Pergamon

Tetrahedron 56 (2000) 2043–2052

TETRAHEDRON

New Synthons for the Synthesis of Lanthanide Containing Macrocyclic Schiff Bases Featuring Substituents Available for Tethering

Arnaud Dumont, Vincent Jacques and Jean F. Desreux*

Coordination and Radiochemistry, University of Liège, Sart Tilman (B6), B-4000 Liège, Belgium

Received 22 July 1999; accepted 2 February 2000

Abstract—2,6-Diacetylpyridine substituted with amine or alcohol groups in the 4-position have been prepared from chelidamic acid. The key 4-chloro derivative was synthesized in high yield via a diazo intermediate and was protected as a bis-1,3-dioxane before substitution with various amino alcohol groups. Lanthanide macrocyclic tetra–imine complexes were obtained by a template procedure that leads to stable paramagnetic and/or fluorescent derivatives with anchor groups available for linkage to macromolecules.

Introduction

Over the last decade, the sustained research activity devoted to the lanthanide ions and their complexes has stemmed in part from the successful applications of these compounds in medicine and in biology. Because of its high magnetic moment and its long NMR relaxation times, gadolinium is currently used in hospitals to improve the contrast of magnetic resonance images (MRI).[1] Moreover, the long excited-state lifetimes of some lanthanides allow time-gated measurements of the luminescence of ions such as Eu^{3+} and Tb^{3+} without interferences from biological molecules. Time-resolved fluoroimmunoassays[2] are commonplace in laboratories and applications in cell sorting have been reported.[3] Finally, lanthanide ions are effective catalysts for the hydrolytic cleavage of RNA.[4] Catalysis becomes highly selective after coupling of a lanthanide to an antisense oligonucleotide.[5,6] All these applications require that the lanthanide ions be used as stable chelates and ligands featuring anchor groups are preferred to ensure that the metal ions always remain tethered to a biologically active macromolecule. In most cases, macrocyclic ligands are preferred to linear ligands because their metal complexes are usually more stable and kinetically more inert. A relatively small number of macrocyclic units are known to form sufficiently stable lanthanide derivatives. The 1,4,7,10-tetraazacyclododecane cycle has been substituted by carboxylic acid, alcohol or amide functions to obtain some of the most stable lanthanide chelates known.[1,7] Highly stable derivatives are also formed by pentadentate porphyrin-like ligands.[8] Finally, inert complexes have been obtained by template reactions leading to the formation of imine or hydrazone-type bonds around a central lanthanide ion in a macrocyclic unit.[6]

It is against this background that we decided to synthesize a series of synthons for the preparation of polyimine or poly-hydrazone macrocyclic complexes by a template reaction in the presence of a lanthanide ion. These synthons feature alcohol or amine substituents that are available for tethering as shown in Scheme 1 (letters a–h are used throughout with the same meaning). The corresponding lanthanide Schiff bases have also been prepared.

Results and Discussion

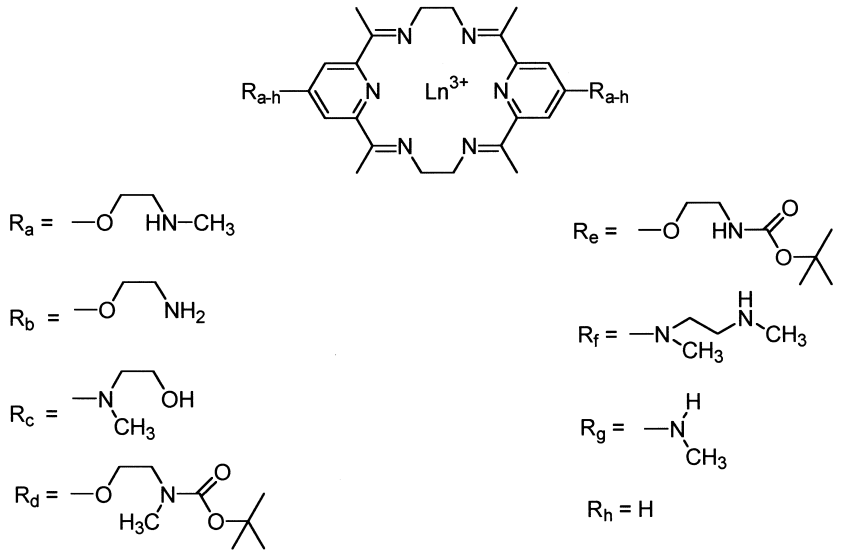
All the syntheses reported herein lead to synthons and hexaaza lanthanide complexes derived from 2,6-diacetyl-pyridine substituted in the 4 position. The synthesis and the chemistry of 4-substituted pyridine rings have been much less explored than that of the more accessible 2- or 3- substituted derivatives, but this molecular arrangement was preferred as it leads to only one isomer position in the final compounds. Moreover, the acetyl group was preferred to the 2,6-diformylpyridine moiety as it seems to form kinetically more inert lanthanide Schiff bases.[9]

The present work was first aimed at preparing a synthon with a simple methylamino function directly grafted onto the pyridine ring despite the risk that this substituent could be poorly reactive because of the electron-withdrawing character of the diacetylpyridine group. As indicated in

Keywords: imines; templates; lanthanides; amino ketones.

* Corresponding author. Tel.: +32-4-366-3501; fax: +32-4-366-4736; e-mail: jf.desreux@ulg.ac.be

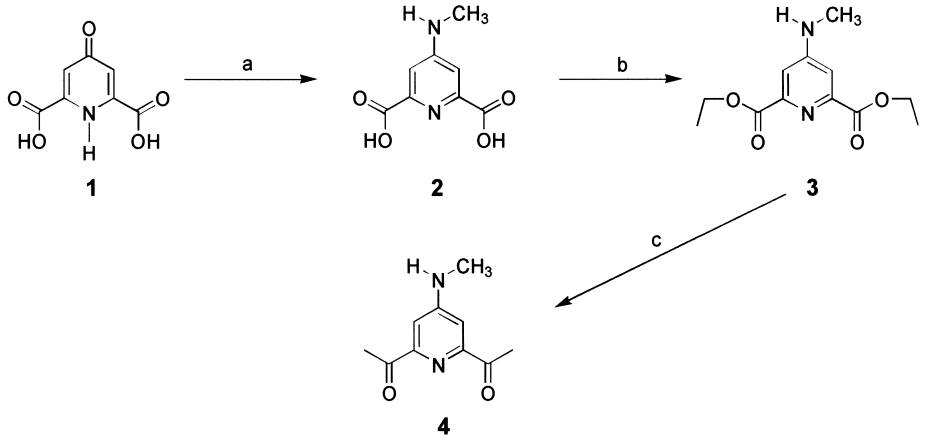
0040–4020/00/$ - see front matter
PII: S0040-4020(00)00104-6



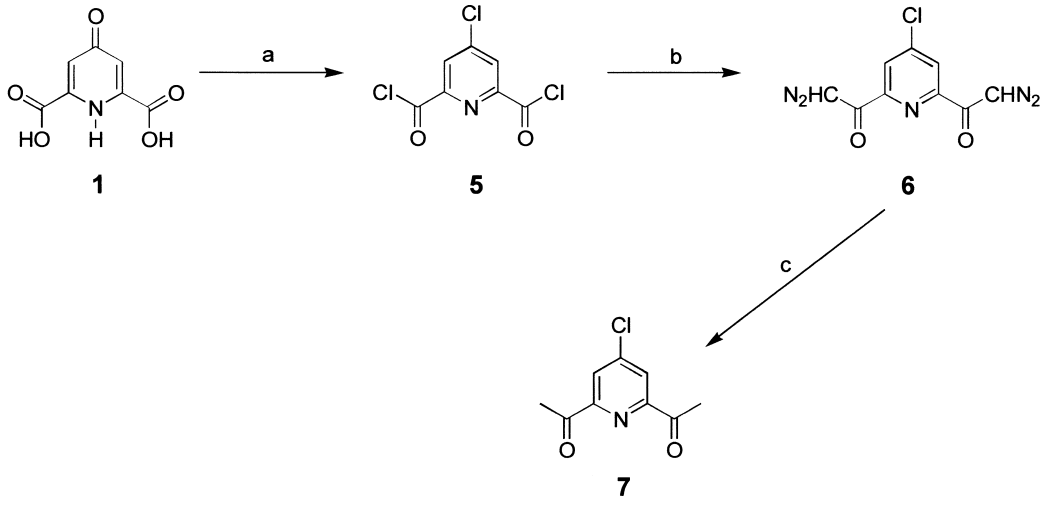
Scheme 1. Substituted polyimine lanthanide macrocyclic complexes.

Scheme 2, 4-(methylamino)pyridine-2,6-dicarboxylic acid, **2**, was obtained in high yields after heating an aqueous solution of methylamine and chelidamic acid, **1**, at 170°C in an autoclave according to a known procedure.[10] In our hands, the reaction gave a mixture of the sought compound and of the corresponding bis-*N*-methylamide, but a treatment with sodium peroxide directly on the reaction mixture transformed the bis-amide into the diacid **2**.

Pyridine mono- and dicarboxylic acids are known to form esters only with great difficulty[11] and the bis-ester **3** was synthesized by forming a silver salt of **2** that was reacted with ethyl iodide. This tedious but classical approach can be replaced in this particular case by a treatment with thionyl chloride and ethanol at the cost of a lower yield (68%) because the methylamino group is quite unreactive as will be shown below. The diketone **4** needed for the template reactions in the presence of a lanthanide ion was prepared by a Claisen condensation leading to the β-keto ester that was subsequently hydrolyzed. This procedure proved poorly reproducible and allowed only unsatisfactory yields (37% at best). Various other attempts at obtaining the β-keto ester intermediate in the Claisen condensation did not prove fruitful. For instance, using the dianion of acetic acid[12] led to the complete decomposition of the pyridine ring. Similarly, a reaction with the dimethylsulfoxide anion[13] followed by a treatment of the β-ketosulfoxide with a zinc amalgam caused a partial decomposition of diester **3**. Finally, treating ester **3** with methylmagnesium iodide and triethylamine[14] yielded the sought compound although in poor yield (18%). It should be noted here that the approach presented in Scheme 2 gives excellent results in the case of the diester of pyridine-2,6-dicarboxylic acid[15] but that similar difficulties have been reported recently.[16] The methylamino group of **3** is probably the site of side reactions that might be avoided after protection of its nitrogen atom. However, as feared, this group was found to be nearly totally unreactive toward substitution. Only 27% of the starting amine was reacted after 24 h in an excess of hot acetyl chloride. The diketone **4** and its derivatives are thus not suited for tethering to other molecules and it was desirable to find more reactive substituents and more practical synthetic schemes for the preparation of substituted diketo pyridines.



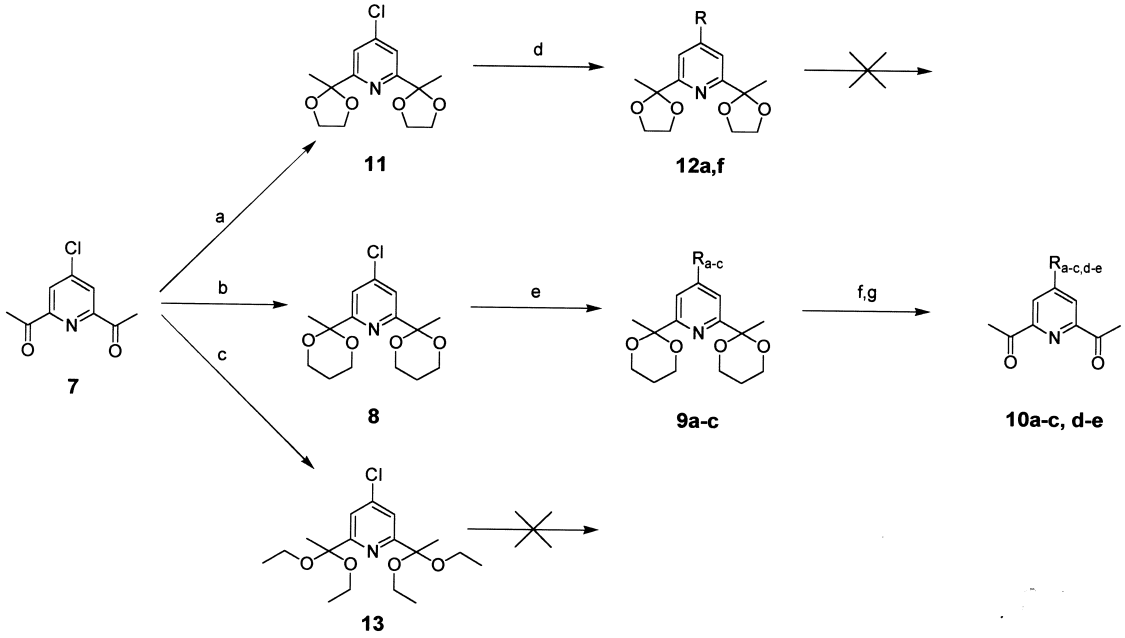
Scheme 2. (a) 1: CH_3NH_2, autoclave, 2: Na_2O_2 (85%); (b) i: NH_4OH, $AgNO_3$ (82%), ii: CH_3CH_2I, C_6H_6 (80%); (c) i: CH_3CH_2Ona, ethyl acetate, iii: HCl (35%).



Scheme 3. (a) $SOCl_2$, DMF (86%); (b) CH_2N_2 (68%); (c) HI (99%).

It was decided to use a protected derivative of 4-chloro-2,6-diacetylpyridine as the starting material for the synthesis of various synthons featuring aliphatic substituents in the 4 position. This approach appeared to have the advantage of versatility but it requested the selection of the proper protecting group and an effective route for the preparation of the diketone. As shown in Scheme 3, chelidamic acid, **1**, was reacted with thionyl chloride in the presence of dimethylformamide in order to avoid auto-quaternization reactions. This led to the acid dichloride **5** in better yield (86%) and more easily than with older procedures.[17,18] The acid dichloride **5** was transformed into the bis-diazoketone derivative **6** (yield 68%), which yielded quantitatively the sought diketone **7** by reaction with hydrogen iodide. Compound **7** was recently obtained[16] in 56% yield by reacting **5** with Meldrum's acid followed by an hydrolysis with aqueous acetic acid.

Scheme 3 proved extremely valuable in the present work. Pyridine tetraketones were also obtained in quantitative yields from the corresponding tetracarboxylic acids.[19] As shown in Scheme 4, adding an amino group on 4-chloro-2,6-diacetylpyridine, **7**, required the prior protection of the ketone groups to avoid formation of imines. Compound **7** was quantitatively converted into the corresponding bis-1,3-dioxolane derivative **11** by reaction with a large excess of 1,2-ethanediol. A high temperature (170°C) condensation of **11** with an excess of *N*,*N*′-dimethyl-1,2-diaminoethane in an autoclave allowed the substitution of the chlorine atom with an amino group in good yields (**12f**, 70%) but the



Scheme 4. (a) ethylene glycol, toluene, p-toluene sulfonic acid (99%); (b) 1,2-propanediol, toluene, p=sulfonic acid (90%); (c) ethyl orthoformate, EtOH (88%); (d) **12a**: CH_3–HN–CH_2–CH_2–OH (50%), **12f**: CH_3–NH–CH_2–CH_2–NH–CH_3(70%); (e) **9a**: NaH, HO–CH_2–CH_2–NH–CH_3, **9b**: NaH, HO–CH2–CH2–NH_2, **9c**: NaH, HO–CH_2–CH_2–NH–CH_3; (f) 2 M HCl **10a** (69%), **10b** (81%), **10c** (45%); (g) $(BOC)_2O$, MeOH, **10d** (97%), **10e** (98%).

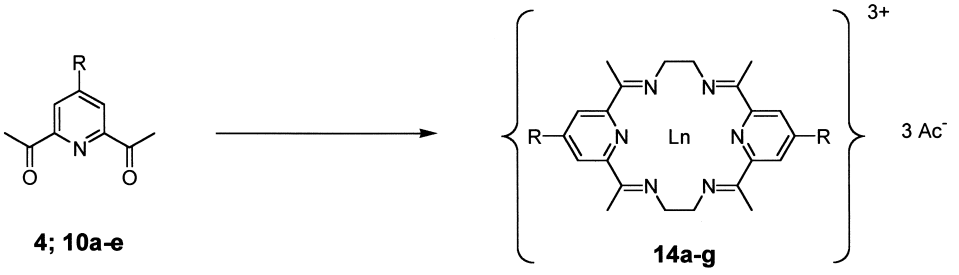
protecting dioxolane groups could not be removed with classical reagents such as silica gel, $MgSO_4$ or even concentrated acids at elevated temperature during several days. Transacetalization was also ineffective. Similarly, removing the dioxolane groups of 4-(2-(*N*-methylamino)ethoxy)-2,6-bis(2-methyl(1,3-dioxolan-2-yl))pyridine, **12a**, could only be performed with difficulty in 6 M HCl.[20] More easily removable protecting groups were obviously needed. The bis-1,3-dioxane **8** and the corresponding bis-ethyl ketal **13** were obtained respectively in 97% and 88% yields by eliminating water either with a Dean–Stark trap or with triethyl orthoformate. However, the substitution of these two compounds with *N*,*N*′-dimethyl-1,2-diaminoethane at elevated temperature in sealed glass tubes led only to their complete decomposition. The aminodiketones derived from **7** thus remained elusive either because the protecting group of the ketone functions could not be removed or because the secondary amine substituent could not be added to the pyridine ring without side reactions. In keeping with these difficulties, a few examples in the literature mention the inertness of the 1,3-dioxolane moiety especially in the presence of an amine function. For example, the deprotection of a piperidine dioxolane derivative required 6 h of reflux in a 6 M HCl solution.[15] The synthesis of **10a,b**, **d–e** with one oxygen atom directly bonded to the pyridine ring instead of one nitrogen atom was then attempted from **8**.

The protected chlorodiketal **8** was reacted in hot xylene with the sodium salt of 2-(methylamino)ethanol. The reaction led exclusively and in high yields to the formation of the 2-(methylamino)ethoxy group in **9a** (yield: 90% provided diketal **8** has been thoroughly purified). Xylene was preferred as a solvent over dimethylformamide as the yields were found to be higher. Hydrolysis of the ketal functions by 2 M HCl was complete within two days (yields: 88%). Compound **10a** can be kept unaltered during several weeks as a solid at 0°C but as expected, it degrades rapidly in solution. The methylamine function was easily protected with di-*tert*-butyl dicarbonate to prevent reactions between the ketone and amine groups (yield 97%). The *tert*-butoxycarbonyl group in **10d** was selected for the protection step since it is easily removed in mild conditions by trimethylsilyl iodide after the template reactions have been carried out as shown below. The diketone synthon **10e** derived from **10b** and featuring a protected primary amine function was prepared according to the strategy already used for **10d**. Very similar yields were achieved but the intermediate **10b** was used immediately without purification for the template synthesis of hexaaza lanthanide complexes.

For the preparation of the alcohol substituted **10c**, the diprotected chloropyridine diketone **8** was added to a xylene solution of 2-(methylamino)ethanol treated with two equivalents of sodium hydride. The amide anion exclusively reacts with **8** to give **9c**. However, the yield of this reaction did not exceed 50% and the separation of **8** and **9c** was not attempted. Instead, removal of the 1,3-dioxane groups was performed immediately with 2 M HCl with an overall yield of 45% in the final compound **10c** after purification. It should be noted here that an interesting comparison of the advantages and drawbacks of the ketal protecting groups can be made since a variety of protected derivatives have been synthesized in the present work. It appears that the removal of the ketal functions is less effective and requires longer reaction times and more drastic conditions if the side chains contain an amine group and/or if 1,3-dioxolane is the protecting group. Complete deprotection of **8** and **11** was achieved with 1 M HCl in less than 10 and 15 min respectively. About 2 days were needed when **9a–c** were treated with 2 M HCl and **12a** required 5 days in 6 M HCl to reach a 68% yield. Finally, **12f** could not be deprotected with 12 M HCl even after 5 days.

All lanthanide complexes **14a–g** were prepared in anhydrous methanol by refluxing during several hours stoichiometric amounts of a substituted diketone, of distilled 1,2-diaminoethane and of a lanthanide tris-acetate (see Scheme 5). Yields ranged between 70 and 90% depending on the lanthanide ion. As noted earlier,[21] the lanthanide complexes exhibit the unusual property of being soluble in water, methanol and chlorinated organic solvents such as chloroform. Cleavage of the *tert*-butoxycarbonyl protective groups of **14d,e** was achieved quantitatively with trimethylsilyl iodide in less than 45 min without any reaction with the ether functions. Iodide ions are liberated in this procedure and the hydrolysis of the trimethylsilyl iodide in excess by methanol produces hydrogen iodide. The acetate ions coordinated to the lanthanides are replaced by iodide ions and the amine groups are protonated. Complete replacement of the iodide ions by acetate ions was carried out by elution on a DOWEX 1×2 200 quaternary ammonium ion exchanger in the acetate form.

The formation of the lanthanide tetra–imine complexes **14a–f** is readily observed by various spectroscopic techniques. The assignment of the NMR peaks listed in the experimental section are based on the shifts and relative areas of the ^1H peaks and on COSY and ^{13}C–^1H correlation 2D spectra. Paramagnetic shifts are induced by lanthanide ions and are useful to unravel the solution structures



Scheme 5. 14c–g: 1,2-ethylenenediamine, lanthanide tris(acetate), MeOH (70–90%); **14a–b**:i: 1,2-ethylenediamine, lanthanide tris(acetate), MeOH (70–90%), ii: $(CH)_3SiI$, Dowex 1×2 200 in acetate form (97%).

provided the interactions between the ligand nuclei and the metal ions are of purely dipolar origin and provided all complexes are isostructural.[22] Previous analyses[23] of the spectra of unsubstituted lanthanide macrocyclic tetra–imine complexes **14h** and of cryptate and aza crown imines clearly showed that these two conditions are not met and we made no attempt at interpreting quantitatively the NMR spectra that were used only for identification purposes. Electrospray and fast atom bombardment mass spectra also clearly showed the formation of the lanthanide complexes. As expected, the ultra-violet peak with the highest wavelength undergoes a red-shift when amino groups are added to the unsubstituted Eu^{3+} complex **14f**: from $\lambda=303$ nm and $\epsilon=9200$ for **14e** to $\lambda=319$ nm and $\epsilon=16000$ for **14g** and to $\lambda=329$ nm and $\epsilon=18800$ for **14c**. Substitution with amino groups has a marked effect on the fluorescence intensity of the $^5D_0-^7F_2$ europium peak ($\lambda_{emission}=622$ nm) that also increases in the sequence **14e**, **14g**, **14c** with relative intensities <5, 79 and 126 and becomes very high in the presence of 4,4,4-trifluoro-1(2-thienyl)butane-1,3-dione (relative intensity 345–360 for all complexes).

In conclusion, we propose herein an approach for the synthesis of synthons featuring anchor groups from which stable macrocyclic polyimine or polyhydrazone lanthanide complexes can be prepared. These complexes feature amino or alcohol groups that can be linked to macromolecules by classical procedures. Derivatives with either one or two anchor groups are available depending on the approach selected for the synthesis of the macrocyclic unit, either a direct condensation between identical units as reported herein or a stepwise approach or a dihydrazone.[6] The synthesis of these new synthons required the careful selection of appropriate conditions and protecting groups but leads to macrocycles in high yields with no ambiguities due to regioisomers as found if the anchor groups are added to the $-CH_2-CH_2-$ side-chains of **14h**.[3]

Experimental

General

All solvents were dried using common techniques and all reactions were carried out under N_2. Chemicals were purchased from Aldrich Chemical Co and used without further purification. 4-Hydroxypyridine-2,6-dicarboxylic acid (chelidamic acid) was obtained from 4-oxo-4*H*-pyrane-2,6-dicarboxylic acid.[24] Melting points are uncorrected. Mass spectra were obtained on a Fisons VGA Platform (electrospray, ES) or a Fisons Autospec mass spectrometer (fast atom bombardment, FAB, in 3-nitrobenzyl alcohol, NOBA, or in glycerol). ^1H and ^{13}C one and two dimensional spectra (COSY, $^{13}C-^1H$ correlation) were acquired on a Bruker AM 400 spectrometer at 400 and 100.6 MHz, respectively as reported elsewhere.[25] Chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane. Splitting patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m).

4-(Methylamino)pyridine-2,6-dicarboxylic acid, 2. Chelidamic acid, **1**, (6 g, 30 mmol) was added to 50 mL of a 40% aqueous solution of methylamine. The reaction mixture was heated in an autoclave at 170°C during 24 h. After cooling to room temperature, the solvents were removed on a rotatory evaporator leaving a brown solid. This solid was dissolved in 40 mL of water and the solution was brought to boiling. Sodium peroxide was added cautiously until no basic vapor could be detected. The solution turned green during this process. The reaction mixture was cooled to 0°C and the pH was lowered to 2.5. The nearly white crystals which formed were collected by filtration, and washed with cold water. Yield: 85% (5 g, 25.5 mmol); mp 255–260°C (decomp., lit.[10] 245–255°). ^1H NMR (D_2O/NaOD): $\delta=2.91$ (s, 3 H, CH_3N), 7.22 (s, 2 H, Hpy); ^{13}C NMR (D_2O/NaOD): $\delta=31.34$, 110.61, 155.60, 159.46, 175.81; ES/MS (CH_3CN/H_2O 50/50): $m/z=197$ $(M+H)^+$, $m/z=195$ $(M-H)^-$. Anal calcd for $C_8H_8N_2O_4$: C, 48.98; H, 4.11; N, 14.28. Found: C, 48.87; H, 4.21; N, 14.33.

Diethyl 4-(methylamino)pyridine-2,6-dicarboxylate, 3. Compound **2** (4 g, 20 mmol) was dissolved in 40 mL of conc. ammonium hydroxide. The solution was brought to dryness in a rotatory evaporator and the remaining solid was dissolved in 200 mL of hot water. In a dark room, a solution of silver nitrate (10.4 g, 60 mmol) in 65 mL water was added under stirring. The solution was chilled in an ice bath to precipitate the silver salt of **2** that was collected by filtration, washed with ethanol and dried under vacuum. The silver salt and freshly distilled ethyl iodide (10.4 mL, 19.5 mmol) were added to 50 mL of dried benzene. The mixture was refluxed in the dark for 8 h. After cooling, the precipitated silver iodide was filtered off and washed with benzene. The filtrate and the washes were evaporated and the remaining yellow oil solidified after several days. Yield: 80% (4.0 g, 16 mmol); mp 61.3–62.7°C. ^1H NMR ($CDCl_3$): $\delta=1.39$ (t, $J=7.1$ Hz, 6 H, CH_3), 2.93 (d, $J=4.2$ Hz, 3 H, CH_3N), 4.40 (q, $J=7.1$ Hz, 4 H, CH_2O), 5.18 (broad, 1 H, NH), 7.39 (s, 2 H, Hpy); ^{13}C NMR ($CDCl_3$): $\delta=14.97$, 30.46, 66.35, 111.60, 149.71, 156.74, 162.94; ES/MS (CH_3CN/H_2O 50/50): $m/z=253$ $(M+H)^+$. Anal calcd for $C_{12}H_{16}N_2O_4$: C, 57.13; H, 6.39; N, 11.10. Found: C, 57.46; H, 6.48; N, 11.23.

4-(Methylamino)-2,6-diacetylpyridine, 4. The diester **3** (3.72 g, 15 mmol) and ethyl acetate (3.12 mL, 32 mmol) were added to 95 mL of xylene previously dried over CaH_2. The solution was added dropwise to 1.13 g (49 mmol) of freshly prepared solid sodium ethoxide. The reaction mixture was refluxed under nitrogen during 40 h. After cooling, conc. HCl (37 mL) and water (18 mL) were added and reflux was carried out for a total of 5 h with violent stirring. All solvents were eliminated under vacuum and 20 mL of conc. HCl in 4 mL of water were added to the remaining material. After refluxing the mixture for 5 h, the solution was brought to dryness, taken up with 25 mL of water and slowly basified with solid Na_2CO_3. The resulting precipitate was filtered, washed with water and dried under vacuum. Yield: 35% (1.0 g, 5.3 mmol); mp 147.2–148.6°C. ^1H NMR ($CDCl_3$): $\delta=2.71$ (s, 6 H, $CH_3C{=}O$), 2.93 (d, $J=4.9$ Hz, 3 H, CH_3N), 4.67 (broad, 1 H, NH), 7.30 (s, 2 H, Hpy); ^{13}C NMR ($CDCl_3$): $\delta=26.51$, 30.55, 108.23, 154.30, 156.52, 201.46; ES/MS (CH_3CN/H_2O 50/50): $m/z=193$ $(M+H)^+$.

4-Chloro-2,6-pyridinedicarboxylic dichloride, 5. Our procedure is adapted from the method of Robison[18] using thionyl chloride instead of phenylphosphonic dichloride. Thionyl chloride (10 mL) was added dropwise to 4 mL of dimethylformamide in a three-neck round-bottom flask equipped with a nitrogen inlet. After agitating the mixture briskly for 5 min, chelidamic acid, **1**, (2.01 g, 11 mmol) was slowly added in portions and agitation was maintained until complete dissolution. The reaction mixture was refluxed during 2 h. After cooling, the excess thionyl chloride was eliminated under vacuum. The remaining solid was dissolved in 10 mL of dry benzene and the solvent was removed by evaporation. This treatment was repeated twice to eliminate the last traces of thionyl chloride. The remaining orange paste was extracted four times with 25 mL of dry ethyl ether. The combined organic phases were brought to dryness yielding a beige solid that was used without any further purification. Yield 86% (2.25 g, 9.5 mmol). ^{1}H NMR ($CDCl_3$): δ=8.16 (s, 2 H, Hpy); ^{13}C NMR ($CDCl_3$): δ=123.58, 150.33, 157.91, 167.95.

4-Chloro-2,6-bis-(diazoacetyl)pyridine, 6. In an atmosphere of nitrogen, using predried glassware, 200 mL of dry diethyl ether containing approximately 3 g of diazomethane (71 mmol) were cooled to 0°C. A solution of **5** (2.25 g, 9.4 mmol) in 100 mL of dry diethyl ether was added dropwise. The reaction flask was agitated manually during the addition to disperse the thick yellow precipitate that formed rapidly. The reaction mixture was stirred manually during 1 h after completing the addition. The precipitate was collected by filtration and washed with 20 mL of ethyl ether. A second crop of the title compound was obtained by reducing the volume of the filtrate to 15 mL. The resulting pale yellow powder was dried under vacuum and kept in the absence of light. Yield: 68% (1.6 g, 6.4 mmol); mp 135–138°C (decomp.). ^{1}H NMR ($CDCl_3$): δ=6.58 (s, 2 H, CHN_2), 8.20 (s, 2 H, Hpy); ^{13}C NMR ($CDCl_3$): δ=55.19, 125.16, 148.26, 153.42, 184.17; FAB/MS (NOBA): m/z=250 $(M+H)^+$.

4-Chloro-2,6-diacetylpyridine, 7. A solution of **6** (1.6 g, 6.41 mmol) in 160 mL of dichloromethane was added dropwise to a briskly agitated mixture of 40 mL of dichloromethane and 10.8 g of a 47% aqueous solution of hydrogen iodide. Stirring was continued for a further 48 h whereupon the reaction mixture turned deep brown and then black. Water (80 mL) was added and the organic phase was decanted off. The aqueous phase was extracted four times with dichloromethane (40 mL). The combined organic phases were treated with a 10% aqueous solution of sodium thiosulfate, washed with water (50 mL), dried over $MgSO_4$ and brought to dryness in a rotatory evaporator at room temperature. The remaining yellow solid was dried under vacuum. Yield: 99% (1.26 g, 6.37 mmol); mp 72.8–74.2°C (lit.[16] 64°C). ^{1}H NMR ($CDCl_3$): δ=2.72 (s, 6 H, CH_3C=O), 8.10 (s, 2 H, Hpy); ^{13}C NMR ($CDCl_3$): δ=25.50, 124.80, 146.78, 153.77, 197.96; ES/MS (CH_3CN/H_2O 50/50): m/z=198 $(M+H)^+$. Anal calcd for $C_9H_8ClNO_2$: C, 54.70; H, 4.08; N, 7.09. Found: C, 54.72; H, 4.30; N, 7.18.

General procedure for the synthesis of 4-chloro-2,6-diacetylpyridine ketals

A solution of **7** (0.72 g, 3.6 mmol), the appropriate diol (54 mmol) and *p*-toluenesulfonic acid (40 mg) in 40 mL of toluene was refluxed under nitrogen for 50 h while eliminating water with a Dean–Stark trap. Evaporation of the solvent gave a yellow glassy solid. This solid was taken up with 5% aqueous sodium carbonate (10 mL). The resulting solution was extracted with dichloromethane (3×20 mL). After drying ($MgSO_4$), the organic solution was evaporated to yield a 4-chloro-2,6-diacetyl ketal that was purified by column chromatography (silica kept overnight in ethyl acetate, dichloromethane/methanol 98:2).

4-Chloro-2,6-bis(2-methyl-(1,3-dioxan-2-yl))pyridine, 8. Yield: 90% (1.04 g, 3.24 mmol); mp 93.1–94.7°C. ^{1}H NMR ($CDCl_3$): δ 1.37 (m, 2 H, CH_2), 1.54 (s, 6 H, CH_3CO_2), 2.04 (m, 2 H, CH_2), 3.75 (m, 4 H, CH_2O), 3.94 (m, like d of t), 4 H, CH_2O), 7.46 (s, 2 H, Hpy); ^{13}C NMR ($CDCl_3$): δ=25.04, 28.51, 61.28, 99.71, 120.95, 145.23, 162.21; ES/MS (CH_3CN/H_2O 50/50): m/z=314 $(M+H)^+$. Anal calcd for $C_{15}H_{20}ClNO_4$: C, 57.42; H, 6.42; N, 4.46. Found: C, 57.44; H, 6.40; N, 4.51.

4-Chloro-2,6-bis(2-methyl-(1,3-dioxolan-2-yl))pyridine, 11. Yield: 99%, (1.02 g, 3.56 mmol); oil. ^{1}H NMR ($CDCl_3$): δ=1.71 (s, 6 H, CH_3CO_2), 3.90 (m, 4 H, CH_2O), 4.06 (m, 4 H, CH_2O), 7.46 (s, 2 H, Hpy); ^{13}C NMR ($CDCl_3$): δ=25.39, 65.90, 109.05, 119.94, 145.72, 163.06; ES/MS (CH_3CN/H_2O 50/50): m/z=286 $(M+H)^+$. Anal calcd for $C_{13}H_{16}ClNO_4$: C, 54.65; H, 5.64; N, 4.90. Found: C, 54.48; H, 5.71; N, 4.88.

4-Chloro-2,6-bis(1,1-diethoxyethyl)pyridine, 13. 4-Chloro-2,6-diacetylpyridine, **7**, (0.2 g, 1 mmol), triethyl orthoformate (1.6 mL, 10 mmol) and 10 mg of *p*-toluenesulfonic acid were added to 2 mL of ethanol. The reaction mixture was refluxed under nitrogen during 20 h. The solvent was eliminated under vacuum and the remaining yellow oil was triturated with 10 mL of a 5% Na_2CO_3 aqueous solution. The mixture was extracted with 3×20 mL of dichloromethane. The organic extracts were dried over $MgSO_4$, the solvent was evaporated and the remaining viscous oil was dried in vacuum at 80°C. Yield: 88% (0.3 g, 0.88 mmol). ^{1}H NMR ($CDCl_3$): δ=1.16 (t, J=7 Hz, 12 H, CH_3), 1.62 (s, 6 H, CH_3CO_2), 3.29 (m, 4 H, CH_2O), 3.48 (m, 4 H, CH_2O), 7.61 (s, 2 H, Hpy); ^{13}C NMR ($CDCl_3$): δ=16.09, 25.09, 57.75, 112.19, 121.42, 144.78, 163.01; ES/MS (CH_3CN/H_2O 50/50): m/z=346 $(M+H)^+$.

General procedure for the synthesis of 4-substituted-2,6-diacetylpyridines

With a glass syringe, the appropriate aminoalcohol or diol (previously dried over KOH and distilled under vacuum) was added under nitrogen to a vigorously stirred suspension of sodium hydride in dry xylene. A solution of **8** or **11** in dry xylene was added into the reaction flask once the evolution of hydrogen had ceased. The resulting brown mixture was refluxed overnight. As determined from the 400 MHz ^{1}H NMR spectrum, the reaction solution consisted of a mixture of the starting material and of the 4-substituted ketal. No purification of the substituted ketal was attempted. The solvent was immediately evaporated and the residue was dissolved in dichloromethane. A 2 M HCl aqueous solution (about 15 mL) was added and stirring was continued during

48 h. The organic phase was decanted and the aqueous phase was extracted with dichloromethane (15 mL). The unreacted **8** was totally found in the organic extract. The aqueous phase was basified with 2 M NaOH and extracted with dichloromethane (3×15 mL). The combined organic layers were washed with water and dried over sodium sulfate. The solvent was eliminated and the remaining solid was dried under vacuum.

4-(2-(*N*-methylamino)ethoxy)-2,6-bis(2-methyl-(1,3-dioxan-2-yl))pyridine, 9a, and 4-(2-(*N*-methylamino) ethoxy)-2,6-diacetylpyridine, 10a. Following the procedure described above and starting from sodium hydride (69 mg, 1.72 mmol in 10 mL of xylene), 2-(methylamino)-ethanol (0.17 mL, 2.13 mmol) and **8** (0.45 g, 1.43 mmol in 25 mL of xylene), there was obtained a 1:12 mixture of the starting material **8** and of **9a**. The crude **9a** was deprotected and after work-up, **10a** was obtained as a pale beige powder (0.27 g, 1.13 mmol, 69%), mp 138.1–140.3°C; ^{1}H NMR ($CDCl_3$): 2.37 (s, 3 H, CH_3N), 2.61 (s, 6 H, $CH_3C{=}O$), 2.89 (t, J=5.1 Hz, 2 H, CH_2N), 4.09 (t, J=5.1 Hz, 2 H, CH_2O), 7.54 (s, 2 H, Hpy); ^{13}C NMR ($CDCl_3$): δ=26.35, 37.01, 50.85, 68.79, 111.47, 155.22, 167.45, 199.92; ES/MS (CH_3CN/H_2O 50/50): m/z=237 $(M+H)^+$. Anal calcd for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86. Found: C, 60.73; H, 6.80; N, 11.69.

4-(2-Aminoethoxy)-2,6-bis(2-methyl-(1,3-dioxan-2-yl))-pyridine, 9b, and 4-(2-aminoethoxy)-2,6- diacetylpyridine, 10b. Following the procedure described above and starting from sodium hydride (145 mg, 3.62 mmol in 10 mL of xylene), 2-aminoethanol (0.28 mL, 4.6 mmol) and **8** (0.95 g, 3.03 mmol in 25 mL of xylene), a 1:9 mixture of the starting material and of **9b** was isolated. The crude **9b** was deprotected and after work-up, **10b** was obtained as a straw-yellow powder that was used immediately for the synthesis of lanthanide complexes. Yield: 81% (0.55 g, 2.45 mmol), mp 87.1–89.3°C. ^{1}H NMR ($CDCl_3$): δ=2.69 (s, 6 H, $CH_3C{=}O$), 3.07 (t, J=5.2 Hz, 2 H, CH_2N), 4.03 (t, J=5.2 Hz, 2 H, CH_2O), 7.63 (s, 2 H, Hpy); ^{13}C NMR ($CDCl_3$): δ=26.43, 41.80, 71.82, 111.62, 156.72, 167.23, 199.32; ES/MS (CH_3CN/H_2O 50/50): m/z=223 $(M+H)^+$.

4-(*N*-hydroxyethyl-*N*-methylamino)-2,6-bis(2-methyl-(1,3-dioxan-2-yl))pyridine, 9c, and 4-(*N*-hydroxyethyl-*N*-methylamino)-2,6-diacetylpyridine, 10c. The synthesis of **10c** was carried out following the procedure described above using 2-(methylamino)ethanol (0.34 g, 4.45 mmol), NaH (0.39 g, 9.8 mmol) suspended in 10 mL of xylene and **8** (1.4 g, 4.46 mmol) in 30 mL of xylene. An approximately 1:1 mixture of **8** and **9c** was obtained after refluxing overnight. Deprotection of crude **9c** to obtain **10c** was performed with 15 mL of 2 M HCl at room temperature during 40 h. A pale yellow solid was isolated. Yield: 45% (2 mmol, 0.47 g), mp 99.3–100.2°C. ^{1}H NMR ($CDCl_3$): δ=2.65 (s, 6 H, $CH_3C{=}O$), 3.08 (s, 3 H, CH_3N), 3.58 (t, J=4.8 Hz, 2 H, CH_2N), 3.80 (t, J=4.8 Hz, 2 H, CH_2O), 7.6 (s, 2 H, Hpy); ^{13}C NMR ($CDCl_3$): δ=26.43, 39.32, 54.35, 60.43, 107.55, 154.11, 155.99, 201.74; ES/MS (CH_3CN/H_2O 50/50): m/z=237 $(M+H)^+$. Anal calcd for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86. Found: C, 60.82; H, 6.94; N, 12.12.

4-(2-(*N*-methylamino)ethoxy)-2,6-bis(2-methyl-(1,3-dioxolan-2-yl))pyridine, 12a. As described above, freshly distilled 2-(methylamino)ethanol (113 mg, 1.5 mmol) was reacted with NaH (48 mg, 1.2 mmol) in 8 mL of dried xylene and **11** (0.29 g, 1 mmol) dissolved in 15 mL of xylene was added to the reaction mixture. After refluxing overnight and elimination of the solvent, 15 mL of water were added and **12a** was isolated by extraction with 3×15 mL of dichloromethane. Yield: 50% (160 mg, 49.3 mmol), light brown oil. ^{1}H NMR ($CDCl_3$): δ=1.69 (s, 6 H, CH_3CO_2), 2.46 (s, 3 H, CH_3N), 2.95 (t, J=5.1 Hz, 2 H, CH_2N), 3.89 (m, 4 H, CH_2O), 4.02 (m, 4 H, CH_2O), 4.09 (t, J=5.1 Hz, 2 H), 6.97 (s, 2 H, Hpy); ^{13}C NMR ($CDCl_3$): δ=25.26, 37.07, 51.23, 65.78, 68.04, 105.79, 109.36, 162.95, 166.31; ES/MS (CH_3CN/H_2O 50/50): m/z=325 $(M+H)^+$. Anal calcd for $C_{16}H_{24}N_2O_5$: C, 59.24; H, 7.46; N, 8.64. Found: C, 59.05; H, 7.60; N, 8.82.

4-(2-(*N*-methylamino)ethylamino)-2,6-bis(2-methyl-(1,3-dioxolan-2-yl))pyridine, 12f. Following the procedure described above and starting from sodium hydride (48 mg, 1.2 mmol in 8 mL of xylene), *N*,*N*′-dimethyl-ethylenediamine (0.11 g, 1.2 mmol) and **11** (0.29 g, 1.0 mmol in 15 mL of xylene), a 1:16 mixture of the starting material and of **12f** was isolated. The mixture was taken up in 10 mL of ethyl acetate, the insoluble material was discarded and the solvent was evaporated under vacuum. Yield: 70% (0.24 g, 0.7 mmol); brownish oil. ^{1}H NMR ($CDCl_3$): δ=1.77 (s, 6H, CH_3CO_2), 2.51 (s, 3H, CH_3N), 2.85 (t, J=7.3 Hz, 2H, CH_2N), 3.08 (s, 3H, CH_3Npy), 3.62 (t, J=7.3 Hz, 2H, CH_2Npy), 3.95 (m, 4H, CH_2O), 4.11 (m, 4H, CH_2O), 6.81 (s, 2H, Hpy); ^{13}C NMR ($CDCl_3$): δ=25.60, 37.19, 38.82, 49.68, 52.08, 65.37, 101.64, 109.55, 152.98, 161.45; ES/MS (CH_3CN/H_2O 50/50): m/z=339 $(M+H)^+$. Anal calcd for $C_{17}H_{27}N_3O_4$: C, 60.51; H, 8.07; N, 12.45. Found: C, 60.55; H, 7.96; N, 12.52.

General procedure for the protection of the amino group of 4-substituted 2,6-diacetyl pyridines

A solution of the appropriate 4-substituted 2,6-diacetylpyridine (1 mmol) and di-*tert*-butyl dicarbonate (0.24 g, 1.1 mmol) in methanol (10 mL) was stirred overnight at room temperature. The reaction mixture was evaporated and the remaining solid was dissolved in 10 mL of water. The aqueous solution was extracted with dichloromethane (3×10 mL). The organic phases were collected and dried over $MgSO_4$. The solvent was eliminated and the remaining oil was dried under vacuum.

4-(2-(*N*-(*t*-butoxycarbonyl)-*N*-methylamino)ethoxy)-2,6-diacetylpyridine, 10d. Pale yellow vitreous solid; yield 97% (0.33 g, 0.97 mmol). ^{1}H NMR ($CDCl_3$): δ=1.39 (s, 9 H, CH_3t-Bu), 2.69 (s, 6 H, $CH_3C{=}O$), 2.91 (s, 3 H, CH_3N), 3.58 (t, J=5.5 Hz, 2 H, CH_2N), 4.19 (broad t, 2 H, CH_2O), 7.62 (s, 2 H, Hpy); ^{13}C NMR ($CDCl_3$): δ=26.35, 29.16, 36.23, 48.74, 69.10, 80.67, 111.54, 155.48, 167.37, 199.97; ES/MS (CH_3CN/H_2O 50/50): m/z=337 $(M+H)^+$. Anal calcd for $C_{17}H_{24}N_2O_5$: C, 60.70; H, 7.19; N, 8.33. Found: C, 60.53; H, 7.17; N, 8.16.

4-(2-(*N*-(*t*-butoxycarbonyl)-amino)ethoxy)-2,6-diacetylpyridine, 10e. Pale yellow vitreous solid; yield 98% (0.32 g, 0.98 mmol). ^{1}H NMR ($CDCl_3$): δ=1.39 (s, 9 H, CH_3*t*-Bu), 2.68 (s, 6 H, CH_3C=O), 3.56 (m, 2 H, CH_2N), 4.04 (t, *J*=5.1 Hz, 2 H, CH_2O), 5.14 (broad, 1H, NH), 7.61 (s, 2 H, Hpy); ^{13}C NMR ($CDCl_3$): δ=26.39, 29.22, 39.42, 68.73, 80.03, 111.56, 155.41, 167.12, 199.95; ES/MS (CH_3CN/H_2O 50/50): *m*/*z*=323 $(M+H)^{+\cdot}$ Anal calcd for $C_{16}H_{22}N_2O_5$: C, 59.61; H, 6.88; N, 8.69. Found: C, 59.72; H, 6.70; N, 8.54.

General procedure for the synthesis of lanthanide complexes

The appropriate substituted 2,6-diacetylpyridine **4** or **10c–e** (1 mmol) and a lanthanide acetate (0.55 mmol) were dissolved in absolute methanol (25 mL). A solution of distilled 1,2-diaminoethane (60 mg, 1.07 mmol) was added dropwise and the reaction mixture was refluxed for 20 h. The resulting yellow solution was brought to dryness in a rotavapor and the remaining pink solid was dissolved in dichloromethane (3 mL). The slightly cloudy solution was clarified by filtration on glasswool and ethyl ether (about 100 mL) was added dropwise under stirring. The solution was filtered through sintered glass with an ethyl ether wash and the collected solid was dried under vacuum. The lanthanide complexes featuring amine functions protected with Boc groups (1 mmol) were placed in a reaction flask equipped with a septum and thoroughly flushed with argon. The solid was dissolved in 60 mL of dichloromethane previously dried over CaH_2 and 0.86 mL (6 mmol) of iodotrimethylsilane were added dropwise with a syringe. A precipitate formed immediately. After stirring during 45 min, methanol (10 mL) was added. The solvents were evaporated in a rotavapor and the remaining solid was stirred with 10 mL of dichloromethane during 15 min. The precipitate was collected by filtration and washed with a few mL of dichloromethane. Elemental analyses, ES/MS and NMR spectra indicated that the complexes were obtained as iodide salts. The corresponding acetate salts were obtained by an ion-exchange procedure. A 14 mL glass column was filled with a DOWEX 1×2 200 resin (14 mL) in the acetate form. The resin was thoroughly washed with methanol and a solution of the metal complex (in 2 mL methanol) was passed onto the column. Elution with methanol (40 mL) and evaporation of the solvent afforded a solid material that did not form a precipitate upon the addition of $AgNO_3$.

Lanthanide 10,21-bis-(2-(*N*-methylamino)ethoxy)-2,7,13,18-tetramethyl-3,6,14,17,23,24-hexaazatricyclo[17.3.1.1^{8,12}]-tetracosa-1(22),2,6,8,10,12(24),13,17,19(23),20-decaene triacetate, 14a. Lanthanum complex: brown solid, yield: 98% (0.36 g, 0.44 mmol); mp 143.3–145.9°C. ^{1}H NMR (CD_3OD): δ=1.87 (s, 9 H, CH_3COO), 2.65 (s, 12 H, CH_3C=N), 2.81 (s, 6 H, CH_3N), 3.53 (t, *J*=4.9 Hz, 4 H, CH_2N), 4.09 (s, 8 H, CH_2N=C), 4.67 (t, *J*=4.9 Hz, 4 H, CH_2O), 7.84 (s, 4 H, Hpy); ^{13}C NMR (CD_3OD): δ=16.72 (CH_3C=N), 23.94 (CH_3COO), 34.59 (CH_3N), 39.01 (CH_2N), 54.18 (CH_2N=C), 67.13 (CH_2O), 114.32 (β-py), 158.74 (α-py), 169.92 (C=N imine), 172.16 (γ-py), 182.63 (CH_3COO); ES/MS (CH_3CN/H_2O 50/50): *m*/*z*=777 $(M-CH_3COO)^+$, 359 $(M-2CH_3COO)^{++}$/2; FAB/MS (NOBA): *m*/*z*=990 $(M+NOBA+H)^+$, 884, 824.

Europium complex: brown vitreous solid, yield: 98% (0.35 g, 0.41 mmol). ^{1}H NMR (CD_3OD): δ=−2.13 (s, 8 H, CH_2N=C), 2.50 (s, 6 H, CH_3N), 3.02 (broad t, 4 H, CH_2N), 3.11 (s, 12 H, CH_3C=N), 3.76 (s, 4 H, Hpy), 3.88 (broad t, 4 H, CH_2O), 8.40 (broad s, 9 H, CH_3COO); ^{13}C NMR (CD_3OD): δ=−20.91 (CH_3C=N), 0.5 (very broad, CH_3COO), 33.90 (CH_3N), 48.66 (CH_2N=C), 52.31 (CH_2N), 65.52 (CH_2O), 85.36 (β-py), 129.64, 158.39, 174.82; ES/MS (CH_3CN/H_2O 50/50): *m*/*z*=789 $(M-CH_3COO)^+$, 365 $(M-2CH_3COO)^{++}$/2; FAB/MS (NOBA): *m*/*z*=1002 $(M+NOBA+H)^+$, 789 $(M-CH_3COO)^+$, 896, 731.

Lanthanide 10,21-bis-(2-aminoethoxy)-2,7,13,18-tetramethyl-3,6,14,17,23,24-hexaazatricyclo[17.3.1.1^{8,12}]-tetracosa-1(22),2,6,8,10,12(24),13,17,19(23),20-decaene triacetate, 14b. Lanthanum complex: brown solid, yield: 97% (0.33 g, 0.40 mmol); mp 128.3–130.2°C. ^{1}H NMR (CD_3OD): δ=1.86 (s, 9 H, CH_3COO), 2.65 (s, 12 H, CH_3C=N), 3.48 (t, *J*=4.9 Hz, 4 H, CH_2N), 4.09 (s, 8 H, CH_2N=C), 4.53 (t, *J*=4.9 Hz, 4 H, CH_2O), 7.84 (s, 4 H, Hpy); ^{13}C NMR (CD_3OD): δ=16.78 (CH_3C=N), 24.21 (CH_3COO), 40.22 (CH_2N), 54.21 (CH_2N=C), 67.94 (CH_2O), 114.34 (β-py), 158.72 (α-py), 170.03 (C=N imine), 172.20 (γ-py), 183.05 (C=O acetate). ES/MS (CH_3CN/H_2O 50/50): *m*/*z*=749 $(M-CH_3COO)^+$, 345 $(M-2CH_3COO)^{++}$/2. FAB/MS (NOBA): *m*/*z*=962 $(M+NOBA+H)^+$, 749 $(M-CH_3COO)^+$, 856, 796, 689.

Lanthanide 10,21-bis-(*N*-hydroxyethyl-*N*-methylamino)-2,7,13,18-tetramethyl-3,6,14,17,23,24-hexaazatricyclo-[17.3.1.1^{8,12}]tetracosa-1(22),2,6,8,10,12(24),13,17,19(23),20-decaene triacetate, 14c. Lanthanum complex: off white solid, yield: 81% (0.34 g, 0.41 mmol); mp 237–240°C (decomp.). ^{1}H NMR ($CDCl_3$): δ=1.61 (s, 9 H, CH_3COO), 2.40 (s, 12 H, CH_3C=N), 3.07 (s, 6 H, CH_3N), 3.62 (t, *J*=4.7 Hz, 4 H, CH_2N), 3.70 (t, *J*=4.7 Hz, 4 H, CH_2O), 3.89 (s, 8 H, CH_2N=C), 7.09 (s, 4 H, Hpy); ^{13}C NMR ($CDCl_3$): δ=15.94 (CH_3C=N), 24.14 (CH_3COO), 38.03 (CH_3N), 52.31 (CH_2N), 54.11 (CH_2N=C), 58.27 (CH_2O), 107.69 (β-py), 155.16 (α-py), 156.65 (γ-py), 169.72 (C=N imine), 183.36 (C=O acetate); ES/MS (CH_3CN/H_2O 50/50): *m*/*z*=777 $(M-CH_3COO)^+$, 359 $(M-2CH_3COO)^{++}$/2; FAB/MS (NOBA): *m*/*z*=990 $(M+NOBA+H)^+$, 777 $(M-CH_3COO)^+$.

Europium complex: straw yellow solid, yield: 96% (0.41 g, 0.48 mmol); mp 372–380°C (decomp). ^{1}H NMR (D_2O): δ=−5.78 (s, 8 H, CH_2N=C), −0.29 (s, 12 H, CH_3C=N), 1.94 (s, 6 H, CH_3N), 2.39 (broad t, 4 H, CH_2N), 2.94 (broad s, 4 H, CH_2O), 3.20 (s, 4 H, Hpy), 8.9 (broad s, 9 H, CH_3COO); ^{13}C NMR (D_2O): δ=−21.37 (CH_3C=N), 3 (broad, CH_3COO), 37.57 (CH_3N), 41.77 (CH_2N=C), 52.96 (CH_2N), 60.95 (CH_2O), 74.97 (β-py), 104.15, 118.76, 148.76, 159.40; ES/MS (CH_3CN/H_2O 50/50): *m*/*z*=789 $(M-CH_3COO)^+$, 365 $(M-2CH_3COO)^{++}$/2; FAB/MS (NOBA): *m*/*z*=1002 $(M+NOBA+H)^+$.

Lanthanide 10,21-bis-(2-*N*-(*t*-butoxycarbonyl)-*N*-methylamino)ethoxy)-2,7,13,18-tetramethyl-3,6,14,17,23,24-hexaazatricyclo[17.3.1.1^{8,12}]tetracosa-1(22),2,6,8,10,

12(24),13,17,19(23),20-decaene triacetate, 14d. Lanthanum complex: pale pink solid, yield: 90% (0.47 g, 0.45 mmol); mp 108.2–112°C (decomp.). ^{1}H NMR ($CDCl_3$): δ=1.43 (s, 18 H, CH_3*t*-Bu), 1.67 (s, 9 H, CH_3COO), 2.52 (s, 12 H, CH_3C=N), 2.95 (s, 6 H, CH_3N), 3.56 (broad t, 4 H, CH_2N), 4.02 (s, 8 H, CH_2N=C), 4.38 (broad t, 4 H, CH_2O), 7.58 (broad s, 4 H, Hpy); ^{13}C NMR ($CDCl_3$): δ=17.22 (CH_3C=N), 25.02 (CH_3COO), 28.99 (CH_3*t*-Bu), 38.14 (CH_3N), 48.46 (CH_2N), 53.43 (CH_2N=C), 68.22 (CH_2O), 80.38 (C*t*-Bu), 113.14 (β-py), 156.65 (NC=O carbamate), 157.52 (α-py), 169.45 (C=N imine), 170.03 (γ-py), 183.11 (C=O acetate). ES/MS (CH_3CN/H_2O 50/50): *m*/*z*=977 $(M-CH_3COO)^+$, 459 $(M-2CH_3COO)^{++}/2$. FAB/MS (NOBA): *m*/*z*=1190 $(M+NOBA+H)^+$.

Europium complex: pale pink solid, yield: 85% (0.45 g, 0.43 mmol); mp 121.6–124.2°C (decomp). ^{1}H NMR ($CDCl_3$): δ=1.15 (broad s, 9 H, CH_3COO), 1.40 (broad s, 30 H, CH_3*t*-Bu and CH_3C=N), 2.83 (s, 6 H, CH_3N), 3.42 (broad t, 4 H, CH_2N), 4.28 (broad t, 4 H, CH_2O), 4.98 (s, 8 H, CH_2N=C), 5.91 (s, 4 H, Hpy); ^{13}C NMR ($CDCl_3$): δ=−17.60 (CH_3C=N), −0.2 (broad, CH_3COO), 28.15 (CH_3C*t*-Bu), 35.65 (CH_3N), 46.99 (CH_2N=C), 57.68 (CH_2N), 66.34 (CH_2O), 78.80 (C*t*-Bu), 75.71 (β-py), 134.63, 155.12, 162.47, 174.74; ES/MS (CH_3CN/H_2O 50/50): *m*/*z*=989 $(M-CH_3COO)^+$, 465 $(M-2CH_3COO)^{++}/2$. FAB/MS (NOBA): *m*/*z*=1203 $(M+NOBA+H)^+$, 989 $(M-CH_3COO)^+$.

Lanthanide 10,21-bis-(2-(*N*-(*t*-butoxycarbonyl)-amino)-ethoxy)-2,7,13,18-tetramethyl-3,6,14,17,23,24-hexaaza-tricyclo[17.3.1.1^{8,12}]tetracosa-1(22),2,6,8,10,12(24),13,17,19(23),20-decaene triacetate, 14e. Lanthanum complex: rosy solid, yield: 85%, (0.43 g, 0.43 mmol); mp 126.6–128.9°C (decomp.). ^{1}H NMR ($CDCl_3$): δ=1.39 (s, 18 H, CH_3*t*-Bu), 1.64 (s, 9 H, CH_3COO), 2.53 (s, 12 H, CH_3C=N), 3.53 (m, 4 H, CH_2N), 4.00 (s, 8 H, CH_2N=C), 4.40 (t, *J*=5.8 Hz, 4 H, CH_2O), 6.19 (broad, 2 H, NH), 7.62 (s, 4 H, Hpy); ^{13}C NMR ($CDCl_3$): δ=16.43 (CH_3C=N), 24.30 (CH_3COO), 29.19 (CH_3C*t*-Bu), 39.98 (CH_2N), 53.55 (CH_2N=C), 68.91 (CH_2O), 80.46 (C*t*-Bu), 113.60 (β-py), 156.64 (NC=O carbamate), 157.63 (α-py), 169.54 (C=N imine), 170.20 (γ-py), 183.06 (C=O acetate). ES/MS (CH_3CN/H_2O 50/50): *m*/*z*=949 $(M-CH_3COO)^+$, 445 $(M-2CH_3COO)^{++}/2$. FAB/MS (NOBA): *m*/*z*=1162 $(M+NOBA+H)^+$, 996.

Lanthanide 10,21-bis-(*N*-methylamino)-2,7,13,18-tetra-methyl-3,6,14,17,23,24-hexa-azatricyclo[17.3.1.1^{8,12}]-tetracosa-1(22),2,6,8,10,12(24),13,17,19(23),20-decaene triacetate, 14g. Lanthanum complex: beige solid, yield: 86% (0.32 g, 0.43 mmol); mp 229.5–232°C. ^{1}H NMR ($CDCl_3$): δ=1.70 (s, 9 H, CH_3COO), 2.39 (s, 12 H, CH_3C=N), 2.88 (d, *J*=4 Hz, 6 H, CH_3N), 3.93 (s, 8 H, CH_2N=C), 7.20 (s, 4 H, Hpy), 8.41 (broad, 2 H, NH); ^{13}C NMR ($CDCl_3$): δ=17.87 (CH_3C=N), 26.25 (CH_3COO), 30.94 (CH_3N), 54.26 (CH_2N), 126.11 (β-py), 154.12 (α-py), 157.94 (γ-py), 169.74 (C=N imine), 183.45 (C=O acetate); ES/MS (CH_3CN/H_2O 50/50): *m*/*z*=689 $(M-CH_3COO)^+$, 315 $(M-2CH_3COO)^{++}/2$; FAB/MS (NOBA): *m*/*z*=902 $(M+NOBA+H)^+$, 689 $(M-CH_3COO)^+$.

Praseodymium complex: beige solid, yield: 83% (0.31 g, 0.42 mmol); mp 248–252°C. ^{1}H NMR (CD_3OD): δ=−2.14 (s, 6 H, CH_3N), 2.10 (broad s, 9 H, CH_3COO), 4.16 (s, 12 H, CH_3C=N), 5.95 (s, 8 H, CH_2N=C), 16.26 (s, 4 H, Hpy). ^{13}C NMR (CD_3OD): δ=24.82, 33.52, 35.78, 37.99, 106.03, 133.49, 170.66, 186.18, 194.02 all broad; ES/MS (CH_3CN/H_2O 50/50): *m*/*z*=691 $(M-CH_3COO)^+$, 316 $(M-2CH_3COO)^{++}/2$; FAB/MS (NOBA): *m*/*z*=905 $(M+NOBA+H)^+$, 691 $(M-CH_3COO)^+$.

Europium complex: beige solid, yield: 84% (0.32 g, 0.42 mmol); mp 137–139.2°C. ^{1}H NMR (CD_3OD): δ=−3.48 (s, 8 H, CH_2N=C), 0.52 (s, 4 H, Hpy), 1.15 (s, 12 H, CH_3C=N), 1.84 (s, 6 H, CH_3N), 9 (broad s, 9 H, CH_3COO); ^{13}C NMR (CD_3OD): δ=−25.93 (CH_3C=N), −5 (broad, CH_3COO), 41.35 (CH_3N), 43.98 (CH_2N=C), 75.71 (β-py), 121.04, 150.84, 160.40; ES/MS (CH_3CN/H_2O 50/50): *m*/*z*=701 $(M-CH_3COO)^+$, 321 $(M-2CH_3COO)^{++}/2$; FAB/MS (NOBA): *m*/*z*=914 $(M+NOBA+H)^+$, 701 $(M-CH_3COO)^+$.

Ytterbium complex: beige solid, yield: 78% (0.30 g, 0.39 mmol); mp 260–265°C (decomp). ^{1}H NMR (CD_3OD): δ=−2.73 (s, 4 H, Hpy), −0.76 (s, 8 H, CH_2N=C), 1.30 (s, 12 H, CH_3C=N), 9.5 (broad s, 6 H, CH_3N), 24.76 (s, 9 H, CH_3COO); ^{13}C NMR (CD_3OD): δ=10.15, 25.90, 79.81, 88.75, 99.23, 145.11, 147.48, all broad; ES/MS (CH_3CN/H_2O 50/50): *m*/*z*=724 $(M-CH_3COO)^+$, 333 $(M-2CH_3COO)^{++}/2$; FAB/MS (NOBA): *m*/*z*=937 $(M+NOBA+H)^+$, 724 $(M-CH_3COO)^+$.

Acknowledgements

We gratefully acknowledge the financial support of the Fonds National de la Recherche Scientifique; V. J. is Chercheur Qualifié at this institution. We are all grateful for support by the Institut Interuniversitaire des Sciences Nucléaires, the Fonds pour la Formation à la Recherche dans l'Industrie et dans l'Agriculture and the European Cooperation in the Field of Scientific and Technical Research COST D8.

References

1. Peters, J. A.; Huskens, J.; Raber, D. J. *Prog. Nucl. Magn. Reson. Spectrosc.* **1996**, *28*, 283–350.
2. Mathis, G. *Clin. Chem.* **1993**, *39*, 1953–1959.
3. Leif, R. C.; Vallarino, L. M. *ACS Symp. Ser.* **1991**, *464*, 41–58.
4. Morrow, J. R.; Buttrey, L. A.; Shelton, V. M.; Berback, K. A. *J. Am. Chem. Soc.* **1992**, *114*, 1903–1905.
5. De Mesmaeker, A.; Häner, R.; Martin, P.; Moser, H. E. *Acc. Chem. Res.* **1995**, *28*, 366–374.
6. (a) Häner, R.; Hall, J.; Rihs, G. *Helv. Chim. Acta* **1997**, *80*, 487–494. (b) Hall, J.; Hüsken, D.; Pieles, U.; Moser, H. E.; Häner, R. *Chem. Biol.* **1994**, *1*, 185–190.
7. Wang, X. Y.; Jin, T. Z.; Comblin, V.; Lopez-Mut, A.; Merciny, E.; Desreux, J. F. *Inorg. Chem.* **1992**, *31*, 1095–1099.
8. Sessler, J. L.; Mody, T. D.; Hemmi, G. W.; Lynch, V. *Inorg. Chem.* **1993**, *32*, 3175–3187.
9. Abid, K. K.; Fenton, D. E. *Inorg. Chim. Acta* **1984**, *95*, 119–125.

10. Koenigs, E.; Friedrich, H.; Jurany, H. *Ber.* **1925**, *58*, 2571–2576.
11. Gorton, B. S.; Shive, W. *J. Am. Chem. Soc.* **1957**, *79*, 670–672.
12. Angelo, B. *C. R. Séances Acad. Sci. Ser. C* **1973**, *276*, 293–296.
13. Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1345–1353.
14. Kikkawa, I.; Yorifuji, T. *Synthesis* **1980**, 877–880.
15. Lukes, R.; Pergal, M. *Collect. Czech. Chem. Commun.* **1959**, *24*, 36–45.
16. Fallahpourt, R.-A.; Constable, E. C. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2263–2264.
17. Chaubet, F.; Nguyen Van Duong, M.; Courtieu, J.; Gaudemer, A.; Gref, A.; Crumbliss, A. L. *Can. J. Chem.* **1991**, *69*, 1107–1116.
18. Robison, M. M. *J. Am. Chem. Soc.* **1958**, *80*, 5481–5483.
19. Cacheris, W. P.; Nickle, S. K.; Sherry, A. D. *Inorg. Chem.* **1987**, *26*, 958–960.
20. Dodd, D. S.; Oehlschlager, A. C.; Georgopapadakou, N. H.; Polak, A.-M.; Hartman, P. G. *J. Org. Chem.* **1992**, *57*, 7226–7234.
21. De Cola, L.; Smailes, D. L.; Vallarino, L. M. *Inorg. Chem.* **1986**, *25*, 1729–1732.
22. Desreux, J. F. *Inorg. Chem.* **1980**, *19*, 1319–1324.
23. (a) Arif, A. M.; Backer-Dirks, J. D. J.; Gray, C. J.; Hart, F. A.; Hursthouse, M. B. *J. Chem. Soc., Dalton Trans.* **1987**, 1665–1673. (b) Casellato, U.; Tamburini, S.; Tomasin, P.; Vigato, P. A.; Aime, S.; Botta, M. *Inorg. Chem.* **1999**, *38*, 2906–2916. (c) Platas, C.; Avecilla, F.; de Blas, A.; Geraldes, C. F. G. C.; Rodriguez-Blas, T.; Adams, H.; Mahia, J. *Inorg. Chem.* **1999**, *38*, 3190–3199.
24. Toomey, R. F.; Riegel, E. R. *J. Org. Chem.* **1952**, *17*, 1492–1493.
25. Jacques, V.; Desreux, J. F. *Inorg. Chem.* **1994**, *33*, 4048–4053.