).

1. Introduction

The design and synthesis of sensors for anions and neutral molecules has been an area of immense study in recent years.[1] The use of metal complexes as sensors in such situations has been discussed in many of these studies.[1,2] Metal complexes can form metal–ligand interactions with anions that are significantly stronger than hydrogen bonding, or other interactions commonly exploited for anion recognition.[3] For instance Fabrizzi et al. have demonstrated the use of Zn(II) complexes as sensors for aromatic carboxylates such as *p*-nitro benzoic acid.[4] Also Pallavicini et al. have employed Cu(II) complexes with tetraaza ligands that can detect coumarin 343.[5] The use of metal complexes for sensing anions has not been confined to transition metals alone. Lanthanides such as Tb(III) and Eu(III) have been shown to displace cations, such as Ca(II), that can be found in the binding sites of proteins; such binding sites contain anionic groups to complex the cation.[6] Excitation of surrounding aromatic residues (such as tyrosine or phenylalanine) in these proteins can result in sensitization of the lanthanide, producing a lanthanide emission.[7] With the ultimate goal of anion detection in vivo the need for stable lanthanide complexes arises. Yu et al. have demonstrated that stable Tb(III) [2.2.2] cryptates can be sensitized in aqueous solutions when coordinated with acac, a β-diketonate chelate.[8] This requires the displacement of the two labile water molecules from the Tb(III) complex. Nocera et al. have shown aromatic carboxylates to act in a similar manner with Tb(III) [2.2.2] cryptates.[9] In work reported by Diamandis, sensitization of Eu(III) and Tb(III) EDTA complexes at pH 11–12 using a number of aromatic carboxylate compounds such as 5-flurosalicylic acid was demonstrated.[10] Reinhoudt et al. also showed similar results using an EDTA-bis(β-cyclodextrin).[11] Parker et al. have reported the synthesis of heptadentate cyclen based lanthanide complexes, which showed great promise as sensors for bicarbonate.[12] Studies carried out in solutions containing MES buffer with pH ranging between 6.4 and 7.3 demonstrated that stable lanthanide complexes could be produced that can detect the presence of anions under near physiological conditions. As discussed, in many of the above cases, coordination to the anionic species displaces the two bound water molecules from the Tb(III) or Eu(III) complexes. However, in this case the coordinating species was not a sensitizer. Instead, its presence as a coordinated species was detected by changes in the emission lifetimes of the lanthanide ion.

We have been interested in the development of lanthanide luminescent devices and we have synthesized several

Keywords: Supramolecular chemistry; Macrocycles; Lanthanide ions; Cyclen.
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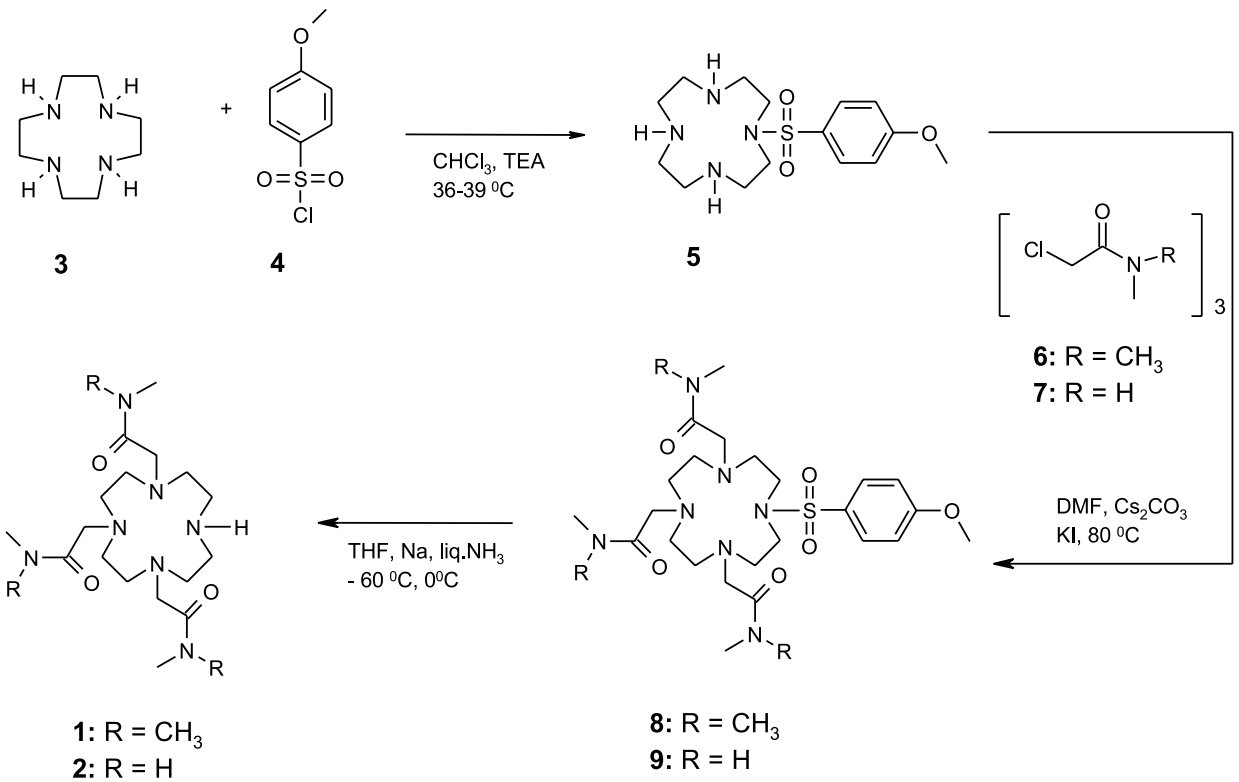
doi:10.1016/j.tet.2003.10.086

Table 1. Data collection and structural refinement details for **9**, **La.9** and **Eu.2**

Structural formula	$C_{25}H_{42}Cl_3N_7O_6S$ (**9**)	$C_{29}H_{46}F_9N_7O_{16}S_4La$ (**La.9**)	$C_{20}H_{35}F_9N_7O_{16}S_3Eu$ (**Eu.2**)
M	675.07	1186.88	1048.69
Crystal size (mm)	0.18×0.16×0.08	0.34×0.28×0.24	0.36×0.23×0.10
Crystal system	Orthorhombic	Monoclinic	Triclinic
Space group (**Z**)	*Pbca* (**8**)	$P2_1/c$ (**4**)	*P*-1 (**2**)
a (Å)	16.886(2)	13.4113(12)	8.992(4)
b (Å)	9.6598(13)	115527(10)	13.112(5)
c (Å)	38.899(5)	29.089(2)	17.623(7)
α (°)	90	90	79.370(6)
β (°)	90	90.684(2)	82.503(6)
γ (°)	90	90	71.816(6)
U (Å^3)	6345.1(15)	4506.6(7)	1934.3(14)
D_c (g cm^{-3})	1.413	1.749	1.800
F(000)	2848	2396	1048
μ(Mo K$_\alpha$) (mm^{-1})	0.405	1.244	1.899
ω scans; 2θ range (°)	2–45	3–57	2–50
R_{int}	0.1796	0.0359	0.0618
Unique reflections	4150	10295	6732
*wR*2(*R*1)	0.2795(0.0944)	0.0991(0.0364)	0.1688(0.0623)

Eu(III) and Tb(III) complexes as luminescent switches,[13] sensors[14] and logic gate mimics.[15] We have also developed several lanthanide based ribonuclease mimics for the cleavage of mRNA and RNA mimic compounds.[16] These compounds have all been based on tetrasubstitued cyclen complexes, which possess a single metal bound water molecule. The synthesis of such compounds is usually achieved in good yields by reacting 4 equiv. of the pendent arm with cyclen.[17] However, the formation of unsaturated heptadentate ligands is a much more challenging task.[12a,18] The purpose of the work described herein was to synthesis heptadentate ligands **1** and **2** and their Eu(III) and Tb(III) complexes **Eu.1**, **Eu.2**, **Tb.1** and **Tb.2**. Furthermore, these complexes were to be evaluated for their ability to coordinate and sense aromatic carboxylates.[19] All these complexes are expected to be photophysically 'silent' upon excitation as no sensitizing groups have been incorporated into ligands, **1** and **2** and so no indirect excitation of the lanthanides can occur. The work presented herein concerns the synthesis of the two ligands **1** and **2** using two different synthetic methods (Method 1 and Method 2), and the analysis of some of the intermediates and final products using X-ray crystallography (Table 1). We have recently discussed the photophysical properties of these molecules and their ability to detect aromatic carboxylates such as salicylic acid over Aspirin.[19]



Scheme 1. The synthetic route undertaken in Method 1. Whereas, ligand **2** was not obtained by this method, ligand **1** was made in overall 9% yield.

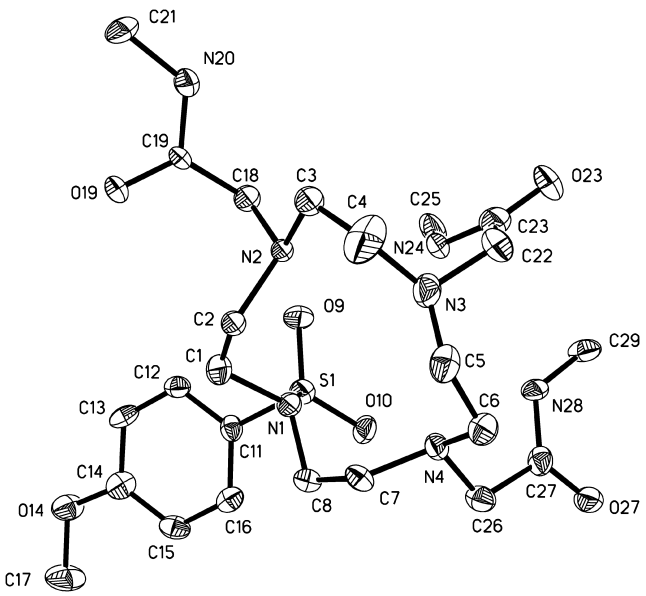


Figure 1. Diagram showing the conformation of ligand **9**. Hydrogen atoms and the disorder are not shown for clarity. Ellipsoids at 30%. A $CHCl_3$ molecule was also found in the unit cell for this structure.

2. Results and discussion

Synthesis of ligands **1** and **2** involved tris *N*-alkylation of cyclen **3**, a macrocycle with four potential alkylation sites. The syntheses of such regioslective *N*-functionalisation of tetraazacycloalkanes is an important area of research.[20] However, often the emphasis has been on developing methods for mono-protection of such macrocyles, which can then be further derivatised, followed by deprotection of the initial protection group.[21] In order to synthesize the proposed ligands herein, two possible synthetic routes were attempted. The first route, Method 1 is shown in Scheme 1, and is based upon the use of a single *N*-protection of cyclen, **3**, in one of its four positions using 1 equiv. of *p*-methoxyphenylsulfonyl chloride, **4**. This technique was first developed by Parker et al.[12a,b] Synthesis of **5** involved dropwise addition of a $CHCl_3$ solution of **4** into a $CHCl_3$ solution of **3** in the presence of triethyl amine at 36–39 °C. The resulting crude product contained a by-product that was determined to be a bis aryl sulfonamide cyclen ligand. Purification by silica gel column chromatography using 90:10 MeCN/MeOH provided **5** in 53% yield. This product was identified from its ^1H NMR spectrum by the presence of two doublets at 7.72 and 7.01 ppm and a singlet at 3.88 ppm resulting from the presence of the aromatic group. Alkylation of **5** using **6** or **7** was carried out in DMF at 80 °C using Cs_2CO_3 as a base and KI to afford **8** or **9**, respectively. The α-chloroamides **6** and **7** were produced from chloroacetyl chloride with the appropriate amine following published procedures.[22] Purification of the tertiary amide **8** was achieved with alumina column chromatography using 97:3 EtOAc/MeOH giving the desired compound as an oil in 50% yield. The secondary amide **9** was purified with alumina column chromatography using CH_2Cl_2/MeOH (1–5%) to give **9** as oil in 41% yield. Both **8** and **9** were characterised by NMR spectroscopy, ESMS, accurate mass and infrared analysis and in the case of **9** by X-ray crystallography. Figure 1 illustrates the crystal structure of **9** and clearly shows the presence of three mono methyl acetamide pendent arms attached to cyclen, along with the *p*-methoxyphenylsulphonamide protection. A summary of selected bond angles and bond lengths is shown in Table 2.

We were also able to form the La(III) complex of **9**, **La.9** by refluxing Lanthanum triflate in EtOH. Upon cooling, hexane was added, ca. 5% and the solution kept cold whereupon crystals were formed. The X-ray crystal structure of this complex is shown in Figure 2, where the ion is coordinated to the four nitrogens of the cyclen ring, the oxygens of the carboxylic amides and to one of the oxygen of the sulfonamide. The average N···La and O···La bond lengths for the coordination of the cyclen ring were 2.855 and 2.494 Å, respectively. Whereas, the distance of the sulfonamide oxygen O···La distance was found to be 2.694 Å. A summary of selected bond angles and bond lengths is shown in Table 2. Furthermore, the lanthanide ion was coordinated to a single triflate (O···La=2.554 Å) and ethanol molecule (O···La=2.577 Å), giving rise to 10 coordinated environments, as expected for La(III) which has

Table 2. Selected bond lengths (Å) and bond angles (°)

(**Tb.1**)		(**9**)		(**Eu.2**)		(**La.9**)		(**Eu.1**)	
Tb1 O15	2.348(3)	C1 C2	1.490(13)	Eu1 O14	2.377(6)	La1 O5	2.458(2)	Eu1 O15	2.342(5)
Tb1 O27	2.326(3)	C3 C4	1.425(13)	Eu1 O22	2.393(6)	La1 O4	2.512(2)	Eu1 O25	2.364(5)
Tb1 O20	2.368(3)	C5 C6	1.520(13)	Eu1 O18	2.399(6)	La1 O3	2.514(2)	Eu1 O19	2.378(5)
Tb1 O1W	2.429(3)	C7 C8	1.494(10)	Eu1 O1W	2.448(6)	La1 O13	2.554(2)	Eu1 O1W	2.418(5)
Tb1 O2W	2.441(3)	N1 C1	1.497(9)	Eu1 O2W	2.485(6)	La1 O1SS	2.577(2)	Eu1 O2W	2.421(5)
Tb1 N1	2.600(4)	N1 C8	1.481(11)	Eu1 N1	2.673(7)	La1 O2	2.694(2)	Eu1 N1	2.605(6)
Tb1 N10	2.656(3)	C19 O19	1.255(10)	Eu1 N10	2.618(7)	La1 N1	2.989(3)	Eu1 N10	2.624(6)
Tb1 N7	2.637(4)	C23 O23	1.247(13)	Eu1 N7	2.670(7)	La1 N10	2.842(3)	Eu1 N7	2.625(6)
Tb1 N4	2.642(4)	C27 O27	1.244(11)	Eu1 N4	2.678(7)	La1 N7	2.808(3)	Eu1 N4	2.647(6)
		C19 N20	1.314(11)			La1 N4	2.784(3)		
		C23 N24	1.334(13)						
O27 Tb1 N10	65.41(11)	C27 N28	1.301(12)	O22 Eu1 N7	65.98(19)	O5 La1 N10	62.57(8)	O25 Eu1 N10	65.39(19)
O20 Tb1 N7	64.53(11)	N1 S1	1.630(8)	O18 Eu1 N4	65.5(2)	O4 La1 N7	61.33(7)	O19 Eu1 N7	64.10(19)
O15 Tb1 N4	65.68(11)	S1 O10	1.440(6)	O14 Eu1 N1	66.1(2)	O3 La1 N4	63.42(7)	O15 Eu1 N4	65.13(19)
01W Tb1 02	71.80	S1 O9	1.431(6)	O1W Eu1 02W	70.9(2)	O2 La1 N1	50.94(7)	O1W Eu1 02W	72.17
N–C–C–O	5.6(7)			N–C–C–O	−30.0(7)	N–C–C–O	−45.0(4)	N–C–C–O	−2.5(11)
N–C–C–O	25.6(6)			N–C–C–O	−32.7(1)	N–C–C–O	−27.8(4)	N–C–C–O	−27.6(10)
N–C–C–O	26.5(6)			N–C–C–O	−36.4(5)	N–C–C–O	31.8(4)	N–C–C–O	−25.4(10)

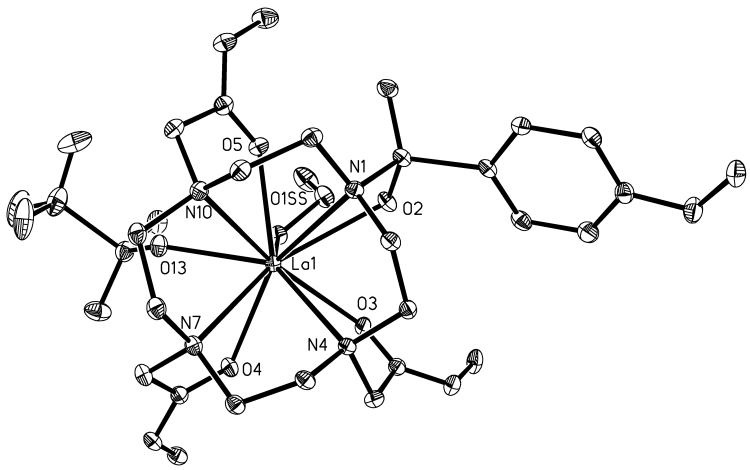
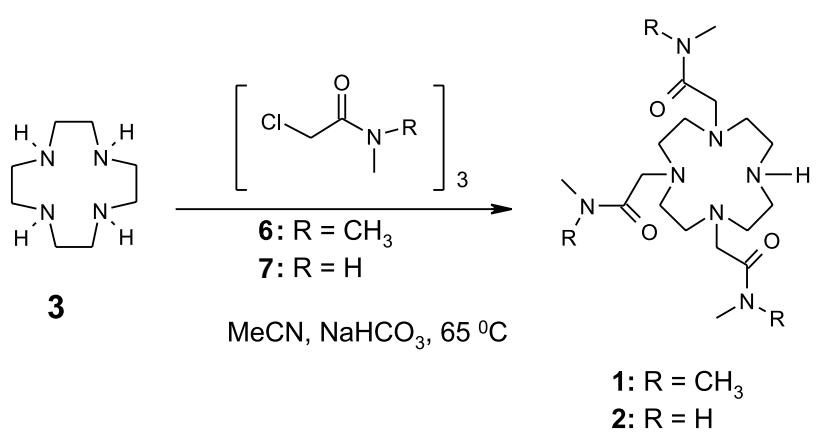


Figure 2. Diagram showing the conformation and binding mode of the La(III) complex **La.9** (**La.9**·$(CF_3SO_3)_3$·EtOH). Hydrogen atoms and lattice anions are not shown for clarity. Ellipsoids at 30%. Three triflate molecules and one ethanol molecuel was also found in the unit cell for this structure.

higher coordination requirements than Eu(III) and Tb(III). Furthermore, the complex adopts a square antiprismatic geometry in solid state, with average N–C–C–N angle of −61.55°. Unfortunately, this complex was found to be unstable and decomposed when dissolved in several solvents, because of this, complete characterizations was not possible. However, it is an important structure since not many La-cyclen structures are known in the literature.[17,23,24]

The final step in the synthesis of **1** and **2** involved deprotection of **8** and **9** using Birch conditions. This was carried out by stirring a THF solution of either **8** or **9** in the presence of Na metal and liquid ammonia at −60 °C.[25] Isolation of these products from the reaction solution involved acid base extraction, which in the case of **2** failed to give the required product, even when continuous extraction techniques were used. However, ligand **1** was isolated in a low yield of 36%, and in 9% overall yield from **3**. The results of this final step in the synthesis of **1** and **2** indicated that this synthetic pathway was not sufficient to synthesize the desired ligands and another method was required. The second route was thus attempted.

The second synthetic route, Method 2, is shown in Scheme 2, and involved direct alkylation of **3** with 3 equiv. of **6** or **7** to yield **1** and **2**, respectively in a single step. A number of variations were attempted using this direct alkylation method, such as high dilution addition of **6** to **3**, by varying the rate addition and concentration of the two reagents, but maintaining the ratio of the reagents (the ratio of **3** to either **6** or **7** was kept as 1:3 or 1:3.1). On many occasions a number of by products were observed and electro spray mass spectral analysis of the reaction mixture showed the presence of mono, bis, tris and tetra-alkylated cyclen. However, these were difficult to isolate successfully and in high purity by column chromatography. Furthermore, the temperature at which these additions were carried out at was also modulated, from 20⟶80 °C, and the use of other solvents such as DMF, were also investigated. However, a successful method was developed, which we present herein. This involved stirring of **3** in a solution of MeCN at 65 °C. To this solution 3 equiv. of **6** or **7** was added in a single addition and the resulting solution was stirred at 65 °C for 72 h. In the case of **1**, the product was isolated as a viscous oil in a 52% yield following purification on an alumina column using 97:3 CH_2Cl_2/MeOH(NH_3), while **2** was isolated in a 59% yield as a white solid following precipitation from ether. Of the two synthetic methods attempted the direct alkylation of **3** was determined to be the most efficient synthetic route for the synthesis of **1** and **2**, with yields over 50% from a one step synthesis compared to total yields of 9% for **1** and 0% for **2** using the initial three step synthesis (Method 1).



Scheme 2. The one-pot syntheses of **1** and **2**.

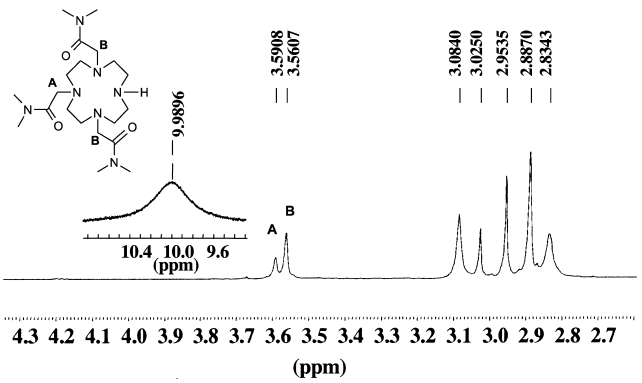
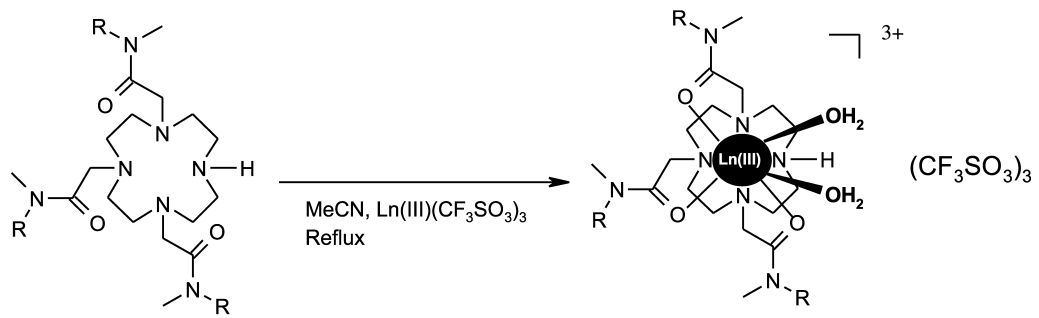


Figure 3. The ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **1**, showing the C_2-symmetry. (Inset: NH peak at 9.98 ppm.)

Ligands **1** and **2** were characterized using standard techniques. However, both were hygroscopic and elemental analysis of these ligands was not possible. Nevertheless, (ESMS) accurate mass spectroscopy was obtained for both. The ^{1}H NMR spectra of both ligands clearly reflect a C_2 symmetry. This C_2 symmetry runs along an axis through the unalkylated amine in position 1 and the tertiary amine in position 7 of the cyclen ring. The ^{1}H NMR spectrum of **1** shown in Figure 3, revealed the presence of one N–H singlet at 9.98 ppm. The two α-protons for the pendant arms appeared as singlets at 3.59 and 3.56 ppm (in a ratio of 2:4), respectively. From C–H cosy experiments the five singlets observed between 3.08 and 2.83 ppm were representative of both the cyclen CH_2 and methyl acetamide CH_3 protons. The ^{1}H NMR spectrum for **2** showed similar characteristics.[19] The ^{13}C NMR spectra for both **1** and **2** contained 10 signals. For **1** this consisted of two quaternary resonances at 170.3 and 170.2 ppm corresponding to the carboxylic amide carbonyls of the pendant arms. Two CH_2 resonance signals at 55.5 and 53.8 ppm were assigned to the pendant arms. Another four CH_2 signals observed from 51.7 to 46.7 ppm correspond to the cyclen ring. The two final signals were found at 36.4 and 35.3 ppm and correspond to the acetamide methyl groups. A similar ^{13}C NMR spectrum was obtained for **2**.[19] We are currently modifying these two ligands by functionalising the remaining amino moiety with various α-amides such as dipeptides and peptide conjugates, as well as incorporating various chomrophores as antennae and sensors for the population of the Tb(III) and Eu(III) excited states. This work will be the subject of future publications.

The synthesis of the lanthanide complexes **Eu.1**, **Tb.1**, **Eu.2** and **Tb.2** involved refluxing **1** and **2** with Eu(III) and Tb(III) as their triflate salts in freshly dried MeCN (Scheme 3). Upon cooling to room temperature the solutions were poured into stirring solutions of dry ether, and in all cases an oily residue was produced. These oils were collected by decanting the organic layers and the resulting residues were rinsed with either CH_2Cl_2 or $CHCl_3$. The resultant complexes were all isolated as powders in yields of ca. 95% after exhaustive drying under vacuum over P_2O_5 for approximately two weeks. These complexes were characterised by elemental analysis, ESMS, accurate mass, IR and NMR spectroscopy. Similar results were observed for all of these complexes. The ^{1}H NMR spectrum showed the presence of the paramagnetic metal centers, as indicated by several broad resonances appearing over a large ppm range as in the case **Eu.2** where these appeared at 27.04, 14.96, 11.44, 5.20, 3.68, 2.76, 2.41, 1.55, −0.09, −1.84, −4.93, −7.35, −10.77, −12.31, −16.66, respectively. Similar results were observed for the other three complexes. These results indicated that all adapted square antiprismatic geometry in solution.[16,17,24] ESMS and accurate mass analysis proved very useful in characterization of these complexes. All four complexes gave similar spectra, which consisted of M+H peaks for the complex with one and two triflate counter anions present. In some instances M+H peak for the complex along with a large number of $M+H_n+Triflate_x/Z_n$ (x=0–3, n=1–3) peaks were found in the ESMS. The peaks generated compared well with the theoretical isotope model, as shown in Figure 4, for **Eu.1**. It should be noted that the presence of the bound water molecules was not seen during analysis by mass spectroscopy. From IR spectroscopy the single carbonyl stretching frequency occurring at 1643 cm^{-1} in **2** was shifted when complexed to Eu(III) or Tb(III) to 1639 cm^{-1}, an indication that the pendent arms were indeed bound to the metal center.[22] Crystals of **Eu.1** **Eu.2** and **Tb.2** were obtained that were suitable for X-ray crystallographic determination. We have shown the structure of the **Eu.1** and **Tb.2** in our previous publications (selective bond angles and bond lengths are shown for comparison in Table 2).[18,19]



1: R = CH_3 **2:** R = H

Eu.1: R = CH_3, Ln(III) = Eu(III)
Tb.1: R = CH_3, Ln(III) = Tb(III)
Eu.2: R = H, Ln(III) = Eu(III)
Tb.2: R = H, Ln(III) = Tb(III)

Scheme 3. The formation of the Eu(III) and Tb(III) complexes of **1** and **2**.

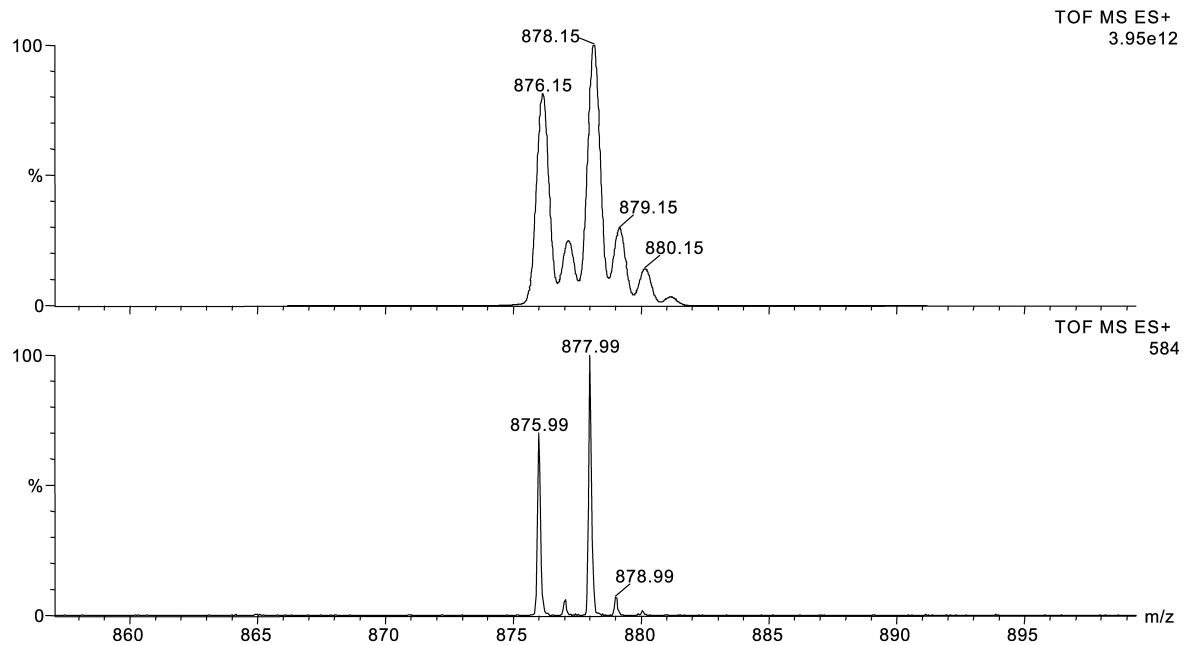


Figure 4. The electro spray mass spectrum of **Eu.1** (bottom) and the calculated isotopic pattern (top).

Crystals of **Eu.2** were obtained by slow evaporation from solutions of MeCN. The structure of **Eu.2** is shown in Figure 5.

All of the structures adopted a square antiprism geometry in the solid state, a common geometry for tetraamide and carboxylate-substituted lanthanide complexes of cyclen, where the metal center was coordinated to the four nitrogens of the macrocycle ring and the three oxygens of the carboxylic amide pendent arms. The Ln(III)–N and Ln(III)–O bond lengths were of similar length in all three complexes with average distances of ca. 2.64 Å and ca. 2.37 Å, respectively. Furthermore, all the crystal structures showed the presence of the two metal bound water molecules. For **Eu.1** and **Tb.1** these bond lengths were similar with an average value of ca. 2.43 Å. This bond length was longer in **Eu.2** with an average of ca. 2.47 Å. The angle that these two water molecules bind to the metal center was also of importance, since the nature of the binding mode with carboxylate anions would depend on the bite angle between the two water molecules. For **Eu.1** the O1W-Eu-O2W bite angle was measured to be 72.17° whereas, for **Tb.1** the O1W-Tb-O2W bite angle was measured to be 71.80° and for **Eu.2** the O1W-Eu-O2W bite angle was measured to be 70.86°. Recently, Dickins et al.[12b,c] reported that related three-arm cyclen complexes can form bidentate adducts with organic anions such as acetate, citrate, glycinate, and lactate through four and five member chelates. The bite angles for all of these complexes

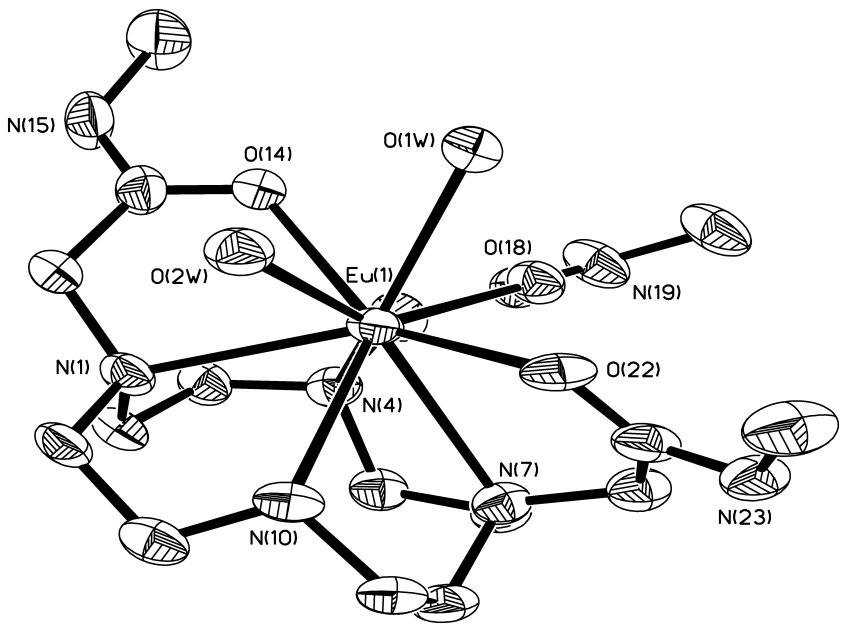


Figure 5. The X-ray crystal structure of **Eu.2** (**Eu2** $(CF_3SO_3)\cdot(H_2O)_2$), showing the seven coordination of the ligand and the two metal bounded water molecules. Hydrogen bonds and lattice anions have been omitted for clarity. Three triflate anions were also found in the unit cell.

were between 54 and 69°. In the case of acetate, this binding was bidentate and occurred through both of the carboxylate oxygens. From these reports and the bite angles calculated for **Eu.1**, **Tb.1** and **Eu.2** it was proposed that aromatic carboxylates would bind in a similar bidentate manner to all the complexes, expelling the two water molecules. This was indeed found to be the case as we have recently reported where the Tb(III) emission of both **Tb.1** and **Tb.2** was 'switched on' (due to the population of the $^5D_4$ excited state of the lanthanide ion through an energy transfer mechanism, involving the excitation of the singlet state of the salicylic acid, followed by intersystem crossing to the triplet state) in the presence of salicylic acid, whereas, no sensitization of the excited state of the lanthanide ion was observed for Aspirin.[19] Furthermore, no binding was found to occur for the Eu(III) complexes, which was caused by much weaker binding to these ions than to the Tb(III) centers.

3. Conclusion

In summary we have synthesized two amide based ligands **1** and **2** using two different synthetic methods. Whereas, the former of these involved three steps, only giving one of the desired products, the second method was quite successful, giving the desired ligands in ca. 50% overall yield in a single step. Even though this method requires elaborate chromatographic purification for one of these products (**1**) the second product was easily obtained by precipitation methods. We were able to obtained both crystals of the ligand **9** the La(III) complex of **9**, one of the intermediates from Method 1. It clearly showed the ability of the ligand to coordinate to the La(III) ion, despite the presence of the sulfonamide. We were also able to grow crystals of three of the four complexes made from **1** and **2**. To the best of our knowledge these were the first examples of such X-ray crystal structures of such heptadentate tri-arm amide based cyclen complexes. The structure of **Eu.2** was reported herein, showing the metal ion coordinating to all the seven coordination sites of the ligand, as well as to two water molecules. As we have demonstrated in our former publication,[18,19] these water molecules could be removed by aromatic carboxylates, in the case of **Tb.1** and **Tb.2**. Of the two synthetic methods investigated herein, Method 2 is superior to Method 1. We are currently improving the use of this method and employing it to develop several peptide based heptadentate tri-arm ligands for the use as molecular sensors and as catalysts for the hydrolysis of mRNA.

4. Experimental

4.1. General

Starting materials were obtained from Sigma Aldrich, Strem Chemicals and Fluka. Columns were run using Silica gel 60 (230–400 mesh ASTM) or Aluminum Oxide (activated, Neutral, Brockmann I STD grade 150 mesh). Solvents were used at GPR grade unless otherwise stated. Infrared spectra were recorded on a Mattson Genesis II FTIR spectrophotometer equipped with a Gateway 2000 4DX2-66 workstation. Oils were analysed using NaCl plates, solid samples were dispersed in KBr and recorded as clear pressed discs. ^{1}H NMR spectra were recorded at 400 MHz using a Bruker Spectrospin DPX-400 instrument. Tetramethylsilane (TMS) was used as an internal reference standard, with chemical shifts expressed in parts per million (ppm or δ) downfield from the standard. ^{13}C NMR were recorded at 100 MHz using a Bruker Spectrospin DPX-400 instrument. ^{19}F NMR were recorded at 376 MHz using a Bruker Spectrospin DPX-400 instrument. Mass spectroscopy was carried out using HPLC grade solvents. Mass spectra were determined by detection using Electrospray on a Micromass LCT spectrometer, using a Shimadzu HPLC or Water's 9360 to pump solvent. The whole system was controlled by MassLynx 3.5 on a Compaq Deskpro workstation.

4.1.1. 1-(4-Methoxy-phenylsulphonyl)-1,4,7,10-tetraazacyclododecane (5). To a 500 mL three neck RBF, (**3**) 1,4,7,10-tetraazacyclododecane (1.00 g, 5.8 mmol) was added along with $CHCl_3$ (50 mL). To this was added TEA (4.11 g, 40 mmol) which was heated at 36–39 °C. 4-Methoxy phenyl sulphonyl chloride (1.20 g, 5.8 mmol) in $CHCl_3$ (100 mL) was added dropwise over a 5-hour period. The solution was then left stirring overnight. The solution temperature was maintained at 36–39 °C. This solution was reduced to approximately 50 mL upon which a white solid was produced that was removed by filtration and the resulting organic solution was reduced to dryness under vacuum to produce a white solid, 1.6 g (80.0%). This was then purified by silica column chromatography using 90:10, MeCN/MeOH (53% recovery), to yield 0.56 g (28% yield) of **5** as a white solid. Mp=137–140 °C. Calculated for $C_{15}H_{27}N_4O_3S$: [M+H peak] m/z=343.1804. Found: 343.1806; δ_H ($CDCl_3$, 400 MHz) 7.72 (d, J=9.0 Hz, 2H, Ar-H), 7.01 (d, J=8.6 Hz, 2H, Ar-H), 3.88 (s, 3H), 3.40 (d, J=4.5 Hz, 4H, CH_2), 3.18 (d, J=5.0 Hz, 4H, CH_2), 3.00 (d, J=4.0 Hz, 4H, CH_2), 2.87 (d, J=5.0 Hz, 4H, CH_2); δ_C ($CDCl_3$, 100 MHz) 162.9, 128.8, 114.1, 55.2, 49.3, 48.5, 48.2, 45.5; Mass Spec (MeCN, ES+) m/z expected: 342.2. Found: 343.2 (M+H); 365.1 (M+Na); IR ν_{max} (cm^{-1}) 3432, 3095, 3008, 2842, 1712, 1594, 1492, 1438, 1363, 1261, 1222, 1155, 1091, 1052, 1024, 927, 890, 842, 804, 761, 701, 561, 530, 466.

4.2. General synthesis of 1 and 2

Compound **5**, 0.68 g (2.0 mmol) was placed in a 100 mL three neck RBF. To this was added **7**, (0.64 g, 6.0 mmol) [or **6**, 3.1 equiv. in the case of **8**], Cs_2CO_3 (1.95 g, 6.0 mmol) and KI (1.0 g, 5.3 mmol). To this was added dry DMF (12 mL). The reaction was freeze pump thawed twice. The flask was then filled with argon and the reaction was stirred at 80 °C overnight. The resulting solution was then filtered through a celite plug filter and reduced by rotatory evaporation. The resulting residue was dissolved in $CHCl_3$ and washed with water (2×50 mL), and brine (2×50 mL). The organic layer was isolated, dried over K_2CO_3 and reduced under vacuum, to produce a viscous oil. This was then purified by alumina column chromatography using CH_2Cl_2/MeOH (1–5%).

4.2.1. 2-[4,7-Bis-dimethylcarbamoylmethyl-10-(4-methoxy-phenylsulfonyl)-1,4,7,10-tetraaza-cyclododec-1-yl]-*N*,*N*-dimethyl-acetamide (8). 600 mg was purified by

alumina column chromatography using 97:3, EtOAc/MeOH, to yield 320 mg of **8** as a pale yellow viscous oil. Calculated for $C_{27}H_{48}N_7O_6S$: [M+H peak] m/z=598.3387. Found: 598.3389; δ_H ($CDCl_3$, 400 MHz) 7.62 (d, J=9.0 Hz, 2H, Ar-H), 6.94 (d, J=9.0 Hz, 2H, Ar-H), 3.79 (s, 6H), 3.56 (m, 6H), 3.26 (m, 8H), 3.08–2.90 (m, 12H), 2.87–2.81 (m, 10H); δ_C ($CDCl_3$,100 MHz) 173.6, 169.3, 163.1, 129.4, 114.2, 55.3, 55.2, 54.5, 53.8, 53.6, 53.2, 51.1, 36.3, 36.1, 34.9; Mass Spec (MeOH, ES+) m/z expected: 597.78. Found: 598.4 (M+H), 620.6 (M+Na); IR ν_{max} (cm^{-1}) 3438, 2962, 2923, 2854, 1735, 1646, 1508, 1457, 1398, 1340, 1261, 1155, 1091, 1022, 867, 804, 701, 559, 474.

4.2.2. 2-[4-(4-Methoxy-phenylsulfonyl)-7,10-bis-methylcarbamoylmethyl-1,4,7,10-tetraaza-cyclododec-1-yl]-*N*-methyl-acetamide (9). 455 mg of **9** was produced as a viscous oil. Calculated for $C_{24}H_{42}N_7O_6S$: [M+H peak] m/z=556.2917. Found: 556.2906; δ_H ($CDCl_3$, 400 MHz); 7.91 (bs, 1H N–H), 7.72 (d, J=8.5 Hz, 2H), 7.63 (bs, 2H, N–H), 7.02 (d, J=9.0 Hz, 2H), 3.88 (s, 3H, OCH_3), 3.47 (s, 4H, CH_2), 3.42 (s, 2H, CH_2) 3.18 (bs, 8H, CH_2), 2.96 (s, 6H), 2.82 (m, 8H, CH_2), 2.08 (s, 3H); δ_C($CDCl_3$, 100 MHz) 171.5, 171.2, 129.4, 114.4, 58.51, 58.10, 55.58, 53.74, 53.33, 53.04, 49.46, 36.35, 31.31, 25.9, 25.8; Mass Spec (MeOH, ES+) m/z expected: 555.3. Found: 556.6, (M+H), 578.6 (M+Na); IR ν_{max} (cm^{-1}) 3421, 3077, 2925, 2854, 1654, 1596, 1542, 1457, 1409, 1338, 1261, 1155, 1093, 1022, 841, 840, 728, 698, 559.

The experimental results for **1** from Method 1 was identical to that obtained for Method 2, which has previously been reported.[19]

4.2.3. 2-(4,10-Bis-dimethylcarbamoylmethyl-1,4,7,10-tetraaza-cyclododec-1-yl)-*N*,*N*-dimethyl-acetamide (1). The ligand **8**, 0.39 g (0.70 mmol) was placed in a 100 mL 3 necked RBF. To this was added dry THF (30 mL) and ethanol (0.3 mL). This was attached to a cold finger condenser and the apparatus was placed into a dry ice/IPA bath where the temperature was dropped to −60 °C. Dry ice and IPA was also added to the condenser. Liquid NH_3 was added to the reaction vessel through the cold finger condenser (approximately 40 mL). Sodium metal (1.2 g, 0.05 mol) was added to this solution. The reaction was left stirring at −60 °C for 4 h during which time the yellow solution turned dark blue. The solution was allowed to warm up to room temperature and left stirring overnight. To this solution THF (20 mL) was added to dissolve the excess (unused) sodium present. Concentrated HCl was added until the solution was at pH 1 and then extracted with DCM. The pH of the solution was then adjusted to pH 14 using KOH pellets and then extracted with chloroform and reduced to yield the desired product. 100 mg (36% yield) of **1** was isolated as a clear residue. Calculated for $C_{20}H_{42}N_7O_3$:[M+H peak] m/z=428.3344. Found: 428.3349; δ_H($CDCl_3$, 400 MHz) 9.98 (broad s, 1H, N–H), 3.59 (s, 2H, CH_2–acetamide), 3.56 (s, 4H, CH_2–acetamide), 3.08 (s, 8H), 3.03 (s, 3H), 2.95 (s, 6H), 2.88 (s, 10H), 2.83 (s, 7H); δ_C($CDCl_3$, 100 MHz) 170.3, 170.2, 55.5, 53.8, 51.7, 50.6, 49.7, 46.7, 36.4, 35.3; Mass Spec (MeOH, ES+) m/z expected: 427.59. Found: 428.33 (M+H), 450.30 (M+Na), 472.30 (M+K); IR ν_{max}(cm^{-1}) 3434, 2927, 2852, 1637, 1508, 1475, 1402, 1338, 1261, 1103, 1064, 1022, 881, 806, 769, 667, 649, 574, 484.

4.2.4. 2-(4,10-Bis-methylcarbamoylmethyl-1,4,7,10-tetraaza-cyclododec-1-yl)-*N*-methyl-acetamide Eu(III) (Eu.2). 94.7 mg, (0.22 mmol) of **2** and 0.26 mmol of Eu(III) triflouromethane sulphonate [$Eu(SO_3CF_3)_3$] was added to a 25 mL single necked RBF which contained 10 mL of freshly dried acetonitrile. The solution was freeze thawed three times, placed under an argon atmosphere and left stirring at 82 °C for 24 h. The resulting solution was cooled to room temperature and then dropped slowly onto 100 mL of dry diethyl ether. The diethyl ether was poured off to leave **Eu.2** as oil that was washed with CH_2Cl_2 and dried under high vacuum. Yield >95%. Calculated for $C_{20}H_{35}N_7O_{12}F_9S_3Eu\cdot(H_2O)_2(CH_2Cl_2)_2$: C, 22.19; H, 3.64; N, 8.24. Found: C, 22.29; H, 3.74; N, 8.38. Calculated for $C_{17}H_{36}N_7O_3Eu$:[M+H peak] m/z=539.2092. Found: 539.2087. Calculated for $C_{18}H_{36}N_7O_6F_3SEu$:[M+H(Trif)] m/z=688.1612. Found: 688.1548. Calculated for $C_{19}H_{36}N_7O_9F_6S_2Eu$:[M+H(Trif)$_2$] m/z=837.1133. Found: 837.1181; δ_H(MeOD, 400 MHz) 27.04, 14.96, 11.44, 5.20, 3.68, 2.76, 2.41, 1.55, −0.09, −1.84, −4.93, −7.35, −10.77, −12.31, −16.66; δ_F(MeOD, 376 MHz) −80.45. Mass Spec (MeCN, ES+) m/z expected: 538.2. Found: 539.2 (M+H), 668.1 (M+H(Trif)), 837.1 (M+H(Trif)$_2$); IR ν_{max}(cm^{-1}) 3455, 3386, 3297, 3143, 3000, 2933, 2885, 1639, 1587, 1465, 1419, 1288, 1245, 1160, 1091, 1027, 725, 638, 576, 516.

4.3. X-ray crystallography

Data were collected on a Bruker SMART diffractometer with graphite monochromated Mo K_α radiation. A crystal was mounted on to the diffractometer at low temperature under dinitrogen at ca. 120 K. Cell parameters were obtained from 300 to 500 accurately centered reflections. ω/ϕ Scans were employed for data collection and Lorentz and polarisation corrections were applied.

The structure was solved using direct methods[26] and the non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen-atom positions were located from difference Fourier maps and fully refined. The function minimised was $\sum[w(|F_o|^2-|F_c|^2)]$ with reflection weights $w^{-1}=[\sigma^2|F_o|^2+(g_1P)^2+(g_2P)]$ where $P=[\max|F_o|^2+2|F_c|^2]/3$. Additional material available from the Cambridge Crystallographic Data Centre comprises relevant tables of atomic coordinates, bond lengths and angles, and thermal parameters Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDCC: copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

Acknowledgements

We thank Kinerton Ltd., Enterprise Ireland (Postgraduate Scholarships to SM and JPL), National Pharamaceutidal Biotechnology Center, Bio Research Ireland and Trinity

College Dublin for financial support. We thank Dr Steven Faulkner, Dr Hazel M. Moncrieff and Dr Brian Conerney for their helpful discussions, and Dr John E. O'Brien for assisting with running NMR.

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