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Synthesis of a tricyclic tetraazatriacetic ligand for gadolinium(III) as potential contrast agent for MRI

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Abstract—A tricyclic tetraazatriacetic compound, which is a rigidified derivative of **PCTA12** ligand with a cyclohexylene bridge replacing an ethylene one, was prepared. Two synthetic routes have been investigated, both of them implying a common functionalized triamine intermediate. Whatever the route, four synthetic steps were necessary to obtain the target tricyclic ligand. The more effective one (Route B) led to the desired compound in 19% overall yield from the triamine intermediate. The corresponding gadolinium complex of 1/1 stoichiometry was then prepared in order to evaluate it as potential contrast agent for MRI.

1. Introduction

Magnetic resonance imaging (MRI) has evolved into a main non-invasive technique in medical diagnostics and biomedical research. MRI images basically visualize the relaxation of water molecules in the human body and, if needed, the contrast of MRI images can be improved with the injection of a paramagnetic contrast agent (CA). In such cases, the contrast enhancement is due to the ability of the paramagnetic substance to shorten the longitudinal and transverse relaxation times of the water protons in tissue in which the agent accumulates. The effectiveness of such pharmaceuticals is usually assessed in vitro by measuring the relaxivities r_1 and r_2, defined as the longitudinal and transverse relaxation rates for a millimolar solution of CA.

The gadolinium-based CAs constitute a major class of paramagnetic substances used for such purpose; they are complexes of Gd(III) with ligands designed to form strong chelates, which actually remain stable in the body and are excreted intact, thereby significantly reducing the toxicity of the free Gd(III) ion. It is now well established that polyamino-polyacetate ligands confer such a stability to the corresponding gadolinium complexes and this class of compounds are the most widely used as CA for MRI.[1,2] In terms of magnetic performance, it appears that the gadolinium chelates routinely used for clinical diagnosis have longitudinal relaxivities ranging from 3 to 5 L/mmol s (25–40 °C, 20 MHz). However, there is still a great effort to find new products of improved performance in terms of relaxivity, so that the CA could be administered at a lower dose, which is probably a key issue to move towards MRI molecular imaging.[3]

The relaxation theory was discussed in detail in previous reviews.[1,4] Several models were needed to relate the observed paramagnetic relaxation rate enhancement to microscopic properties of the gadolinium complex, and the fine and accurate control of the numerous, often dependent, parameters involved in these models proved to be a real challenge. For some of them, the influence of structural elements is still being debated.

Recently, it has been postulated that the rigidification of the chelate structure could be favourable to a higher longitudinal relaxivity.[5,6] In such a context, the conformational mobility and relaxometric properties of polymethylated **DOTA** analogues have been reported.[6] Unfortunately, the proposed design proved to have little influence on the relaxivity, perhaps owing to insufficient rigidification by grafting methylene groups on the **DOTA** scaffold.

These preliminary results encouraged us to find a more efficient element of rigidification that would not alter the stability of the resulting gadolinium complex. On the one hand,

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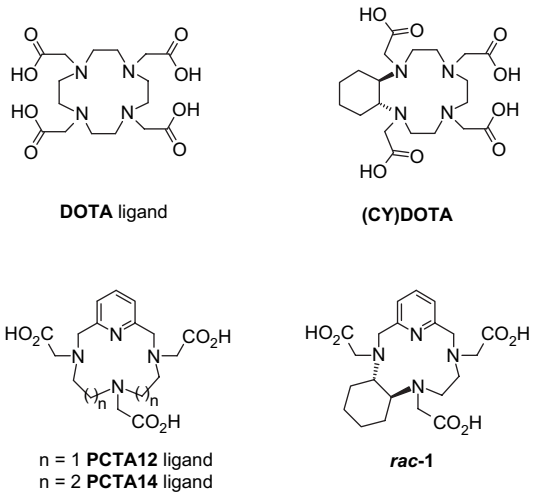


Figure 1. Some 12-membered polyamino-polyacetic macrocyclic ligands for the complexation of Gd^{3+} ion.

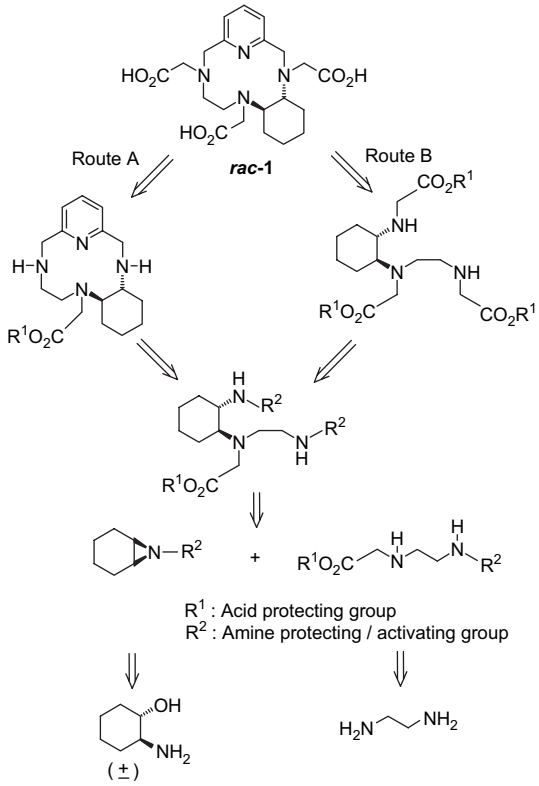
we found that the replacement of an ethylene bridge by a cyclohexylene one in a polyazacyclophane scaffold may induce a better kinetic stability of the resulting Gd(III) complex as it was the case for **DOTA** versus **(CY)DOTA** gadolinium complexes (Fig. 1).[7] On the other hand, the macrocycle **PCTA12** ligand, which is a 12-membered pyridine-containing macrocycle (PC-type ligand) in which the three N-atoms bear an acetic acid arm (Fig. 1) was reported to form a stable complex with Gd(III) ($\log K$=20.8)[8] with an improved longitudinal relaxivity (r_1=6.9 L/mmol s, 20 MHz, 25 °C)[1] in comparison with that of the marketed gadolinium-based CAs. Since then, other PC-type ligands were prepared and exhibited always higher relaxivities ($8.1<r_1<10.5$ L/mmol s, 20 MHz, 25 °C).[9,10]

With these structural aspects in mind, we decided to prepare the rigidified **PCTA12** derivative ***rac*-1** (Fig. 1) in which one ethylene bridge connecting two N-atoms would be replaced by a cyclohexylene bridge. The results presented here detail the two synthetic routes developed to prepare the tricyclic PC-ligand **1**. The complexation with Gd(III) is also reported in order to appreciate its potential activity as contrast agent for MRI.

2. Results and discussion

2.1. Preparation of the ligand

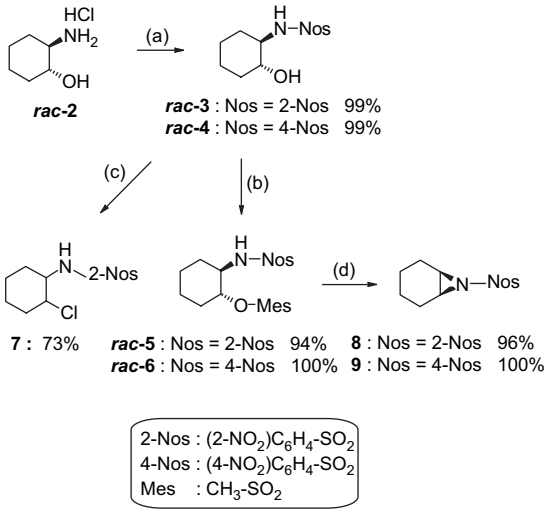
Considering our previous work for the preparation of 12- and 14-membered PC-type macrocycles,[11,12] together with other reported works for larger structures,[13,14] two synthetic routes could be envisaged to obtain the target tricyclic compound **1** (Scheme 1). Both of the routes involve a common triamine intermediate bearing one of the three N-grafted pendant arms (in our case, an acetate chain). In Route A, the two last pendant arms would be grafted on a preformed pyridine-containing azamacrocyclic intermediate bearing one pendant arm while, in Route B, the macrocyclisation step would involve a triamine block already bearing the three pendant arms. The construction of the key triamine block, common intermediate of the two routes, could result from the ring opening of an activated cyclic aziridine with a selectively functionalized derivative of ethylenediamine. The preparation of the aziridine could be envisaged from the commercially available *trans*-2-amino-cyclohexanol. Moreover, we planned to apply the Fukuyama's 2-nitro-phenylsulfonamide strategy (R^2=(2-NO_2)C_6H_4-SO_2) to control the selective regiofunctionalization of the polyamine skeleton.[15]



Scheme 1. Synthetic pathways envisaged for the preparation of the target pyridine-containing macrocycle **1**.

The first synthon involved in the building of the common triamine precursor is the activated aziridine **8** (Scheme 2). Instead of the direct copper-catalyzed nitrene transfer to cyclohexene reported for the preparation of analogous *N*-sulfonyl aziridines (see Scheme 1: R^2=(4-CH_3)C_6H_4-SO_2, (4-NO_2)C_6H_4-SO_2, (2,4-(NO_2)$_2$)C_6H_3-SO_2⋯),[16,17] a previously described three-step method from *trans*-2-amino-cyclohexanol **2** was preferred to prepare the aziridine **8**.[18] Indeed, even longer, this latter method involved the cheaper 2-nitro-phenylsulfonyl chloride as sulfonyl precursor in comparison with the corresponding sulfonamide required for the preparation of the nitrene precursor.[16] Moreover, the procedure was reported to give aziridine **8** with a satisfying 71% overall yield requiring a single purification step by flash chromatography at the end of the three-step process. Slight modifications were however done to this original procedure so that our method afforded a crude form of the desired aziridine **8** pure enough to be directly employed in the next step,[19] with an improved overall yield of 89%. Moreover, our method can be adapted for the preparation of the regioisomer **9** with again an improved overall yield of 99% thus appearing more efficient than the one-step nitrene transfer reported method.[16] Lastly, for both aziridines **8** and **9**, our method was amenable to large-scale

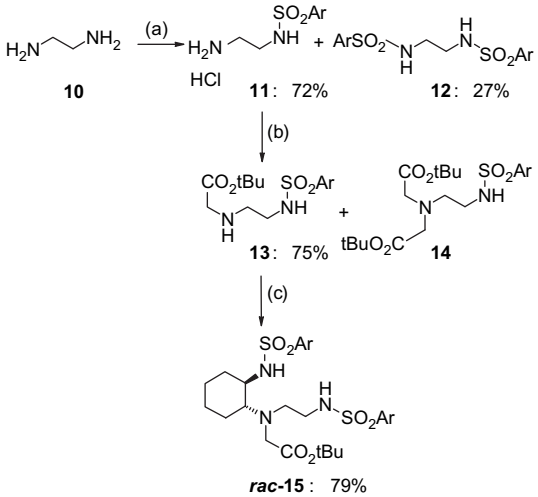
preparations (up to 60 mmol, about 17 g) without any loss of purity and with similar enhanced overall crude yields.



Scheme 2. Syntheses of the sulfonyl aziridines **8** and **9**. Reagents and conditions: (a) Nos-Cl (1.1 equiv), $NaHCO_3$ (4 equiv), THF, 0 °C to rt, overnight; (b) Mes-Cl (1.1 equiv), TEA (1.5 equiv), anhydrous THF, −5 to 0 °C, 1.5 h; (c) Mes-Cl (1.2 equiv), TEA (3 equiv), anhydrous THF, rt to 70 °C, 1 day; (d) K_2CO_3 (4 equiv), CH_3CN, 50 °C, 1.5 h.

By reaction with a stoichiometric amount of 2- or 4-nitrophenylsulfonyl chloride in the presence of sodium hydrogen carbonate in tetrahydrofuran, the *trans*-2-amino-cyclohexanol hydrochloride **2** was chemoselectively mono-*N*-sulfonylated to afford the sulfonamides **3** or **4** in 99% yield. Subsequent activation of the hydroxyl function was chemoselectively realized by reaction with a stoichiometric amount of methanesulfonyl chloride in the presence of a slight excess of triethylamine at low temperature in anhydrous tetrahydrofuran and led to the mono-*O*-mesylated compounds **5** and **6** in 94 and 100% yield, respectively. It is interesting to note that when the same reaction was applied to sulfonamide **3** in refluxing solvent and in the presence of a 3-fold excess of triethylamine, the 2-chloro derivative **7** was isolated exclusively (73%). Moreover, when the reaction occurred at temperature above 5 °C, the di-*N*,*O*-mesylated side product could be detected even if the quantity of the methanesulfonyl chloride had been limited to 1 mol equiv. With the idea to transform the two later steps in a one-pot procedure, we first tried the aziridination of compound **5** in the presence of triethylamine in tetrahydrofuran. Refluxing the reaction overnight was necessary to obtain the desired aziridine **8** in a moderate yield of 52%. We then found that, in the presence of potassium carbonate in acetonitrile and with moderate warming, the cyclization was much more efficient as the crude *O*-mesylated compounds **5** and **6** afforded the corresponding aziridines **8** and **9** in 96 and 100% respective yields, and with a satisfying purity that allowed to use the crude forms.

The second counterpart involved in the building of the common triamine intermediate derived from ethylenediamine **10** (Scheme 3). The monosulfonamide **11** had been already prepared in a one-step procedure, by reacting ethylenediamine **10** with 2-nitro-phenylsulfonyl chloride in a 3:1 molar ratio in slightly warmed benzene.[20] In these conditions, the hydrochloride salt of monosulfonamide **11** was isolated in 23% yield. Since then, Fukuyama and co-workers reported an improved procedure for homologous diamines where the selective monosulfonylation proceeded in ethanol at −20 °C, always by reacting the two compounds in a 3:1 molar ratio; in their conditions, the corresponding monosulfonamides were isolated with yields ranging from 77 to 87%.[21] Another effective three-step procedure, with a 72% overall yield, was reported for the preparation of the hydrochloride salt of monosulfonamide **11** and was based on a selective monocarbamatation prior to the sulfonylation step that was thus followed by a selective deprotection step.[22] We decided to use a one-step procedure where a sub-stoichiometric amount (0.33 equiv) of the expensive 2-nitro-phenylsulfonyl chloride was involved. We found that the selective monosulfonylation of ethylenediamine **10** occurred in tetrahydrofuran at 0 °C with a yield greatly improved in comparison with that of the original method.[20] Indeed, the hydrochloride salt of monosulfonamide **11** was isolated in 72% and was easily separated from the competitive disulfonamide **12**[20,23–25] in the work-up procedure; the latter disulfonamide was isolated by crystallization in 27% yield. The aminosulfonamide **11** was then treated with an excess of *tert*-butyl bromoacetate in the presence of triethylamine. At this step, a strict monitoring of the reaction (by TLC) was required to control the portionwise addition of the alkylating agent in order to reach the completion of the reaction while limiting the formation of the competitive symmetric di-*N*-alkylated compound **14**.[26] In such conditions, the chemoselectivity was satisfactory as the mono-N-alkylation of the primary amine was favoured and furnished compound **13** in 75% yield.

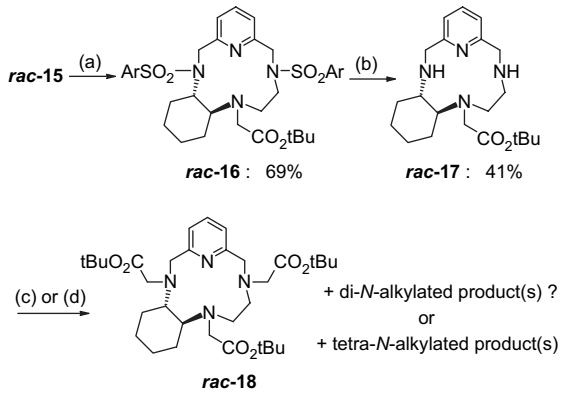


Scheme 3. Preparation of the triamine **15**. Reagents and conditions: Ar=$(2\text{-}NO_2)C_6H_4$. (a) (i) $ArSO_2Cl$ (0.33 equiv), THF, 0 °C to rt, 2.5 h; (ii) HCl; (b) *tert*-butyl bromoacetate (2 equiv), TEA (4 equiv), THF, rt, overnight; (c) **8** (1 equiv), anhydrous CH_3CN, reflux, 2 days.

The ring opening of the *meso*-sulfonylaziridine **8** then occurred by reaction with the previously prepared amine **13** in prolonged refluxing acetonitrile and furnished the expected functionalized racemic triamine **15** in 79% yield.

With the common triamine precursor **15** in hand, the first Route A envisaged was analogous to the synthetic ways

we developed to prepare several regioselectively functionalized **PCTA12** and **PCTA14** derivatives (Fig. 1).[11,12] In this approach, the 2,6-bis(bromomethyl)pyridine was reacted with the activated triamine **15** in the presence of potassium carbonate in *N*,*N*-dimethylacetamide at 100 °C, and afforded the corresponding macrocycle **16** in 69% yield (Scheme 4).

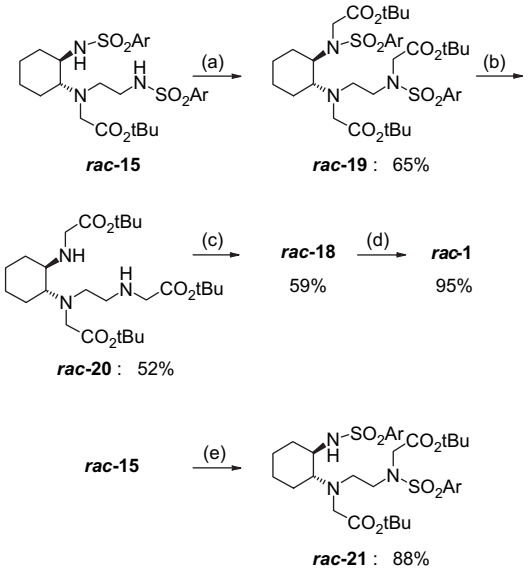


Scheme 4. Route A. Reagents and conditions: Ar=(2-NO_2)C_6H_4. (a) 2,6-Bis(bromomethyl)pyridine (1.8 equiv), K_2CO_3 (4 equiv), anhydrous *N*,*N*-dimethylacetamide, 100 °C, 4.5 h; (b) PhSH (2.2 equiv), Na_2CO_3 (3 equiv), anhydrous DMF, rt, overnight; (c) (i) anhydrous K_2CO_3 (6 equiv), CH_3CN, reflux, 2 h; (ii) *tert*-butyl bromoacetate (6 equiv), 60 °C, 40 h; (d) *tert*-butyl bromoacetate (3.5 equiv), TEA (3.5 equiv), anhydrous THF, 55 °C, 7 h.

When *N*,*N*-dimethylacetamide was replaced by DMF, the isolated yield was slightly lowered (57%), and it decreased dramatically when the reaction was done in acetonitrile at reflux as the desired macrocycle **16** was isolated in only 35% yield. The poor yield obtained in such conditions resulted from the competitive formation of [2+2] adducts.[27] Also, the ^1H and ^{13}C NMR spectra of the desired [1+1] adduct **16** proved to be more complex than expected. We attributed this to the presence, at room temperature, of a mixture of rotamers in the NMR solution ($CDCl_3$) probably due to prevented free rotations generated by the bulky 2-nitrophenylsulfonyl and/or cyclohexyl subunits.

The cleavage of the 2-nitro-phenylsulfonamides was realized following a conventional method,[28] by treatment with thiophenate in DMF at room temperature. In such conditions, the desulfonylated macrocycle **17** was isolated in 41% yield. When acetonitrile was used in the place of DMF, a slight warming (50 °C) proved to be necessary and the desired product **17** was isolated in similar yield (44%).[19]

The subsequent di-N-alkylation step was envisaged following two protocols, each of them proceeding with an excess of alkylating agent under slight warming. In the first protocol, an excess of potassium carbonate was used in acetonitrile for a prolonged warming time; in the second one, a lower excess of triethylamine was used in THF with moderate warming. On the basis of mass spectroscopic analyses, the more drastic first conditions led to a mixture of the desired product **18** together with tetra-*N*-alkylated one(s) that could not be separated by chromatography.[29] The milder second conditions never gave tetra-*N*-alkylated species even if other portions of both alkylating agent and base were added. However, on the basis of ^1H and ^{13}C NMR spectra together with mass spectroscopic analyses, we thought that the product isolated was an inseparable mixture of di-*N*-alkylated species together with the desired tri-*N*-alkylated one **18**.[30] This led us to envisage the alternative Route B that should unambiguously lead to the unique tri-*N*-alkylated product **18** as the macrocyclization step would involve the triamine **19** already bearing the three acetate pendant arms (Scheme 5).



Scheme 5. Route B. Reagents and conditions: Ar=(2-NO_2)C_6H_4. (a) (i) Anhydrous K_2CO_3 (4 equiv), CH_3CN, reflux, 2 h; (ii) *tert*-butyl bromoacetate (4 equiv), CH_3CN, reflux, overnight; (b) 2-mercaptoethanol (11 equiv), DBU (4.5 equiv), CH_3CN, rt, 2 h; (c) (i) anhydrous Na_2CO_3 (4 equiv), anhydrous DMF, 100 °C, 15 min; (ii) 2,6-bis(bromomethyl)pyridine (1.9 equiv), anhydrous DMF, 100 °C, 3.5 h; (d) (i) anhydrous HCl (ca. 100 equiv), Et_2O, rt, overnight; (ii) anion-exchange resin; (e) (i) Na_2CO_3 (2 equiv), CH_3CN, reflux, 2 h; (ii) *tert*-butyl bromoacetate (2 equiv), CH_3CN, reflux, overnight.

We noticed a dramatic influence of the nature of the base on the outcome of the N-alkylation of sulfonamide **15**. Indeed, by reacting compound **15** with a 4-fold excess of *tert*-butyl bromoacetate in the presence of sodium carbonate in acetonitrile for a prolonged warming time, the major product obtained was the mono-*N*-alkylated product **21** (Scheme 5).[31] By replacing sodium carbonate by anhydrous potassium carbonate, we found that the disulfonamide **15** was di-*N*-alkylated to afford the desired compound **19** in 65% yield.

Attempt to cleave the sulfonyl groups following the Fukuyama's standard procedure[28] (thiophenol, potassium carbonate in acetonitrile at room temperature) led to mono-sulfonylated product(s) in 51% yield. By slightly warming up to 50 °C, the conversion of the mono-sulfonylated intermediate(s) seemed total but the desired triamine **20** was isolated in only 32% yield. A more effective method was thus envisaged and, by using 2-mercaptoethanol in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in acetonitrile,[32,33] the cleavage of the sulfonamides proceeded smoothly at room temperature and led to the functionalized triamine **20** in 52% yield. It should be noted that, on standing at room temperature, the tri-aminoacetate **20** spontaneously and regioselectively cyclized in a lactam derivative.[34]

The reaction of triamine **20** with 2,6-bis(bromomethyl)pyridine in the presence of sodium carbonate in warmed dimethylformamide led to the desired macrocyclic compound **18** in 59% yield. When treated with anhydrous hydrogen chloride, the triester **18** was converted to the target macrocyclic triacetic acid **1** isolated with high yield (95%) as its neutral form after an ion-exchange chromatography.

2.2. Preparation of the gadolinium complex

With the target tricyclic ligand **1** in hand, we decided to prepare the corresponding gadolinium complex in order to evaluate it as potential contrast agent for MRI. Several examples of gadolinium complexes formed with PC-type ligands exhibited a 1/1 stoichiometry.[8–10,35,36] We postulated a similar stoichiometry for the gadolinium complex formed with ligand **1** and, by mixing stoichiometric amounts of our PC-type ligand **1** and gadolinium chloride in water at pH 5 (optimum pH in order to prevent the formation of the insoluble gadolinium hydroxide and to limit the proton competitive association to the ligand as well), the expected Gd-**1** complex was formed.

We recently reported the physicochemical properties of this complex,[37] and it appeared that the Gd-**1** complex was stable during several days, at 37 °C and physiological pH, in the presence of competitive endogenous Zn^{2+} cations. Moreover, we found that the longitudinal relaxivity of Gd-**1** was slightly higher in comparison with that of the parent Gd-**PCTA12** (r_1=6.1 L/mmol s vs 5.4 L/mmol s at 20 MHz and 37 °C) reflecting the ratio of their molecular weight (588.7 and 534.6 g/mol, respectively). This result was not surprising and suggested that the dominant parameter of relaxivity is the rotational correlation time. Other relaxometric studies[37] demonstrated that the rigidification of the **PCTA** scaffold had no impact on the electronic relaxation of Gd-**1**. However, the rigidity of this complex induced an acceleration of the exchange rate of the inner-sphere water molecules as a result of steric crowding around the gadolinium ion. The value of the exchange rate of the inner-sphere water molecules thus approached the optimal value required to attain high relaxivity once the chelate is immobilized by covalent or non-covalent binding to macromolecules.

These promising results encouraged us to pursue our research program aimed to analyze the impact of skeleton modification on the relaxometric properties of the resulting gadolinium complexes.

3. Conclusion

In order to evaluate the influence of an increased rigidity of the ligand skeleton on the stability and the relaxometric properties of the corresponding gadolinium complex, we decided to synthesize the tricyclic pyridine-containing tetraazatriacetic ligand **1**, which is a rigidified analogue of the well-known **PCTA12** ligand. Two synthetic routes have been envisaged to prepare the macrocycle **1**. Both of them imply a common racemic triamine **15** and, whatever the route, four synthetic steps led to the target ligand **1**. Route B proved to be more effective way to obtain unequivocally the desired target isolated in 19% overall yield from triamine **15**. The corresponding gadolinium complex of 1/1 stoichiometry was then prepared and the resulting gadolinium complex Gd-**1** proved to be promising as contrast agent for MRI application.[37]

4. Experimental

4.1. General

4.1.1. Chemicals. All reactions were monitored for completion by thin layer chromatography (TLC) performed on precoated silica gel plates (60 F_{254}, Merck); TLC plates were viewed under UV (254 nm) and in an iodine chamber; frontal retention values R_f have been mentioned when necessary. Preparative chromatography was performed by elution from columns of silica gel 60 (particle size 0.040–0.063 mm, Merck) or of activated neutral aluminium oxide gel (Brockmann I, ca. 150 mesh, Aldrich). Unless stated otherwise, all reagents were purchased from commercial sources and used without additional purification.

4.1.2. Physical measurements. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker AM400 400 MHz spectrometer, at room temperature, in $CDCl_3$ ($CHCl_3$ at δ=7.26 ppm and $CDCl_3$ at δ=77.1 ppm (central shift) as internal standards for ^{1}H and ^{13}C NMR spectra, respectively), in D_2O (HOD at δ=4.80 ppm as internal standard for ^{1}H NMR spectra and 3-trimethylsilyl-1-propanesulfonic acid sodium salt as external reference for ^{13}C NMR spectra), or in DMSO-d_6 (DMSO-d_6 at δ=2.50 ppm (central shift) and at δ=39.5 ppm (central shift) as internal standards for ^{1}H and ^{13}C NMR spectra, respectively). In the assignments of the NMR signals, 'Nos' was used as the abbreviation for 2-nitro-phenylsulfonyl. Moreover, we chose the convention presented in Figure 2 to simplify the assignment of the nuclei. Chemical shifts δ are given in parts per million. Coupling constants J are measured in hertz. For a given ^{1}H NMR spectrum, $J_{H,H}(1)$, $J_{H,H}(2)$, … can be used for easier association of protons coupled each together. Coupling patterns are described by abbreviations: s (singlet), d (doublet), t (triplet), ddd (doublet of a doublet of doublet), m (multiplet). Concerning the two diastereotopic protons of an AB system: (i) when $\delta_A \approx \delta_B$, the group of four neighbouring signals with respective chemical shifts δ_1, δ_2, δ_3 and δ_4 integrates for two protons; in this case, the AB system is described by giving the two extreme chemical shifts δ_1 and δ_4 together with the corresponding $^2J_{H,H}$ calculated between δ_1 and δ_2 (or δ_3 and δ_4); (ii) when $\delta_A \ll \delta_B$, each proton A and B of the AB system is described by a 'doublet' (d of AB); in this case, the 'doublets' are described by giving δ_1 and δ_2 for the first one, and δ_3 and δ_4 for the second one.

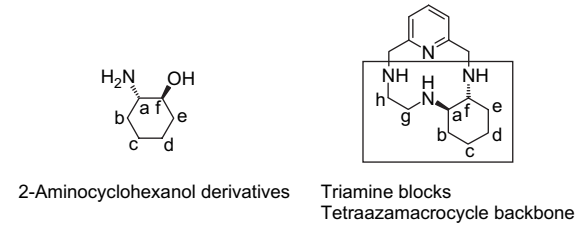


Figure 2. Convention adopted to assign signals of ^{1}H and ^{13}C NMR spectra.

Infrared spectra were measured as KBr discs with a Nicolet FT-IR Avatar 320 spectrometer.

Melting points (mp) were obtained using a Büchi Tottoli apparatus.

All the mass spectra were taken in the positive-ion mode. High-resolution mass spectra were performed with a JEOL MS700 mass spectrometer either from chemical ionization (CI-HRMS) using CH_4 as the ionizing gas or from fast atom bombardment ionization (FAB-HRMS) using 'Magic Bullet' (dithioerythritol) as the matrix. Spectra from ionization by electrospray (ESI-HRMS) were acquired on a Waters Micromass spectrometer with an ESI/APCI source. The HRMS analyses have been done on samples whose purity was checked by HPLC and/or ^{1}H NMR ($\geq$95%). Low-resolution mass spectra from chemical ionization (CI-LRMS) were performed with a JEOL MS700 mass spectrometer using NH_3 as the ionizing gas. The mass spectrum from electrospray ionization (ESI-LRMS) was performed with a Waters Micromass Quattro-II mass spectrometer. At last, the mass spectra resulting from ionization by electronic impact (EI-LRMS) were acquired on a 5973 Network MSD (Agilent). For the LRMS, *m/z* resulting from fragmentation processes were indicated, and sometimes assigned; the corresponding ionic abundances were reported in percentage relative to the more abundant ion.

The HPLC analyses of the free ligand **1** and of its gadolinium complex were realized with a reverse phase Column A (Symmetry® C18, 5 μm stationary phase, 250 mm× 4.6 mm) and a gradient of elution (see below) at a flow rate of 1 mL/min, using a single wavelength detector (220 nm for compound **1**; 201 nm for the gadolinium complex). The other HPLC analyses used a photodiode array detector; all the detections occurred at 260 nm; moreover, an isocratic system of elution was always used. The analyses were realized either with a normal phase Column B (Hypersil Si60, 5 μm stationary phase, 250 mm×4.6 mm) or with a reverse phase Column C (Hypersil ODS-C18, 5 μm stationary phase, 150 mm×4.6 mm). The retention times t_R are expressed in minutes in the decimal system.

4.2. Preparation of the sulfonyl aziridines 8 and 9

4.2.1. General procedure for the preparation of *N*-(2-hydroxy-cyclohexyl)sulfonamides 3 and 4. A solution of 2 (or 4)-nitro-phenylsulfonyl chloride (12.90 g, 58.21 mmol, 1.1 equiv) in THF (100 mL) was added dropwise (over 2 h) to a cooled (0 °C) suspension of (±) *trans* 2-amino-cyclohexanol hydrochloride **2** (8.0 g, 52.76 mmol) and sodium hydrogen carbonate (17.8 g, 211.9 mmol, 4 equiv) in THF (80 mL). At the end of the addition, the resulting mixture was allowed to warm up to room temperature and was stirred overnight.

4.2.1.1. (±) *trans* *N*-(2-Hydroxy-cyclohexyl)-2-nitro-phenylsulfonamide 3. The crude mixture was concentrated, then taken up in CH_2Cl_2 (350 mL). The organic solution was washed with water until neutrality, dried and concentrated. The title compound **3** was isolated as a whitish solid (15.7 g, 52.27 mmol, 99%). Its purity was checked by HPLC (Column B, *n*-heptane/EtOAc 75:25 v/v, 1.5 mL/min, t_R=29.9 min). Mp 126 °C. ^{1}H NMR ($CDCl_3$): δ=1.13–1.33 (m, 4H, $H_{b,ax}$, $H_{e,ax}$, C*H*H_c and C*H*H_d), 1.59–1.70 (m, 2H, C*H*H_c and C*H*H_d), 1.82–1.87 (m, 1H, $H_{b,eq}$), 1.99–2.04 (m, 1H, $H_{e,eq}$), 2.39 (br s, 1H, O*H*), 3.02–3.12 (m, 1H, H_a), 3.36 (ddd, $^3J_{H,H}(1)=^3J_{H,H}(2)$=9.8 Hz, $^3J_{H,H}(3)$= 4.4 Hz, 1H, H_f), 5.55 (d, $^3J_{H,H}(4)$=7.4 Hz, 1H, N*H*), 7.70–7.79 (m, 2H, CH_{ar}), 7.84–7.89 (m, 1H, CH_{ar}CNO_2), 8.15–8.19 (m, 1H, CH_{ar}CSO_2) ppm. ^{13}C NMR ($CDCl_3$): δ=23.8 (C_c or C_d), 24.6 (C_c or C_d), 32.1 (C_b), 33.6 (C_e), 60.5 (C_a), 73.1 (C_f), 125.4 (*C*H_{ar}CNO_2), 131.0 (*C*H_{ar}CSO_2), 133.0 (*C*H_{ar}), 133.6 (*C*H_{ar}), 134.4 ($C_{quat}SO_2$), 147.7 ($C_{quat}NO_2$) ppm. IR (KBr): ν=3547, 3334, 1537, 1359, 1325, 1161 cm^{-1}. CI-HRMS: *m/z* calcd for $C_{12}H_{17}N_2O_5S$, 301.0858; found, 301.0861 $[M+H]^+$.

4.2.1.2. (±) *trans* *N*-(2-Hydroxy-cyclohexyl)-4-nitro-phenylsulfonamide 4. The crude mixture was concentrated. The solid residue obtained was then taken up in CH_2Cl_2 (800 mL); the organic solution was washed with water until neutrality, dried and concentrated. The title compound **4** was isolated as a whitish solid (15.7 g, 52.27 mmol, 99%). Its purity was checked by HPLC (Column B *n*-heptane/EtOAc 75:25 v/v, 1.2 mL/min, t_R=26.7 min). Mp 168 °C. ^{1}H NMR (DMSO-d_6): δ=0.97–1.21 (m, 4H, $H_{b,ax}$, $H_{e,ax}$, C*H*H_c and C*H*H_d), 1.41–1.59 (m, 2H, C*H*H_c and C*H*H_d), 1.60–1.83 (m, 2H, $H_{b,eq}$ and $H_{e,eq}$), 2.77–2.91 (m, 1H, H_a), 3.08–3.22 (m, 1H, H_f), 4.47 (d, $^3J_{H,H}(1)$=5.3 Hz, 1H, O*H*), 7.91 (d, $^3J_{H,H}(2)$=7.2 Hz, 1H, N*H*), 8.03–8.11 (m, 2H, CH_{ar}CSO_2), 8.33–8.40 (m, 2H, CH_{ar}CNO_2) ppm. ^{13}C NMR (DMSO-d_6): δ=23.1 (C_c or C_d), 23.7 (C_c or C_d), 31.7 (C_b), 33.5 (C_e), 58.7 (C_a), 70.7 (C_f), 124.1 (*C*H_{ar}CNO_2), 128.0 (*C*H_{ar}CSO_2), 148.0 ($C_{quat}SO_2$), 149.1 (C_{quat}-NO_2) ppm. IR (KBr): ν=3575, 3342, 1526, 1350, 1308, 1163 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{12}H_{16}N_2NaO_5S$, 323.0678; found, 323.0661 $[M+Na]^+$.

4.2.2. General procedure for the preparation of cyclohexyl methanesulfonates 5 and 6. Methanesulfonyl chloride (4.5 mL, 58.14 mmol, 1.1 equiv) was added dropwise (over 30 min), under argon, to a cooled (−5 to 0 °C) solution of (±) *trans* *N*-(2-hydroxy-cyclohexyl)sulfonamide **3** or **4** (15.7 g, 52.27 mmol) and triethylamine (11 mL, 78.92 mmol, 1.5 equiv) in anhydrous THF (400 mL). At the end of the addition, the resulting mixture was stirred over 1 h. The salts formed during the reaction were filtered off through a Celite® pad then the filtrate was concentrated.

4.2.2.1. (±) *trans* 2-(2-Nitro-phenylsulfonylamino)-cyclohexyl methanesulfonate 5. The solid residue obtained was taken up in CH_2Cl_2 (300 mL). The organic solution was washed with water until neutrality, dried, then concentrated to give the title compound **5** as a white solid (18.6 g, 49.15 mmol, 94%). Its purity was checked by HPLC (Column B, *n*-heptane/EtOAc 75:25 v/v, 1.5 mL/min, t_R= 18.9 min). Mp 150 °C. ^{1}H NMR ($CDCl_3$): δ=1.24–1.44 (m, 3H, $H_{b,ax}$, C*H*H_c and C*H*H_d), 1.58–1.67 (m, 2H, C*H*H_c and $H_{e,ax}$), 1.73–1.78 (m, 1H, C*H*H_d), 1.91–1.97 (m, 1H, $H_{b,eq}$), 2.21–2.28 (m, 1H, $H_{e,eq}$), 3.00 (s, 3H, CH_3), 3.46–3.56 (m, 1H, H_a), 4.46 (ddd, $^3J_{H,H}(1)=^3J_{H,H}(2)$=9.7 Hz, $^3J_{H,H}(3)$=4.4 Hz, 1H, H_f), 5.59 (d, $^3J_{H,H}(4)$=7.8 Hz, 1H, N*H*), 7.73–7.80 (m, 2H, CH_{ar}), 7.87–7.91 (m, 1H, CH_{ar}CNO_2), 8.14–8.18 (m, 1H, CH_{ar}CSO_2) ppm. ^{13}C NMR ($CDCl_3$): δ=23.3 (C_c or C_d), 23.7 (C_c or C_d), 32.1 (C_e),

32.4 (C_b), 38.8 (CH_3), 56.7 (C_a), 81.5 (C_f), 125.6 ($CH_{ar}CNO_2$), 130.6 ($CH_{ar}CSO_2$), 133.2 (CH_{ar}), 133.7 (CH_{ar}), 134.8 ($C_{quat}SO_2$), 147.9 ($C_{quat}NO_2$) ppm. IR (KBr): ν=3342, 1545, 1356, 1340, 1167 cm^{-1}. CI-HRMS: *m/z* calcd for $C_{13}H_{19}N_2O_7S_2$, 379.0634; found, 379.0639 $[M+H]^+$.

4.2.2.2. (±) *trans* 2-(4-Nitro-phenylsulfonylamino)-cyclohexyl methanesulfonate 6. The solid residue obtained was taken up in AcOEt (300 mL). The organic solution was washed with a saturated aqueous solution of NaCl (100 mL) and the aqueous layer was further extracted with AcOEt (2×150 mL). The combined organic layers were dried, then concentrated to give the title compound **6** as a whitish solid (19.78 g, 52.27 mmol, 100%). Its purity was checked by HPLC (Column B, *n*-heptane/EtOAc 75:25 v/v, 1.5 mL/min, t_R=18.7 min). Mp 150 °C. ^{1}H NMR (DMSO-d_6): δ=1.07–1.35 (m, 3H, $H_{b,ax}$, C*H*H_c and C*H*H_d), 1.40–1.66 (m, 4H, $H_{e,ax}$, $H_{b,eq}$, C*H*H_c and C*H*H_d), 2.00–2.14 (m, 1H, $H_{e,eq}$), 3.05 (s, 3H, C*H*$_3$), 3.21–3.39 (m, 1H, H_a), 4.46 (ddd, $^3J_{H,H}(1)=^3J_{H,H}(2)$=9.8 Hz, $^3J_{H,H}(3)$=4.5 Hz, 1H, H_f), 8.02–8.12 (m, 2H, C*H*$_{ar}CSO_2$), 8.27 (d, $^3J_{H,H}(4)$=9.0 Hz, 1H, N*H*), 8.36–8.45 (m, 2H, C*H*$_{ar}CNO_2$) ppm. ^{13}C NMR (DMSO-d_6): δ=22.8 (C_c or C_d), 23.0 (C_c or C_d), 31.5 (C_b and C_e)$^{\$}$, 37.9 ($CH_3$), 55.1 ($C_a$), 81.9 ($C_f$), 124.6 ($CH_{ar}CNO_2$), 127.8 ($CH_{ar}CSO_2$), 147.5 ($C_{quat}SO_2$), 149.4 ($C_{quat}NO_2$) ppm. $^{\$}$This unique signal accounts for the two mentioned populations of ^{13}C. IR (KBr): ν=3336, 1528, 1355, 1336, 1325, 1171 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{13}H_{18}N_2NaO_7S_2$, 401.0453; found, 401.0444 $[M+Na]^+$.

4.2.3. *N*-(2-Chloro-cyclohexyl)-2-nitro-phenylsulfonamide 7. A solution of methanesulfonyl chloride (0.43 mL, 5.55 mmol, 1.2 equiv) in anhydrous THF (20 mL) was added dropwise (over 1.5 h), at room temperature, under argon, to a solution of (±) *trans* *N*-(2-hydroxy-cyclohexyl)-2-nitro-phenylsulfonamide **3** (1.42 g, 4.73 mmol) and triethylamine (2 mL, 14.3 mmol, 3 equiv) in anhydrous THF (20 mL). At the end of the addition, the resulting mixture was stirred for 5 h at room temperature then warmed to 70 °C overnight. The crude mixture was filtered and the filtrate was concentrated. The residue was taken up in CH_2Cl_2 (50 mL). The organic solution was washed with water until neutrality, dried, then concentrated to give a crude product that was purified by chromatography on silica gel (*n*-heptane/EtOAc, 7:3) to give the title compound **7** as a whitish solid (1.11 g, 3.48 mmol, 73%). Its purity was checked by HPLC (Column B, *n*-heptane/EtOAc 70:30 v/v, 1.0 mL/min, t_R=5.4 min). Mp 121 °C. ^{1}H NMR ($CDCl_3$): δ=1.20–1.50 (m, 3H, $H_{b,ax}$, C*H*H_c and C*H*H_d), 1.54–1.80 (m, 3H, $H_{e,ax}$, C*H*H_c and C*H*H_d), 2.15–2.30 (m, 2H, $H_{b,eq}$ and $H_{e,eq}$), 3.29–3.42 (m, 1H, H_a), 3.73 (ddd, $^3J_{H,H}(1)=^3J_{H,H}(2)$=10.0 Hz, $^3J_{H,H}(3)$=4.2 Hz, 1H, H_f), 5.67 (d, $^3J_{H,H}(4)$=6.4 Hz, 1H, N*H*), 7.70–7.76 (m, 2H, C*H*$_{ar}$), 7.89–7.92 (m, 1H, C*H*$_{ar}CNO_2$), 8.13–8.16 (m, 1H, C*H*$_{ar}CSO_2$) ppm. ^{13}C NMR ($CDCl_3$): δ=23.9 (C_c or C_d), 24.7 (C_c or C_d), 34.4 (C_e or C_b), 35.6 (C_e or C_b), 60.3 (C_a), 62.2 (C_f), 125.5 ($CH_{ar}CNO_2$), 130.7 ($CH_{ar}CSO_2$), 133.0 (CH_{ar}), 133.5 (CH_{ar}), 134.5 ($C_{quat}SO_2$), 147.5 ($C_{quat}NO_2$) ppm. IR (KBr): ν=3366, 1540, 1355, 1169 cm^{-1}.

4.2.4. General procedure for aziridination. A suspension of cyclohexyl methanesulfonate **5** or **6** (19.78 g, 52.27 mmol) and anhydrous K_2CO_3 (28.87 g, 208.9 mmol, 4 equiv) in CH_3CN (600 mL) was warmed (50 °C) for 1.5 h. The mixture was then concentrated.

4.2.4.1. 7-(2-Nitro-phenylsulfonyl)-7-aza-bicyclo-[4.1.0]heptane 8.[18] The yellow solid residue obtained was taken up in CH_2Cl_2 (300 mL). The organic solution was washed with water until neutrality, dried, then concentrated to give the title compound **8** as a yellow solid (14.17 g, 50.19 mmol, 96%). Its purity was checked by HPLC (Column B, *n*-heptane/EtOAc 75:25 v/v, 1.5 mL/min, t_R=4.7 min). Mp 126 °C. ^{1}H NMR ($CDCl_3$): δ=1.19–1.31 (m, 2H, C*H*H_c), 1.36–1.46 (m, 2H, C*H*H_c), 1.82–1.98 (m, 4H, H_b), 3.22–3.27 (m, 2H, H_a), 7.71–7.77 (m, 3H, C*H*$_{ar}$), 8.17–8.22 (m, 1H, C*H*$_{ar}CSO_2$) ppm. ^{13}C NMR ($CDCl_3$): δ=19.4 (C_c), 22.9 (C_b), 42.5 (C_a), 124.3 ($CH_{ar}CNO_2$), 130.8 ($CH_{ar}CSO_2$), 132.1 (CH_{ar}), 134.0 (CH_{ar}), 132.9 ($C_{quat}SO_2$), 148.0 ($C_{quat}NO_2$) ppm. IR (KBr): ν=1545, 1367, 1330, 1168 cm^{-1}. CI-HRMS: *m/z* calcd for $C_{12}H_{15}N_2O_4S$, 283.0753; found, 283.0746 $[M+H]^+$.

4.2.4.2. 7-(4-Nitro-phenylsulfonyl)-7-aza-bicyclo-[4.1.0]heptane 9.[38] The whitish solid residue obtained was taken up in AcOEt (300 mL). The organic solution was washed with water (100 mL) and the aqueous layer was further extracted with AcOEt (2×150 mL). The combined organic layers were dried, then concentrated to give the title compound **9** as a pale yellow solid (15.0 g, 52.27 mmol, 100%). Its purity was checked by HPLC (Column B, *n*-heptane/EtOAc 75:25 v/v, 1.2 mL/min, t_R=4.3 min). Mp 138 °C.

4.3. Preparation of the ethylenediamine derivatives

4.3.1. *N*-(2-Amino-ethyl)-2-nitro-phenylsulfonamide hydrochloride 11[20] **and *N*-[2-(2-nitro-phenylsulfonyl)-amino-ethyl]-2-nitro-phenylsulfonamide 12.**[20,23] A solution of 2-nitro-phenylsulfonyl chloride (10.98 g, 49.54 mmol) in THF (50 mL) was added dropwise (over 2 h) to a cooled (0–5 °C) solution of ethane-1,2-diamine (8.94 g, 148.75 mmol, 3 equiv) in THF (25 mL). At the end of the addition, the resulting mixture was allowed to warm up to room temperature and was stirred for an additional 30 min. The crude mixture was then concentrated, and the residue obtained was taken up in CH_2Cl_2 (50 mL) and H_2O (50 mL). The aqueous layer was further extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried and concentrated. The oily residue obtained was then treated with a concentrated aqueous solution of hydrogen chloride (15 mL). The instantaneously formed precipitate was separated by filtration to yield *N*-[2-(2-nitro-phenylsulfonyl)amino-ethyl]-2-nitro-phenylsulfonamide **12** as a whitish solid (2.90 g, 6.74 mmol, 27%). Mp 160 °C. ^{1}H NMR ($CDCl_3$): δ=3.32 (s, 4H), 5.67 (br s, 2H, N*H*), 7.75–7.77 (m, 4H), 7.87–7.90 (m, 2H), 8.10–8.12 (m, 2H) ppm. The resulting orange aqueous filtrate was concentrated to give a solid that was dried and led to the title compound **11** as a bright yellow solid (10.10 g, 35.85 mmol, 72%). Mp 164 °C. ^{1}H NMR (D_2O): δ=3.20 (t, $^3J_{H,H}(1)$=5.6 Hz, 2H), 3.38 (t, $^3J_{H,H}(1)$=5.6 Hz, 2H), 7.79–7.86 (m, 2H), 7.89–7.96 (m, 1H), 8.02–8.09 (m, 1H) ppm. IR (KBr): ν=3210–2860 (broad), 1544, 1367, 1340, 1158 cm^{-1}.

4.3.2. *tert*-Butyl [2-(2-nitro-phenylsulfonylamino)ethyl-amino]acetate 13. A solution of *tert*-butyl bromoacetate (2.6 mL, 17.83 mmol, 1 equiv) in THF (75 mL) was added dropwise (over 1 h), at room temperature, to a suspension of aminosulfonamide hydrochloride **11** (4.996 g, 17.70 mmol) and triethylamine (7.4 mL, 53.1 mmol, 3 equiv) in THF (75 mL). Two other portions of both triethylamine (1.3 mL, 9.3 mmol, 0.5 equiv) and *tert*-butyl bromoacetate (1.3 mL, 8.9 mmol, 0.5 equiv) in solution in THF (30 mL) were added dropwise (over 0.5 h), which was necessary to achieve the complete conversion of *N*-(2-amino-ethyl)-2-nitro-phenylsulfonamide. After stirring overnight at room temperature, the crude mixture was concentrated and the residue was taken up in CH_2Cl_2 (100 mL) and H_2O (50 mL). The aqueous layer was then further extracted with CH_2Cl_2 (2×100 mL). The combined organic layers were dried and concentrated. The oily yellow residue obtained was purified by chromatography on silica gel (*n*-heptane/EtOAc, 2:8 to 0:10) and gave the title compound **13** as a yellow oil (4.79 g, 13.328 mmol, 75%). ^{1}H NMR ($CDCl_3$): δ*=1.43 (s, 9H, CH_3), 2.72–2.79 (m, 2H, CH_2), 3.09–3.17 (m, 2H, CH_2), 3.19 (s, 2H, CH_2CO), 7.69–7.76 (m, 2H, CH_{ar}), 7.82–7.88 (m, 1H, CH_{ar}CNO$_2$), 8.09–8.16 (m, 1H, CH_{ar}CSO$_2$) ppm. *The signals accounting for N*H* were not distinguished. ^{13}C NMR ($CDCl_3$): δ=28.2 (*C*H$_3$), 43.3 (*C*H$_2$), 48.0 (*C*H$_2$), 51.1 (*C*H$_2$CO), 81.6 [*C*(CH$_3$)$_3$], 125.4 (*C*H$_{ar}$CNO$_2$), 131.2 (*C*H$_{ar}$CSO$_2$), 132.7 (*C*H$_{ar}$), 133.5 (*C*H$_{ar}$), 133.8 (C_{quat}SO$_2$), 146.0 (C_{quat}NO$_2$), 171.7 (*C*O) ppm. IR (KBr): ν=3334, 1732, 1542, 1366, 1342, 1165 cm^{-1}.

4.4. Preparation of the triamine blocks

4.4.1. (±) *trans tert*-Butyl {[2-(2-nitro-phenylsulfonyl-amino)cyclohexyl]-[2-(2-nitro-phenylsulfonylamino)-ethyl]amino}acetate 15. A solution of aziridine **8** (4.50 g, 15.94 mmol, 1 equiv) in anhydrous CH_3CN (100 mL) was added dropwise to a solution of diamine **13** (5.72 g, 15.92 mmol) in anhydrous CH_3CN (120 mL) at reflux. After 2 days, the crude mixture was concentrated and the residue was purified by chromatography on silica gel (*n*-heptane/EtOAc, 6:4 to 4:6) and gave the title compound **15** as a yellow oil (8.08 g, 2.43 mmol, 79%). ^{1}H NMR ($CDCl_3$): δ=1.09–1.20 (m, 4H, H$_{b,ax}$, H$_{e,ax}$, C*H*H$_c$ and C*H*H$_d$), 1.42 (s, 9H, CH_3), 1.58–1.65 (m, 1H, C*H*H$_c$ or C*H*H$_d$), 1.70–1.77 (m, 1H, C*H*H$_c$ or C*H*H$_d$), 1.84–1.92 (m, 1H, H$_{b,eq}$), 2.09–2.16 (m, 1H, H$_{e,eq}$), 2.30 (ddd, $^3J_{H,H}(1)=^3J_{H,H}(2)$=10.6 Hz, $^3J_{H,H}(3)$=3.7 Hz, 1H, H$_a$), 2.77 (t, $^3J_{H,H}(4)$=6.3 Hz, 2H, H$_g$), 3.03–3.12 (m, 2H, H$_h$), 3.13–3.22 (m, 3H, CH_2CO$_2$ and H$_f$), 6.05 (t, $^3J_{H,H}(5)$=5.5 Hz, 1H, N*H*CH$_2$), 6.35 (d, $^3J_{H,H}(6)$=3.3 Hz, 1H, N*H*CH), 7.66–7.79 (m, 5H, CH_{ar}), 7.80–7.85 (m, 1H, CH_{ar}), 8.10–8.17 (m, 2H, CH_{ar}CSO$_2$) ppm. ^{13}C NMR ($CDCl_3$): δ=24.4 (C$_c$ or C$_d$), 25.3 (C$_c$ or C$_d$), 26.8 (C$_b$), 28.1 (*C*H$_3$), 33.4 (C$_e$), 42.8 (C$_h$), 51.5 (C$_g$), 53.1 (*C*H$_2$CO$_2$), 55.3 (C$_f$), 65.8 (C$_a$), 82.0 [*C*(CH$_3$)$_3$], 125.0 (*C*H$_{ar}$CNO$_2$), 125.2 (*C*H$_{ar}$CNO$_2$), 130.4 (*C*H$_{ar}$CSO$_2$), 131.1 (*C*H$_{ar}$CSO$_2$), 132.6 (*C*H$_{ar}$), 132.8 (*C*H$_{ar}$), 133.3 (*C*H$_{ar}$), 133.4 (*C*H$_{ar}$), 133.8 (C_{quat}SO$_2$), 135.0 (C_{quat}SO$_2$), 148.0 (C_{quat}NO$_2$), 148.1 (C_{quat}NO$_2$), 171.8 (*C*O) ppm. IR (KBr): ν=3291 (broad), 1729, 1544, 1366, 1173 cm^{-1}. CI-HRMS: *m*/*z* calcd for $C_{26}H_{36}N_5O_{10}S_2$, 642.1904; found, 642.1904 [M+H]$^+$.

4.4.2. (±) *trans tert*-Butyl ({2-[(*tert*-butoxycarbonyl-methyl)-(2-nitro-phenylsulfonyl)amino]cyclohexyl}-{2-[(*tert*-butoxycarbonylmethyl)-(2-nitro-phenylsulfonyl)-amino]ethyl}amino)acetate 19. A suspension of triamine **15** (8.04 g, 12.53 mmol) and anhydrous K_2CO_3 (6.92 g, 50.07 mmol, 4 equiv) in CH_3CN (300 mL) was refluxed for 2 h and became orange coloured. A solution of *tert*-butyl bromoacetate (7.41 mL, 50.14 mmol, 4 equiv) in CH_3CN (20 mL) was added dropwise (45 min) and the resulting mixture was further refluxed overnight. The crude mixture was concentrated and the residue was purified by chromatography on silica gel (*n*-heptane/EtOAc, 7:3 to 6:4) to give the title compound **19** as a yellowish solid (7.09 g, 8.15 mmol, 65%). Mp 82 °C. ^{1}H NMR ($CDCl_3$): δ=1.00–1.55 (m, 4H, H$_{b,ax}$, H$_{e,ax}$, C*H*H$_c$ and C*H*H$_d$), 1.27 (s, 9H, CH_3), 1.31 (s, 9H, CH_3), 1.46 (s, 9H, CH_3), 1.66–1.82 (m, 2H, C*H*H$_c$ and C*H*H$_d$), 2.00–2.19 (m, 2H, H$_{b,eq}$ and H$_{e,eq}$), 2.49–2.74 (m, 2H, C*H*H$_g$ and H$_a$), 2.93 (ddd, $^2J_{H,H}(1)=^3J_{H,H}(1)$=11.3 Hz, $^3J_{H,H}(2)$=5.1 Hz, 1H, C*H*H$_g$), 3.20 and 3.28 (AB, $^2J_{H,H}(2)$=16.6 Hz, 2H, (CH$_2$)(CH)NCH_2CO$_2$), 3.39 (ddd, $^2J_{H,H}(3)$=15.0 Hz, $^3J_{H,H}(3)$=10.7 Hz, $^3J_{H,H}(2)$=5.1 Hz, 1H, C*H*H$_h$), 3.61 (ddd, $^2J_{H,H}(3)$=15.0 Hz, $^3J_{H,H}(1)$=11.3 Hz, $^3J_{H,H}(4)$=4.5 Hz, 1H, C*H*H$_h$), 3.81 and 3.86 (d of AB, $^2J_{H,H}(4)$=19.2 Hz, 1H, (Nos)NC*H*HCO$_2$), 3.92–4.05 (m, 1H, H$_f$), 4.08 and 4.23 (AB, $^2J_{H,H}(5)$=18.5 Hz, 2H, (Nos)NCH_2CO$_2$), 4.37 and 4.42 (d of AB, $^2J_{H,H}(4)$=19.2 Hz, 1H, (Nos)NC*H*HCO$_2$), 7.51–7.71 (m, 6H, CH_{ar}), 7.95–8.03 (m, 1H, CH_{ar}CSO$_2$), 8.05–8.11 (m, 1H, CH_{ar}C-SO$_2$) ppm. ^{13}C NMR ($CDCl_3$): δ=25.4 (C$_b$ or C$_c$ or C$_d$), 25.8 (C$_b$ or C$_c$ or C$_d$), 26.6 (C$_b$ or C$_c$ or C$_d$), 27.8 and 28.1 (3 *C*H$_3$)$^\$$, 32.5 (C$_e$), 45.3* (*C*H$_2$CO$_2$), 47.9 (C$_h$ or *C*H$_2$CO$_2$), 48.7* (*C*H$_2$CO$_2$), 49.4 (C$_h$ or *C*H$_2$CO$_2$), 54.8* (C$_f$ or C$_g$), 59.8* (C$_f$ or C$_g$), 63.0 (C$_a$), 80.9 [*C*(CH$_3$)$_3$], 81.6 [*C*(CH$_3$)$_3$], 81.7 [*C*(CH$_3$)$_3$], 123.7 (*C*H$_{ar}$CNO$_2$), 123.8 (*C*H$_{ar}$CNO$_2$), 130.8 (*C*H$_{ar}$CSO$_2$), 131.2 (*C*H$_{ar}$CSO$_2$), 131.3 (*C*H$_{ar}$), 131.6 (*C*H$_{ar}$), 132.9 (*C*H$_{ar}$), 133.1 (*C*H$_{ar}$), 133.5 (C_{quat}SO$_2$), 135.3 (C_{quat}SO$_2$), 147.95 (C_{quat}NO$_2$), 148.05 (C_{quat}NO$_2$), 167.9 (*C*O), 168.7 (*C*O), 171.3 (*C*O) ppm. $^\$$These two signals account for the three populations of *C*H$_3$. *This signal has an uncommon shape: very small and broad. IR (KBr): ν=1745, 1546, 1370, 1353, 1156, 1126 cm^{-1}. CI-HRMS: *m*/*z* calcd for $C_{38}H_{56}N_5O_{14}S_2$, 870.3265; found, 870.3272 [M+H]$^+$.

4.4.3. (±) *trans tert*-Butyl {[2-(*tert*-butoxycarbonylmethyl-amino)cyclohexyl]-[2-(*tert*-butoxycarbonylmethylamino)-ethyl]amino}acetate 20. 2-Mercaptoethanol (5.33 mL, 76.0 mmol, 11 equiv) and DBU (4.6 mL, 30.55 mmol, 4.5 equiv) were added to a solution of disulfonamide **19** (5.91 g, 6.79 mmol) in CH_3CN (300 mL). The resulting mixture was stirred at room temperature for 2 h. The crude mixture was then concentrated and the residue was taken up in CH_2Cl_2 (300 mL) and H_2O (300 mL). The aqueous layer was further extracted with CH_2Cl_2 (3×300 mL). The combined organic layers were dried and concentrated. The oily yellow residue obtained was purified by chromatography on silica gel (CH_2Cl_2/MeOH, 98:2) and gave the title compound **20** as a yellowish oil (1.757 g, 3.516 mmol, 52%). ^{1}H NMR ($CDCl_3$): δ=0.98–1.35 (m, 4H, H$_{b,ax}$, H$_{e,ax}$, C*H*H$_c$ and C*H*H$_d$), 1.37–1.49 (m, 27H, CH_3), 1.63–1.78 (m, 2H, C*H*H$_c$ and C*H*H$_d$), 1.81–1.89 (m, 1H, H$_{b,eq}$ or H$_{e,eq}$), 1.95–2.05 (m, 1H, H$_{b,eq}$ or H$_{e,eq}$), 2.25–2.44 (m, 4H, H$_a$, H$_f$ and N*H*), 2.63–2.81 (m, 4H, H$_g$ and H$_h$), 3.06

and 3.11 (d of AB, $^{2}J_{H,H}(1)$=17.3 Hz, 1H, NC*H*HCO$_2$ or (CH)NHC*H*HCO$_2$), 3.22 and 3.26 (d of AB, $^{2}J_{H,H}(2)$= 17.3 Hz, 1H, NC*H*HCO$_2$ or (CH)NHC*H*HCO$_2$), 3.30–3.42 (m, 4H, (CH)NHC*H*HCO$_2$, NC*H*HCO$_2$ and (CH$_2$)NHC*H*$_2$CO$_2$) ppm. ^{13}C NMR ($CDCl_3$): δ=24.6 (C$_c$ or C$_d$), 25.7 (C$_c$ or C$_d$), 28.2 (3*C*H$_3$)$^{\$}$, 29.8 (C$_b$ or C$_e$), 31.2 (C$_b$ or C$_e$), 48.2, 48.4, 51.8 and 53.0 (C$_g$, C$_h$ and 3 *C*H$_2$CO$_2$)*, 57.4 (C$_a$ or C$_f$), 65.9 (C$_a$ or C$_f$), 80.7 and 81.0 [3*C*(CH$_3$)$_3$]$^{£}$, 171.5 and 171.9 (3 *C*O)$^{\#}$ ppm. $^{\$}$This unique signal accounts for the three populations of *C*H$_3$.*These four signals account for the five populations of *C*H$_2$ mentioned. $^{£}$These two signals account for the three populations of *C*(CH$_3$)$_3$. $^{\#}$These two signals account for the three populations of *C*O. CI-HRMS: *m*/*z* calcd for $C_{26}H_{50}N_3O_6$, 500.3700; found, 500.3691 [M+H]$^+$.

4.4.4. (±) *trans tert*-Butyl ({2-[(2-nitro-phenylsulfonyl)-amino]cyclohexyl}-{2-[(*tert*-butoxycarbonylmethyl)-(2-nitro-phenylsulfonyl)amino]ethyl}amino)acetate 21. A suspension of triamine **15** (0.50 g, 0.78 mmol) and dried Na_2CO_3 (0.165 g, 1.56 mmol, 2 equiv) in anhydrous CH_3CN (25 mL) was refluxed for 2 h. *tert*-Butyl bromoacetate (0.25 mL, 1.55 mmol, 2 equiv) in CH_3CN was added dropwise and the resulting mixture was further refluxed overnight. The crude mixture was then concentrated, and the residue obtained was taken up in CH_2Cl_2 (30 mL) and H_2O (20 mL). The aqueous layer was further extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were dried and concentrated. The residue obtained was purified by chromatography on silica gel (*n*-heptane/EtOAc, 6:4) and gave the title compound **21** as a yellow solid (0.52 g, 0.688 mmol, 88%). Its purity was checked by HPLC (Column B, *n*-heptane/EtOAc 70:30 v/v, 1.3 mL/min, t_R= 11.5 min). ^{1}H NMR ($CDCl_3$): δ=1.10–1.24 (m, 4H, H$_{b,ax}$, H$_{e,ax}$, C*H*H$_c$ and C*H*H$_d$), 1.36 (s, 9H, C*H*$_3$), 1.45 (s, 9H, C*H*$_3$), 1.58–1.66 (m, 1H, C*H*H$_d$), 1.71–1.80 (m, 1H, C*H*H$_c$), 1.83–1.92 (m, 1H, H$_{b,eq}$), 2.20–2.28 (m, 1H, H$_{e,eq}$), 2.29–2.38 (m, 1H, H$_a$), 2.64–2.74 (m, 1H, C*H*H$_g$), 2.76–2.86 (m, 1H, C*H*H$_g$), 3.12–3.23 (m, 3H, (CH$_2$)(CH)NC*H*$_2$CO$_2$ and H$_f$), 3.38 (t, $^{3}J_{H,H}$=7.8 Hz, 2H, *H*$_h$), 4.05 (s, 2H, (Nos)(CH)NC*H*$_2$CO$_2$), 6.75 (br d, $^{3}J_{H,H}$=1.7 Hz, 1H, N*H*), 7.57–7.60 (m, 1H, C*H*$_{ar}$CSO$_2$), 7.64–7.78 (m, 5H, C*H*$_{ar}$), 8.08–8.16 (m, 2H, C*H*$_{ar}$C-SO$_2$) ppm. ^{13}C NMR ($CDCl_3$)$^{£}$: δ=24.3 (C$_d$), 25.3 (C$_c$), 25.8 (C$_b$), 27.9 (*C*H$_3$), 28.2 (*C*H$_3$), 33.3 (C$_e$), 48.3 (C$_h$), 50.2 ((Nos)N*C*H$_2$CO$_2$), 53.3 (N*C*H$_2$CO$_2$), 55.0 (C$_f$), 65.0 (C$_a$), 81.8 [*C*(CH$_3$)$_3$], 82.4 [*C*(CH$_3$)$_3$], 123.9 (*C*H$_{ar}$CNO$_2$), 125.0 (*C*H$_{ar}$CNO$_2$), 130.4 (*C*H$_{ar}$CSO$_2$), 131.1 (*C*H$_{ar}$CSO$_2$), 132.0 (*C*H$_{ar}$), 132.4 (*C*H$_{ar}$), 133.0 (*C*$_{quat}$SO$_2$), 133.2 (*C*H$_{ar}$), 133.5 (*C*H$_{ar}$), 135.1 (*C*$_{quat}$SO$_2$), 148.1$^{\$}$ (*C*$_{quat}$NO$_2$), 167.7 (*C*O), 171.2 (*C*O) ppm. $^{£}$The signal relative to C$_g$ was not found. $^{\$}$This signal may account for the two populations of *C*$_{quat}$NO$_2$. FAB-HRMS: *m*/*z* calcd for $C_{32}H_{46}N_5O_{12}S_2$, 756.2584; found, 756.2569 [M+H]$^+$.

4.5. Macrocyclisations

4.5.1. (±) *trans tert*-Butyl [3,13-bis(2-nitro-phenylsulfonyl)-3,10,13,19-tetraaza-tricyclo[13.3.1.0^{4,9}]nonadeca-1(19),15,17-trien-10-yl]acetate 16. A suspension of disulfonamide **15** (1.00 g, 1.56 mmol) and anhydrous K_2CO_3 (0.86 g, 6.23 mmol, 4 equiv) in anhydrous *N*,*N*-dimethylacetamide (30 mL) was stirred at 100 °C under argon for several minutes. A solution of 2,6-bis(bromomethyl)pyridine (0.74 g, 2.80 mmol, 1.8 equiv) in anhydrous *N*,*N*-dimethylacetamide (15 mL) was added dropwise (20 min) in the previous mixture while stirring at 100 °C. At the end of the addition, heating and warming were maintained for an additional 4 h. The crude mixture was then concentrated and the residue obtained was taken up in CH_2Cl_2 (70 mL) and H_2O (30 mL). The aqueous layer was further extracted with CH_2Cl_2 (4×30 mL). The combined organic layers were dried and concentrated. The brown oil obtained was purified by chromatography on silica gel (*n*-heptane/EtOAc/MeOH, 5:5:0 to 0:6:4) and gave the title compound **16** as a light brown oil (0.81 g, 1.08 mmol, 69%). IR (KBr): ν=1736, 1544, 1371, 1162 cm^{-1}. CI-HRMS: *m*/*z* calcd for $C_{33}H_{41}N_6O_{10}S_2$, 745.2326; found, 745.2321 [M+H]$^+$.

4.5.2. (±) *trans tert*-Butyl [3,13-bis(*tert*-butoxycarbonyl-methyl)-3,10,13,19-tetraaza-tricyclo[13.3.1.0^{4,9}]nonadeca-1(19),15,17-trien-10-yl]acetate 18. A suspension of triamine **20** (1.65 g, 3.30 mmol) and anhydrous Na_2CO_3 (1.48 g, 14.0 mmol, 4 equiv) in anhydrous DMF (110 mL) was stirred at 100 °C under argon for 15 min. A solution of 2,6-bis(bromomethyl)pyridine (1.67 g, 6.30 mmol, 1.9 equiv) in anhydrous DMF (20 mL) was added dropwise (20 min) in the previous mixture while stirring at 100 °C. At the end of the addition, heating and warming were maintained for an additional 3 h. The crude mixture was then concentrated and the residue obtained was taken up in CH_2Cl_2 (50 mL) and H_2O (20 mL). The aqueous layer was further extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried and concentrated. The residue obtained was purified by chromatography on silica gel (CH_2Cl_2/MeOH, 99:1 to 95:5) and gave the title compound **18** as a light brown oil (1.178 g, 1.95 mmol, 59%). Its purity was checked by HPLC (Column C, MeOH/phosphate buffer (pH 2) 98:2 v/v, 1.2 mL/min, t_R=12.2 min). ^{1}H NMR ($CDCl_3$): δ=0.30–1.10 (m, 4H), 1.10–1.31 (m, 27H), 1.31–1.55 (m, 4H), 1.65–2.20 (m, 4H), 2.40–2.75 (m, 2H), 2.85–3.25 (m, 5H), 3.32–3.87 (m, 5H), 6.90–7.08 (m, 2H), 7.45–7.56 (m, 1H) ppm. ^{13}C NMR ($CDCl_3$)$^{\$}$: δ=23.0, 23.4, 23.8, 24.2, 24.5, 24.8, 25.0 and 26.8 (4*C*H$_2$), 27.2, 27.3, 27.4 and 27.5 (3*C*H$_3$), 46.5, 50.6, 51.6, 53.2, 55.0, 56.2, 56.9, 60.2, 61.1, 62.2 and 63.4 (7*C*H$_2$), 56.6, 63.7 and 65.5 (2*C*H), 82.1, 82.2, 82.3, 82.4 and 82.5 [3*C*(CH$_3$)$_3$], 120.4, 121.0, 121.9 and 122.3 (2*C*H$_{ar}$), 138.1 and 138.2 (1*C*H$_{ar}$), 156.8, 156.9, 157.4 and 157.6 (2*C*$_{quat,ar}$), 172.1, 172.4, 172.7, 172.9 and 173.4 (3*C*O). $^{\$}$Nearly all the ^{13}C signals are doubled that may be attributed to the presence of rotamers in $CDCl_3$ solution; an analogue shape of the ^{13}C NMR spectrum was obtained for a solution in DMSO-d_6; the number of population of ^{13}C and their parity are indicated in parentheses. IR (neat): ν=1724, 1244, 1231, 1158 cm^{-1}. CI-LRMS: *m*/*z* 603.4 [M+H]$^+$ (100%), 489.4 [M−CH$_2$CO$_2$*t*Bu+2H]$^+$ (<5%). CI-HRMS: *m*/*z* calcd for $C_{33}H_{55}N_4O_6$, 603.4122; found, 603.4117 [M+H]$^+$.

4.6. Deprotection of macrocyclic compounds

4.6.1. (±) *trans tert*-Butyl (3,10,13,19-tetraaza-tricyclo-[13.3.1.0^{4,9}]nonadeca-1(19),15,17-trien-10-yl)acetate 17. Thiophenol (0.18 mL, 1.75 mmol, 2.2 equiv) was added to a suspension of disulfonamide **16** (0.58 g, 0.78 mmol) and Na_2CO_3 (0.25 g, 2.36 mmol, 3 equiv) in anhydrous DMF

(30 mL). The resulting mixture was stirred at room temperature overnight. The crude mixture was then concentrated and the residue was taken up in CH_2Cl_2 (60 mL) and H_2O (30 mL). The aqueous layer was further extracted with CH_2Cl_2 (5×20 mL). The combined organic layers were dried and concentrated. The residue obtained was purified by chromatography on aluminium oxide gel (EtOAc/MeOH, 10:0 to 8:2) and gave the title compound **17** as a yellowish oil (0.120 g, 0.32 mmol, 41%). ^{1}H NMR ($CDCl_3$): δ*=0.75–1.22 (m, 4H, $H_{b,ax}$, $H_{e,ax}$, C*H*H_c and C*H*H_d), 1.46 (m, 9H, C*H*$_3$), 1.53–1.87 (m, 4H, H_f, $H_{b,eq}$, C*H*H_c and C*H*H_d), 1.98–2.08 (m, 1H, $H_{e,eq}$), 2.09–2.35 (m, 3H, H_a, H_g or H_h), 2.38–2.54 (m, 1H, C*H*H_g or C*H*H_h), 2.93–3.08 (m, 1H, C*H*H_g or C*H*H_h), 3.30 (m, 2H, C*H*$_2$CO$_2$), 3.59 and 3.63 (d of AB, $^2J_{H,H}(1)$=16.5 Hz, 1H, NHC*H*H), 3.71 and 3.75 (d of AB, $^2J_{H,H}(2)$=15.7 Hz, 1H, NHC*H*H), 3.97 and 4.00 (d of AB, $^2J_{H,H}(2)$=15.7 Hz, 1H, NHC*H*H), 4.18 and 4.22 (d of AB, $^2J_{H,H}(1)$=16.5 Hz, 1H, NHC*H*H), 6.92 (d, $^3J_{H,H}(1)$=7.6 Hz, 1H, C*H*ar), 6.94 (d, $^3J_{H,H}(2)$=7.6 Hz, 1H, C*H*ar), 7.48 (dd, $^3J_{H,H}(1)$=$^3J_{H,H}(2)$=7.6 Hz, 1H, C*H*ar) ppm. *The signals accounting for N*H* were not distinguished. ^{13}C NMR ($CDCl_3$): δ=24.5 (C_b or C_c or C_d), 25.4 (C_b or C_c or C_d), 25.9 (C_b or C_c or C_d), 28.2 (*C*H$_3$), 31.8 (C_e), 47.8 (C_g or C_h), 49.4 (C_g or C_h), 49.6 (*C*H$_2$NH), 55.0 (*C*H$_2$NH), 55.4 (C_f), 57.4 (*C*H$_2$CO$_2$), 68.4 (C_a), 80.9 [*C*(CH$_3$)$_3$], 119.1 (*C*H$_{ar}$C), 120.5 (*C*H$_{ar}$C), 136.3 (*C*H$_{ar}$CH), 159.2 (Cquat $_{ar}$), 159.6 (Cquat $_{ar}$), 171.9 (*C*O) ppm. IR (KBr): ν=3396 (broad), 1728, 1156, 1114 cm^{-1}. CI-HRMS: *m*/*z* calcd for $C_{21}H_{35}N_4O_2$, 375.2760; found, 375.2769 $[M+H]^+$.

4.6.2. (±) *trans* 3,10,13,19-Tetraaza-tricyclo[13.3.1.0^{4,9}]-nonadeca-1(19),15,17-triene-3,10,13-triacetic acid 1. A solution of anhydrous HCl in Et_2O (ca. 1.6 M, 100 mL, ca. 100 equiv) was poured over the macrocyclic tri-*tert*-butyl ester **18** (1.06 g, 1.76 mmol). A white precipitate appeared after several minutes and stirring was maintained at room temperature overnight. The precipitate formed was then filtered and washed with Et_2O. The crude solid was purified by chromatography on an ion-exchange resin (Dowex® 1X8-50, formate form, elution with distilled water than with a 0.02 M aqueous solution of formic acid) to provide the title compound **1** as a white solid that became deliquescent on standing under ambient conditions (0.730 g, 1.68 mmol, 95%). Its purity was checked by HPLC (Column A, H_2O–TFA (pH 2.8)/CH_3CN gradient 98:2 to 40:60 v/v in 60 min, 1.0 mL/min, t_R=9.5 min). IR (KBr): ν=3409 (broad), 1738, 1445, 1405, 1201 cm^{-1}. FAB-HRMS: *m*/*z* calcd for $C_{21}H_{31}N_4O_6$, 435.2244; found, 435.2235 $[M+H]^+$.

4.7. Gadolinium complexation

Gadolinium(III) chloride hexahydrate (0.035 g, 0.094 mmol, 1.0 equiv) was added to a solution of macrocyclic ligand **1** (0.04 g, 0.092 mmol) in H_2O (2 mL). The initial pH 5.8 was adjusted to pH 5.0. The resulting mixture was stirred for 3 h at room temperature while pH maintained at 5.0. The pH was then adjusted to 6.7 and the resulting mixture was filtered on a Millex filter (0.22 μm) to obtain 3.5 mL of a final aqueous solution. The purity of the complex in solution was checked by HPLC (Column A, H_2O–TFA (pH 2.8)/CH_3CN gradient 9:1 to 6:4 v/v in 20 min, 1.0 mL/min, t_R=13.1 min). ESI-LRMS: more abundant *m*/*z* 590.0 $[C_{21}H_{28}{}^{158}GdN_4O_6]^+$. The presence of free Gd(III) ions was checked by the usual Arsenazo III test[39] and assessed to 0.4% mol/mol.

References and notes

1. Caravan, P.; Ellison, J. J.; McMurry, T. J.; Lauffer, R. B. *Chem. Rev.* **1999**, *99*, 2293–2352.
2. Rohrer, M.; Bauer, H.; Mintorovitch, J.; Requardt, M.; Weinmann, H.-J. *Invest. Radiol.* **2005**, *40*, 715–724.
3. Jacques, V.; Desreux, J. F. *Top. Curr. Chem.* **2002**, *221*, 123–164.
4. Aime, S.; Fasano, M.; Terreno, E. *Chem. Soc. Rev.* **1998**, *27*, 19–29.
5. Jaszberenyi, Z.; Sour, A.; Toth, E.; Benmelouka, M.; Merbach, A. E. *Dalton Trans.* **2005**, 2713–2719.
6. Ranganathan, R. S.; Raju, N.; Fan, H.; Zhang, X.; Tweedle, M. F.; Desreux, J. F.; Jacques, V. *Inorg. Chem.* **2002**, *41*, 6856–6866.
7. Comblin, V.; Gilsoul, D.; Hermann, M.; Humblet, V.; Jacques, V.; Mesbahi, M.; Sauvage, C.; Desreux, J. F. *Coord. Chem. Rev.* **1999**, *185–186*, 451–470.
8. Aime, S.; Botta, M.; Crich, S. G.; Giovenzana, G. B.; Jommi, G.; Pagliarin, R.; Sisti, M. *Inorg. Chem.* **1997**, *36*, 2992–3000.
9. Aime, S.; Botta, M.; Frullano, L.; Crich, S. G.; Giovenzana, G.; Pagliarin, R.; Palmisano, G.; Sirtori, F. R.; Sisti, M. *J. Med. Chem.* **2000**, *43*, 4017–4024.
10. Aime, S.; Gianolio, E.; Corpillo, D.; Cavallotti, C.; Palmisano, G.; Sisti, M.; Giovenzana, G. B.; Pagliarin, R. *Helv. Chim. Acta* **2003**, *86*, 615–632.
11. Dioury, F.; Sylvestre, I.; Siaugue, J.-M.; Wintgens, V.; Ferroud, C.; Favre-Réguillon, A.; Foos, J.; Guy, A. *Eur. J. Org. Chem.* **2004**, 4424–4436.
12. Siaugue, J.-M.; Segat-Dioury, F.; Sylvestre, I.; Favre-Reguillon, A.; Foos, J.; Madic, C.; Guy, A. *Tetrahedron* **2001**, *57*, 4713–4718.
13. Galaup, C.; Carrie, M.-C.; Tisnes, P.; Picard, C. *Eur. J. Org. Chem.* **2001**, 2165–2175.
14. Galaup, C.; Couchet, J. M.; Picard, C.; Tisnes, P. *Tetrahedron Lett.* **2001**, *42*, 6275–6278.
15. Kan, T.; Fukuyama, T. *Chem. Commun.* **2004**, 353–359.
16. Sodergren, M. J.; Alonso, D. A.; Bedekar, A. V.; Andersson, P. G. *Tetrahedron Lett.* **1997**, *38*, 6897–6900.
17. Müller, P.; Baud, C.; Jacquier, Y.; Moran, M.; Naegeli, I. *J. Phys. Org. Chem.* **1996**, *9*, 341–347.
18. Bridger, G.; Skerlj, R.; Kaller, A.; Harwig, C.; Bogucki, D.; Wilson, T. R.; Crawford, J.; McEachern, E. J.; Atsma, B.; Nan, S.; Zhou, Y.; Schols, D. PCT Int. Appl., WO0056729, 2000.
19. Dioury, F.; Guené, E.; Di Scala-Roulleau, A.; Ferroud, C.; Guy, A.; Port, M. *Tetrahedron Lett.* **2005**, *46*, 611–613.
20. Kirsanov, A. V.; Kirsanova, N. A. *J. Gen. Chem. USSR* **1962**, *32*, 887–892.
21. Hidai, Y.; Kan, T.; Fukuyama, T. *Tetrahedron Lett.* **1999**, *40*, 4711–4714.
22. Wilson, M. E.; Nowick, J. S. *Tetrahedron Lett.* **1998**, *39*, 6613–6616.
23. Aicher, T. D.; Chen, Z.; Chen, Y.; Faul, M. M.; Krushinski, J. H., Jr.; Le Huerou, Y.; Pineiro-Nunez, M. M.; Rocco, V. P.; Ruley, K. M.; Schaus, J. M.; Thompson, D. C.; Tupper, D. E. PCT Int. Appl., WO03082877, 2003.
24. Johnson, F.; Gupta, R. C. PCT Int. Appl., WO9852552, 1998.

25. Tsangaris, J. M.; Baxevanidis, G. T. *Hem. Hron., Nei Seira* **1972**, *1*, 247–254.
26. ^{1}H NMR ($CDCl_3$): δ=1.43 (s, 18H, CH_3), 2.87 (t, $^{3}J_{H,H}$=5.5 Hz, 2H, CH_2N), 3.09–3.16 (m, 2H, CH_2NH), 3.30 (s, 4H, CH_2CO), 6.67 (br t, $^{3}J_{H,H}$=5.1 Hz, 1H, N*H*), 7.67–7.73 (m, 2H, CH_{ar}), 7.79–7.85 (m, 1H, C$H_{ar}CNO_2$), 8.10–8.16 (m, 1H, C$H_{ar}CSO_2$) ppm. ^{13}C NMR ($CDCl_3$): δ=28.1 (*C*H_3), 41.7 (*C*H_2NH), 53.4 (*C*H_2N), 56.3 (*C*H_2CO), 81.6 (*C*$(CH_3)_3$), 125.0 (*C*$H_{ar}CNO_2$), 130.9 (*C*$H_{ar}CSO_2$), 132.3 (*C*H_{ar}), 133.2 (*C*H_{ar}), 134.0 (*C*$_{quat}SO_2$), 148.2 (*C*$_{quat}NO_2$), 170.7 (*C*O) ppm.
27. The [2+2] adducts were easily separated from the desired [1+1] adduct **16** by chromatography on silica gel (*n*-heptane/EtOAc/MeOH, 5:5:0 to 0:8:2 v/v/v). The mixture of [2+2] adducts is less polar than the [1+1] adduct **16** (*n*-heptane/EtOAc 3:7 v/v, [2+2]: 0.5<R_f<0.6; [1+1]: 0<R_f <0.1). An LC–MS analysis pointed the presence of two signals accounting for [2+2] adducts. HPLC: Column B, *n*-heptane/EtOAc 4:6 v/v, 0.8 mL/min, t_R=16.2 and 19.3 min. The corresponding mass spectra for these two signals were analogous; ESI-LRMS: *m*/*z* 745.4 (*z*=2) $[M+2H]^{2+}$ (100%), 717.4 (*z*=2) $[M-{}^{t}Bu+3H]^{2+}$ (5%).
28. Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373–6374.
29. CI-LRMS: *m*/*z* 603.3 $[M_{tri\text{-}alkylated}+H]^{+}$ (57%), 717.4 $[M_{tetra\text{-}alkylated}]^{+}$ (22%); CI-HRMS: *m*/*z* calcd for $C_{39}H_{65}N_4O_8$, 717.4802; found, 717.4809 $[M_{tetra\text{-}alkylated}]^{+}$.
30. The ^{1}H NMR spectrum was too complex to be assigned but it appeared consistent with the expected product **18**. In the ^{13}C NMR spectrum, nearly all the signals were split. CI-LRMS: *m*/*z* 489 $[M_{di\text{-}alkylated}+H]^{+}$ (21%), 603 $[M_{tri\text{-}alkylated}+H]^{+}$ (100%). It should be however noted that the ^{1}H and ^{13}C NMR spectra of the expected product **18** obtained later from Route B proved to be identical to these ones. Moreover, the *m*/*z* 489 signal corresponding to the di-*N*-alkylated product was also present, but in lesser abundance (<5%), in the low-resolution mass spectrum of product **18** obtained from Route B. These results led us to conclude that, at least, a part of the *m*/*z* 489 signal may result from a fragmentation process during the mass spectrometric analysis. In this case, a prolonged reaction with other portions of alkylating agent and base would probably have led to the tri-*N*-alkylated product **18** exclusively.
31. By using a 2-fold excess of alkylating agent, the reaction was rendered regioselective as the mono-*N*-alkylated product **21** was isolated in 88% yield.
32. Rew, Y.; Goodman, M. *J. Org. Chem.* **2002**, *67*, 8820–8826.
33. Nihei, K.-I.; Kato, M. J.; Yamane, T.; Palma, M. S.; Konno, K. *Synlett* **2001**, 1167–1169.
34. On the basis of GC–MS and ^{1}H NMR analyses, the spontaneous lactame formation was highly regioselective (≥90%). Spectral characterization of the major regioisomer: ^{1}H NMR ($CDCl_3$): δ*=1.00–1.30 (m, 4H, C*H*H_b, C*H*H_c, C*H*H_d and C*H*H_e), 1.42 (s, 9H, CH_3), 1.43 (s, 9H, CH_3), 1.60–1.88 (m, 3H), 1.92–2.10 (m, 1H), 2.30–2.48 (m, 2H, H_a and H_f), 2.53–2.72 (m, 1H), 2.92–3.02 (m, 1H), 3.18–3.55 (m, 6H), 3.91 and 4.10 (AB, 2H, $^{2}J_{H,H}$=17.3 Hz) ppm. *The signal accounting for N*H* was not distinguished. ^{13}C NMR ($CDCl_3$): δ=21.9, 24.3 and 25.2 (3*C*H_2), 28.08 (*C*H_3), 28.14 (*C*H_3), 30.6, 44.6, 47.5, 48.2, 48.3 and 52.9 (6*C*H_2), 56.3 and 65.9 (2*C*H), 81.5 and 81.9 [2*C*$(CH_3)_3$], 168.05, 168.11 and 171.2 (3*C*O) ppm. EI-LRMS: *m*/*z* 425 $[M]^{+}$ (92%), 369 $[M-{}^{t}Bu+H]^{+}$ (49%), 352 $[M-O{}^{t}Bu]^{+}$ (13%), 324 $[M-CO_2{}^{t}Bu]^{+}$ (84%), 313 (100%), 296 $[M-NHCH_2CO_2{}^{t}Bu+H]^{+}$ (27%), 281 $[M-CH_2NHCH_2CO_2{}^{t}Bu+H]^{+}$ (4%), 268 $[M-CH_2CH_2NHCH_2CO_2{}^{t}Bu+H]^{+}$ (70%), 254 (10%), 238 (29%), 225 (29%), 212 (14%), 197 (31%), 183 (11%), 171 (39%), 156 (44%), 139 (24%), 127 (18%), 112 (77%), 96 (30%), 81 (47%), 70 (43%), 57 $[{}^{t}Bu]^{+}$ (97%).
35. Nachman, I.; Port, M.; Raynal, I.; Rousseaux, O. PCT Int. Appl., WO03074523, 2003.
36. Hovland, R.; Glogard, C.; Aasen, A. J.; Klaveness, J. *Org. Biomol. Chem.* **2003**, *1*, 644–647.
37. Port, M.; Raynal, I.; Vander Elst, L.; Muller, R. M.; Dioury, F.; Ferroud, C.; Guy, A. *Contrast Med. Mol. Imag.* **2006**, *1*, 121–127.
38. Müller, P.; Baud, C.; Jacquier, Y. *Tetrahedron* **1996**, *52*, 1543–1548.
39. Kumar, K.; Chang, C. A.; Tweedle, M. F. *Inorg. Chem.* **1993**, *32*, 587–593.