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# Synthesis of two stereoisomeric polydentate ligands, *trans* and *cis* cyclopentane-1,2-diaminotetraacetic acids, and complexation by $^{111}$In and $^{153}$Sm

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**Abstract**—Two polyaminocarboxylic acid chelating agents were synthesized. Complexation properties regarding $^{111}$In and $^{153}$Sm, two radionuclides suitable for applications in immunoscintigraphy and radioimmunotherapy were investigated. The synthesis of aminodiacetic acid derivatives **7a** and **7b** involved preliminary stereoselective synthesis of the corresponding amines, *cis* and *trans* cyclopentane-1,2-diamines. $^{111}$In labelling confirmed the complexation abilities of the two ligands. An additional comparative study to probe the relationship between ligand structure and metal complex was performed with $^{153}$Sm. © 2002 Elsevier Science Ltd. All rights reserved.

## 1. Introduction

Polyaminocarboxylate groups, which have often been used for the design of polydentate ligands such as ethylenediamine tetraacetic acid (EDTA) and diethylenetriaminepentaacetic acid (DTPA), generally show high affinity for metal cations.[1,2] These ligands are widely used as chelating agents in fundamental research[3] or as diagnostic tools in the pharmaceutical industry[4,5] and are particularly suitable for magnetic resonance imaging (MRI),[6–10] nuclear medicine,[11–13] and more recently scintigraphy[14] or radiotherapy,[15–18] when coupled to a metallic radionuclide capable of visualising or destroying a malignant tumour. Such applications are highly efficient if the radioactive metal is specifically directed at the cancer cells. Thus, immunoscintigraphy (IS) and radioimmunotherapy (RIT) with radiolabelled antibodies linked chelate allow relatively specific diagnostic and therapeutic targeting of certain cancers and their recurrences.[19] In this context, various preclinical and clinical studies have demonstrated the benefit of using the affinity enhancement system (AES) associating a bispecific antibody with a bivalent hapten bearing a bifunctional chelating agent (BCA).[20]

This paper reports the synthesis of two chelating agents (precursors of BCAs) with a semi-rigid structure. This type of structure is essential to preorganisation, an important ligand property that increases the stability of the metal complex. Preorganisation (the tendency for a free ligand to adopt a favourable conformation for complexation of a metal ion)[21] minimises the degree of freedom of donor atoms, so that the structure of the chelate before complexation is similar to that with complex. Thus, the metal complexes of *trans*-CDTA (cyclohexanediaminetetraacetic acid) are often two to three times more stable than those of EDTA, because of the restricted movement of the aminodiacetic arms with CDTA.[22,23] Moreover, preorganisation of a polydentate chelator provides increased kinetic inertness of the metal complex as well as high thermodynamic stability.

The purpose of this study was to prepare chelates with a more rigid structure than that of CDTA. Two original stereoisomeric ligands with a *cis* and *trans* configuration were synthesised according to two parallel pathways: *cis*- and *trans*-cyclopentane-1,2-diamine-*N*,*N*,*N′*,*N′*-tetraacetic acid. The complexation properties of these two new compounds were confirmed with samarium-153 and indium-111.

## 2. Results and discussion

### 2.1. Synthesis of ligands

Commercially available cyclopentene was used as the

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*Keywords*: chelating agent synthesis; polyaminocarboxylic acid; cyclopentane-1,2-diamine; radionuclides.

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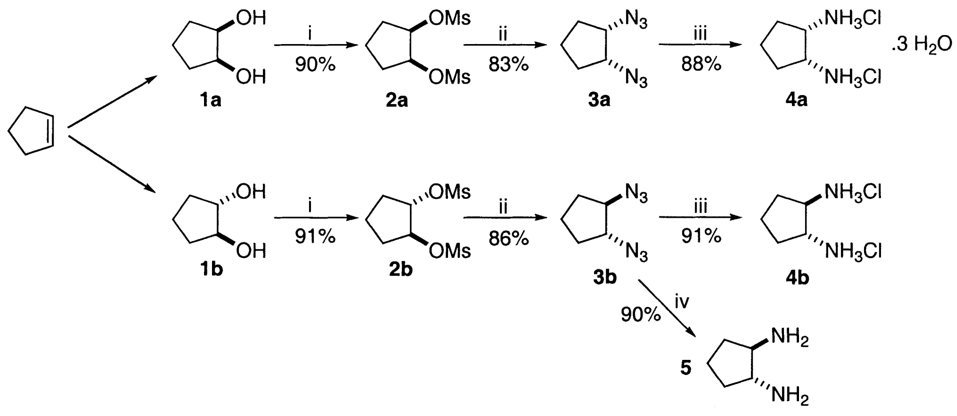


**Scheme 1.** Synthesis of cyclopentane-1,2-diamine dihydrochloride **4a** and **4b**. *Reagents and conditions*: (i) MsCl, $Et_3N$, $CH_2Cl_2$, 0°C, 4 h, then rt, 3 h; (ii) $NaN_3$, 15-crown-5, DMF, 85°C, 24 h; (iii) $Pd(OH)_2$, MeOH, HCl 2N, $H_2$, rt, 8 h; (iv) Pd/C 10%, EtOH, $H_2$, rt, 6 h.

starting reagent for the synthesis of *cis*- and *trans*-cyclopentane-1,2-diaminotetraacetic acid (Scheme 1). The key step in this synthetic process was the preparation of the two corresponding cyclopentane-1,2-diamine dihydrochlorides, **4a** and **4b**.

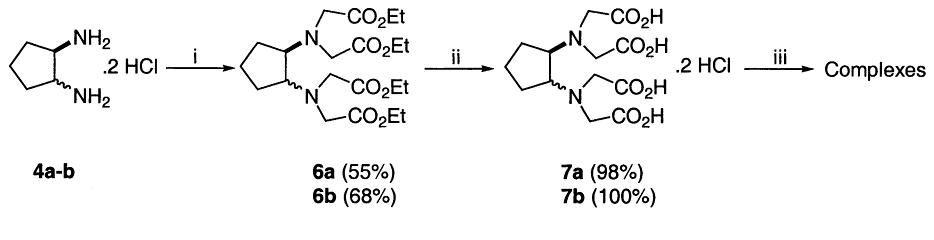
The preparation of cyclopentane-1,2-diamine, as performed in previous reports, required long and relatively inefficient synthesis or involved drastic acid conditions.[24–26] A recent patent filed by Abbott Laboratories mentions stereoselective synthesis, but does not describe the experimental protocol.[27] Otherwise, the group of Husson has reported the selective synthesis of *trans*-cyclopentane-1,2-diamine alone by means of a double Curtius rearrangement, a process using a very expensive starting product, *trans*-cyclopentane-1,2-dicarboxylic acid, and achieving a relatively poor overall yield.[28]

Our approach is rapid, efficient and stereoselective for the preparation of *cis*- and *trans*-cyclopentane-1,2-diamine dihydrochlorides **4a** and **4b** according to a similar protocol.

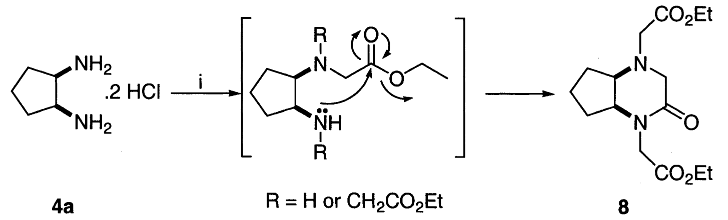
The *cis*- and *trans*-cyclopentane-1,2-diol compounds **1a** and **1b** were obtained according to methods previously described in the literature. For diol *cis* **1a**, a Sharpless oxidation[29–31] was performed using osmium tetroxide, and for diol *trans* **1b** the reaction involved the formation of an intermediate epoxide.[32] Using cyclopentane-1,2-diols **1a** and **1b**, the corresponding compounds **3a** and **3b** were not obtained directly by the Mitsunobu reaction, a method often employed for the synthesis of azides.[33,34] The hydroxyl functions of compounds **1a** and **1b** were activated in methanesulfonyl derivatives and converted into diazides **3a** and **3b** by treatment with sodium azide. This reaction performed in dimethylformamide at 85°C for 24 h requires the presence of a catalytic amount of 15-crown-5 to provide the expected compounds with a yield of around 85%.[35] However, the reduction of vicinal diazides raised several problems. Only *trans*-cyclopentane-1,2-diamine **5** could be isolated (90% yield) when hydrogenation was performed under atmospheric pressure with palladium on charcoal in methanol. Unfortunately, this compound proved extremely unstable and degraded upon use, even under an inert atmosphere. Starting with compound **3a**, regardless of the operating conditions (Pd on charcoal, $PtO_2$, $SnCl_3$, $LiAlH_4$, etc.), it was impossible to obtain *cis*-diamine. The diamine was too unstable and degraded during the reaction, or as *cis* vicinal diamines are excellent ligands for metal chelation, the catalyst may have been poisoned during the reaction. As a result, palladium hydroxide on charcoal was used in acid medium (Pearlman's catalyst) to obtain protected diamines in the form of dichlorohydrates **4a** and **4b**, giving yields respectively of 88 and 91%.[36] Thermogravimetric analyses, allowed determination of the number of water molecules complexed to the diamines.

After the synthesic key step of *cis*- and *trans*-cyclopentane-1,2-diamines dihydrochlorides, the amine functions were alkylated by ethyl bromoacetate according to the conditions described by Studer[37,38] (KI and $K_2CO_3$) to provide tetraesters **6** (Scheme 2), with yields of 55% for **6a** and 68% for **6b**.

The *cis*-diethylpiperazin-2-one-*N*,*N*′-diacetate **8** was formed by intramolecular cyclisation with one of the aminoacetate arms of the adjacent nitrogen. This accounted for the modest yield obtained with compound **6a** (Scheme 3). Cyclisation was not observed with



**Scheme 2.** Synthesis of ligands **7a–b** and corresponding complexes. *Reagents and conditions*: (i) ethyl bromoacetate, $K_2CO_3$, KI, $CH_3CN$, 60°C, 48 h; (ii) HCl 3N, reflux, 12 h; (iii) $SmCl_3$ or $InCl_3$, 1 h or 30 min, pH 5.5–5.8, 37°C.



**Scheme 3.** Synthesis of *cis*-diethylpiperazin-2-one-*N*,*N*′-diacetate **8**. *Reagents and conditions*: (i) ethyl bromoacetate, $K_2CO_3$, KI, $CH_3CN$, 60°C, 48 h.

*trans*-cyclopentane-1,2-diamine **6b** because of the spatial separation of the two nitrogen atoms. Finally, hydrolysis of the ester functions was performed in hydrochloric acid 3 M to provide the two polyaminocarboxylic acid ligands **7a** and **7b** with quantitative yields. After six steps, the overall yield was around 30% for **7a** and **7b**.

After the synthesis and characterisation of these two new chelates, it was necessary to determine their capacity for complexing radioactive metals.

## 2.2. Complexation tests

The preparation of complexes for immunoscintigraphy, a major diagnostic technique, involved the use of $^{111}$In [half-life of 67.4 h, $\gamma$ emission with an energy of 173 keV (83%), 247 keV (94%)]. This radionuclide was chosen because of its relatively medium size ($R$=0.80 Å) and the fact that indium complexes are generally hexacoordinated.[39] Thus, $^{111}$In was suitable for determining the capacity of ligands **7a** and **7b** to complex medium sized metals, which possess six co-ordination sites. Radioactive indium complexes were formed by the reaction in buffered medium of 1 mol equiv. of $In^{3+}$ ($2\times10^{-2}$ mCi) with 1 mol equiv. of each chelating agent. Incubation for 30 min at 37°C resulted in 100% complexation of $^{111}$In with **7a** and **7b**. These results are quite similar to those obtained under the same conditions with EDTA and CDTA. This procedure showed the aptitude of ligands **7a** and **7b** to complex, with a rapid kinetic formation, medium-sized metals with six co-ordination sites. The efficacy of these ligands will be then evaluated by stability tests in serum medium and competition tests with good indium complexes.

These promising results led us to study the influence of the chelating structure, i.e. the effect of cage size on complexation. One of the objectives of our research is to prepare BCA suitable for radioimmunotherapy and complexed by lanthanides. Ligand geometry needs to be optimal, so that the complexation cavity could be subsequently enlarged to increase the number of co-ordination sites. Because of its greater size ($R$=0.96 Å) and number of co-ordination sites (8–10 co-ordination sites), $^{153}$Sm was chosen to determine the influence of nitrogen-nitrogen distance on complexation. Accordingly, comparative complexation tests were performed between EDTA, CDTA (its semi-rigid homologue), and our two ligands **7a** and **7b** to determine the ratio of chelating agent to radionuclide needed to achieve maximum $^{153}$Sm chelation efficiency and avoid free $^{153}$Sm contamination in solutions. To form $^{153}$Sm chelating agent complexes, a fixed quantity of $^{153}$Sm stock solution was added to a range of 1, 2, 5 and 50 equiv. of each chelating agent (EDTA, CDTA, **7a** and **7b**).

The results of the experiments are summarised in Table 1. The four ligands show considerable differences in reactivities, even though all the samarium was complexed with a high ligand concentration (50 equiv.). The mean complexation percentages for all ligands with 1 mol equiv. of radionuclide are attributable to a deficiency of donor atoms in each ligand, i.e. samarium vacant co-ordination sites occupied by electron lone pair of the oxygen atom from water molecules. Compound **7b** and EDTA can be considered as poor ligands for lanthanides, whereas CDTA is an efficient complexing agent as ligand-to-metal ratio equal 2. Ligand **7a** showed very low affinity for $^{153}$Sm, even at relatively high concentrations (5 equiv.). The difference between compounds **7a** and **7b** is related to the spatial position of the aminodiacetic arms on the carbon skeleton. When the polyaminocarboxylate groups are in *cis* position on the cyclopentane, semi-emperical calculations with the AM1 method clearly show a considerable reduction in the size of the complexation cage as compared to *trans* analogue **7b** (3.1 versus 3.8 Å). This indicates that the cavity for **7a** is too small and not sufficiently flexible to accept lanthanides such as $^{153}$Sm. The difference in samarium complexation by CDTA and **7b** could be due to the markedly greater flexibility of cyclohexane in adapting to radionuclide size.

**Table 1.** Effect of ligand concentration on chelator-labelling efficiency

| Mole equivalent | % $^{153}$Sm chelated | | | |
|---|---|---|---|---|
| | EDTA | CDTA | **7a** | **7b** |
| 1 | 20 | 33 | 5 | 21 |
| 2 | 53 | 98 | 11 | 50 |
| 5 | 58 | 99 | 21 | 54 |
| 50 | 96 | 99 | 90 | 95 |

[$^{153}$Sm]=1.5 nmol mL$^{-1}$; reaction period=1 h; pH=5.5–5.8; temperature=37°C; final chelation volume=500 μL; 0.1 M sodium acetate buffer.

## 3. Conclusion

In summary, two new stereoisomeric polydentate ligands were developed by a process involving rapid, efficient, and stereoselective synthesis. Their good complexation ability was demonstrated for medium size cations such as $^{111}$In suitable for immunoscintigraphic applications. Tests with samarium preliminary to the preparation of bifunctional chelating agents for radioimmunotherapy showed the major influence of cavity geometry on the complexation rate and the more favourable characteristics of *trans* than *cis* geometry. To develop an efficient ligand for $^{153}$Sm, our research will now be directed at synthesising a compound with polyaminocarboxylate arms in *trans* position and a greater number of co-ordination functions.

## 4. Experimental

### 4.1. General

All reagents were purchased from Acros Organics and Aldrich. All chemicals were reagent grade and used without further purification, and all solvents were freshly distilled before use. The CNRS Analysis Laboratory (Vernaison) performed the elemental analyses. Column chromatography was conducted over silica gel 60 (40–63 μm), available from E. Merck. Thin-layer chromatography was performed on 0.5 mm×20 cm×20 cm E. Merck silica gel plates (60 F-254). Melting points measured using a Reichert microscope are uncorrected. The $^{13}$C and $^{1}$H NMR spectra were recorded at room temperature using a Bruker AC200 operating at 50 and 200 MHz, respectively. Chemical shifts ($\delta$) are given in ppm downfield from tetramethylsilane as internal standard. Mass spectra were determined with a Hewlett Packard 5989 spectrometer. TLC FAB-MS were obtained on a Jeol SX 102 (*m*-nitrobenzyl alcohol matrix). A Perkin–Elmer TGS2 thermogravimetric analyser was used to obtain TGA thermograms, that were run in air atmosphere from room temperature to 300°C at a scan rate of 2°C/min. The IR spectra were obtained using a Bruker Vector 22 spectrometer.

### 4.2. General procedure for preparation of 1,2-dimethylsulphonyloxycyclopentane (2)

To a solution of cyclopentane-1,2-diol **1** (9.8 mmol) in dichloromethane (60 mL) was added triethylamine (48.9 mmol) at 0°C under Ar. The reaction was stirred at 0°C for 10 min, and methanesulfonyl chloride (48.9 mmol) was added dropwise during 10 min. The reaction was stirred at 0°C for 4 h and allowed to warm to room temperature for 3 h. The organic phase was washed with 1 M hydrochloric acid (2×50 mL), 2 M sodium hydroxide (50 mL), and 50 mL of water. The organic phase was dried ($MgSO_4$), filtered, and evaporated. **2** was crystallised from ethanol as a white solid.

**4.2.1. *cis*-1,2-Dimethylsulfonyloxycyclopentane (2a).** Yield 90%; Mp 69°C; $^{1}$H NMR ($CDCl_3$) $\delta$ 1.60–2.20 (m, 6H, $3\mathrm{C}\mathit{H}_2$), 3.09 (s, 6H, $2\mathrm{C}\mathit{H}_3$), 5.00 (m, 2H, $2\mathrm{C}\mathit{H}$); $^{13}$C NMR ($CDCl_3$) $\delta$ 18.4 (1C, $\mathrm{CH_2}\mathit{C}\mathrm{H_2CH_2}$), 28.6 (2C, $\mathit{C}\mathrm{H_2CH_2}\mathit{C}\mathrm{H_2}$), 38.7 (2C, $\mathit{C}\mathrm{H_3}$), 80.5 (2C, $\mathit{C}\mathrm{H}$); MS (CI), *m*/*z* (%) 276 (100, $M^+ + NH_4^+$); MS (EI), *m*/*z* (%) 162 (13), 101 (34), 83 (100), 55 (62); IR (KBr) 2975 (s), 2951 (s), 1362 (vs), 1392 (s).

**4.2.2. *trans*-1,2-Dimethylsulfonyloxycyclopentane (2b).** Yield 91%; Mp 95°C; $^{1}$H NMR ($CDCl_3$) $\delta$ 1.75–2.35 (m, 6H, $3\mathrm{C}\mathit{H}_2$), 3.07 (s, 6H, $2\mathrm{C}\mathit{H}_3$), 5.07 (m, 2H, $2\mathrm{C}\mathit{H}$); $^{13}$C NMR ($CDCl_3$) $\delta$ 21.0 (1C, $\mathrm{CH_2}\mathit{C}\mathrm{H_2CH_2}$), 30.6 (2C, $\mathit{C}\mathrm{H_2CH_2}\mathit{C}\mathrm{H_2}$), 38.5 (2C, $\mathit{C}\mathrm{H_3}$), 84.9 (2C, $\mathit{C}\mathrm{H}$); MS (CI), *m*/*z* (%) 276 (100, $M^+ + NH_4^+$); MS (EI), *m*/*z* (%) 258, 162 (17), 101 (32), 83 (100), 55 (53); IR (KBr) 2941 (s), 1344 (vs), 1181 (s), 980 (s).

### 4.3. General procedure for preparation of 1,2-diazidocyclopentane (3)

Sodium azide (30.8 mmol) and 15-crown-5 (0.1 equiv.) was added to a stirred solution of 1,2-dimethylsulfonyloxycyclopentane **2** (6.4 mmol) in anhydrous DMF (30 mL). The mixture was heated at 85°C for 24 h under Ar. After cooling, the solution was poured into water (50 mL), extracted with dichloromethane (50 mL), and washed with water (4×50 mL). Organic phase was collected, dried ($MgSO_4$), and the solvent removed under vacuum. The residue was purified by flash chromatography over silica using dichloromethane as eluent to afford **3** as colourless oil.

**4.3.1. *cis*-1,2-Diazidocyclopentane (3a).** Yield 83%; $^{1}$H NMR ($CDCl_3$) $\delta$ 1.50–2.10 (m, 6H, $3\mathrm{C}\mathit{H}_2$), 3.82 (m, 2H, $2\mathrm{C}\mathit{H}$); $^{13}$C NMR ($CDCl_3$) $\delta$ 20.0 (1C, $\mathrm{CH_2}\mathit{C}\mathrm{H_2CH_2}$), 28.0 (2C, $\mathit{C}\mathrm{H_2CH_2}\mathit{C}\mathrm{H_2}$), 64.5 (2C, $\mathit{C}\mathrm{H}$); MS (FAB+), *m*/*z* (%) 152 (100, $M^+$).

**4.3.2. *trans*-1,2-Diazidocyclopentane (3b).** Yield 86%; $^{1}$H NMR ($CDCl_3$) $\delta$ 1.50–2.20 (m, 6H, $3\mathrm{C}\mathit{H}_2$), 3.74 (m, 2H, $2\mathrm{C}\mathit{H}$); $^{13}$C NMR ($CDCl_3$) $\delta$ 20.9 (1C, $\mathrm{CH_2}\mathit{C}\mathrm{H_2CH_2}$), 29.3 (2C, $\mathit{C}\mathrm{H_2CH_2}\mathit{C}\mathrm{H_2}$), 67.0 (2C, $\mathit{C}\mathrm{H}$); MS (FAB+), *m*/*z* (%) 152 (100, $M^+$).

### 4.4. General procedure for preparation of cyclopentane-1,2-diamine dihydrochloride (4)

A mixture of **3** (1.58 mmol), 5 mL of methanol, 140 mg (0.2 mmol) of 20% palladium hydroxide on carbon (Pearlman's catalyst), and 5 mL of 2N hydrochloric acid was stirred under hydrogen pressure (1 atm) for 8 h. The catalyst was filtered and the filtrate concentrated to dryness to afford a white amorphous solid.

**4.4.1. *cis*-Cyclopentane-1,2-diamine dihydrochloride trihydrate (4a).** Yield 88%; mp 270°C; $^{1}$H NMR ($D_2O$) $\delta$ 1.93 (m, 4H, $\mathrm{C}\mathit{H}_2\mathrm{CH_2C}\mathit{H}_2$), 2.26 (m, 2H, $\mathrm{CH_2C}\mathit{H}_2\mathrm{CH_2}$), 3.94 (m, 2H, $2\mathrm{C}\mathit{H}$); $^{13}$C NMR ($D_2O$) $\delta$ 22.4 (1C, $\mathrm{CH_2}\mathit{C}\mathrm{H_2CH_2}$), 30.5 (2C, $\mathit{C}\mathrm{H_2CH_2}\mathit{C}\mathrm{H_2}$), 56.3 (2C, $\mathit{C}\mathrm{H}$); MS (CI), *m*/*z* (%) 136 (100, $M^+ - HCl - 3H_2O$); MS (EI), *m*/*z* (%) 101 (12), 82 (34), 56 (95), 36 (100); IR (KBr) 3520 (s), 3349 (s), 1500 (s), 1090 (s); TGA room temperature to 300°C, % water loss 23.8%.

**4.4.2. *trans*-Cyclopentane-1,2-diamine dihydrochloride (4b).** Yield 91%; mp 280°C; $^{1}$H NMR ($D_2O$) $\delta$ 1.86 (m, 4H, $\mathrm{C}\mathit{H}_2\mathrm{CH_2C}\mathit{H}_2$), 2.33 (m, 2H, $\mathrm{CH_2C}\mathit{H}_2\mathrm{CH_2}$), 3.79 (m, 2H, $2\mathrm{C}\mathit{H}$); $^{13}$C NMR ($D_2O$) $\delta$ 25.2 (1C, $\mathrm{CH_2}\mathit{C}\mathrm{H_2CH_2}$), 33.2 (2C, $\mathit{C}\mathrm{H_2CH_2}\mathit{C}\mathrm{H_2}$), 58.7 (2C, $\mathit{C}\mathrm{H}$); MS (CI), *m*/*z* (%) 136 (100, $M^+ - HCl$); IR (KBr) 3400 (s), 3339 (s), 1492 (s), 1010 (s); TGA room temperature to 300°C, % water loss 0%.

**4.4.3. *trans*-Cyclopentane-1,2-diamine (5).** To a stirred solution of *trans*-1,2-diazidocyclopentane (**3b**) (2.07 mmol) in ethyl alcohol (15 mL), Pd 10% on charcoal was added (50 mg) and the mixture was hydrogenated at atmospheric pressure at room temperature for 6 h. The catalyst was filtered off and washed with ethanol. Alcohol was removed under vacuum, and the product was dried to afford a yellow oil (yield 90%). $^1$H NMR ($D_2O$) $\delta$ 1.50–1.80 (m, 8H, $CH_2CH_2CH_2+2NH_2$), 1.96 (m, 2H, $CH_2CH_2CH_2$), 3.73 (m, 2H, 2C*H*); $^{13}$C NMR ($D_2O$) $\delta$ 20.2 (1C, $CH_2CH_2CH_2$), 33.7 (2C, $CH_2CH_2CH_2$), 61.5 (2C, *C*H); MS (CI), *m*/*z* (%) 100 (100, $M^+$).

### 4.5. General procedure for the preparation of tetraethylcyclopentane-1,2-diamine-*N*,*N*,*N*′,*N*′-tetraacetate (6)

To a solution of dihydrochloride **4** (2.2 mmol) in freshly distilled acetonitrile (30 mL) were added potassium carbonate (14.5 mmol) and potassium iodide (3.2 mmol). After stirring the mixture for 18 h at 60°C, ethyl bromoacetate (14.8 mmol) was added dropwise. The reaction mixture was kept at this temperature over a period of 48 h under Ar prior to cooling to room temperature, filtration, and concentration under reduced pressure. The resulting residue was partitioned between diethyl ether (125 mL) and 0.5 M hydrochloric acid (125 mL). The organic extract was washed with 0.56 M sodium hydroxide (125 mL), dried ($MgSO_4$), filtered and evaporated. The residue was purified by flash chromatography on silica gel using a dichloromethane:ethyl acetate (9:1) mixture as eluent to give **6** as a colourless oil.

**4.5.1. Tetraethyl *cis*-cyclopentane-1,2-diamine-*N*,*N*,*N*′,*N*′-tetraacetate (6a).** Yield 55%; $^1$H NMR ($CDCl_3$) $\delta$ 1.26 (t, 12H, $4CH_2CH_3$, *J*=7.2 Hz), 1.30–2.00 (m, 6H, $3CH_2$), 3.38 (m, 2H, 2C*H*), 3.67 and 3.80 (2d, 8H, $4NCH_2$, *J*=17.4 Hz), 4.14 (q, 8H, $CH_2CH_3$, *J*=7.2 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 14.3 (4C, $CH_2CH_3$), 21.6 (1C, $CH_2CH_2CH_2$), 28.4 (2C, $CH_2CH_2CH_2$), 53.8 (4C, $NCH_2$), 60.2 (4C, $CH_2CH_3$), 62.9 (2C, *C*H), 172.2 (4C, C═O); MS (CI), *m*/*z* (%) 445 (100, $M^+$+H); MS (EI), *m*/*z* (%) 444 (13), 228 (57), 168 (65), 29 (100); Anal. Found: C, 56.52; H, 8.23; N, 6.44. Calcd for $C_{21}H_{36}O_8N_2$ requires C, 56.76; H, 8.11; N, 6.31%.

**4.5.2. Tetraethyl *trans*-cyclopentane-1,2-diamine-*N*,*N*,*N*′,*N*′-tetraacetate (6b).** Yield 68%; $^1$H NMR ($CDCl_3$) $\delta$ 1.24 (t, 12H, $4CH_2CH_3$, *J*=7.1 Hz), 1.35–1.96 (m, 6H, $3CH_2$), 3.29 (m, 2H, 2C*H*), 3.59 and 3.71 (2d, 8H, $4NCH_2$, *J*=17.4 Hz), 4.13 (q, 8H, $CH_2CH_3$, *J*=7.1 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 14.3 (4C, $CH_2CH_3$), 22.0 (1C, $CH_2CH_2CH_2$), 27.8 (2C, $CH_2CH_2CH_2$), 53.2 (4C, $NCH_2$), 60.5 (4C, $CH_2CH_3$), 66.6 (2C, *C*H), 171.8 (4C, C═O); MS (EI), *m*/*z* (%) 444 (7), 371 (10), 228 (13), 168 (23), 116 (19), 29 (100); Anal. Found: C, 56.64; H, 8.36; N, 6.28. Calcd for $C_{21}H_{36}O_8N_2$ requires C, 56.76; H, 8.11; N, 6.31%.

### 4.6. General procedure for the preparation of cyclopentane-1,2-diamine-*N*,*N*,*N*′,*N*′-tetraacetic acid (7)

A mixture of **6** (0.6 mmol) and 30 mL of 3 M hydrochloric acid was stirred overnight under reflux. The condenser was removed, and the reaction mixture was kept at 70°C to evaporate the ethanol. Additional 3 M hydrochloric acid (30 mL) was then added, and the solution was heated to dryness to give acid **7** as a white powdery solid, which was dried under vacuum and kept under nitrogen. Acid **7** is a very hygroscopic compound.

**4.6.1. *cis*-Cyclopentane-1,2-diamine-*N*,*N*,*N*′,*N*′-tetraacetic acid (7a).** Yield 98%; $^1$H NMR ($D_2O$) $\delta$ 1.50–2.20 (m, 6H, $3CH_2$), 3.70–4.20 (m, 10H, $2CH+4NCH_2$); $^{13}$C NMR ($D_2O$) $\delta$ 20.7 (1C, $CH_2CH_2CH_2$), 26.0 (2C, $CH_2CH_2CH_2$), 54.5 (4C, $NCH_2$), 66.0 (2C, *C*H), 172.6 (4C, *C*═O); MS, *m*/*z* (%) 332 (100, $M^+$).

**4.6.2. *cis*-Cyclopentane-1,2-diamine-*N*,*N*,*N*′,*N*′-tetraacetic acid (7b).** Yield 100%; $^1$H NMR ($D_2O$) $\delta$ 1.60–2.18 (m, 6H, $3CH_2$), 3.74–4.12 (m, 10H, $2CH+4NCH_2$); $^{13}$C NMR ($D_2O$) $\delta$ 23.5 (1C, $CH_2CH_2CH_2$), 34.0 (2C, $CH_2CH_2CH_2$), 52.6 (4C, $NCH_2$), 65.3 (2C, *C*H), 170.4 (4C, *C*═O); MS, *m*/*z* (%) 332 (100, $M^+$).

### 4.7. Complexation tests

**4.7.1. Complexation studies with $^{111}$In.** To a fixed quantity of each chelating agent (37.7 nmol) in 0.1 M sodium acetate buffer was added 2 μL ($3\times10^{-2}$ nmol) of a radioactive solution of $^{111}InCl_3$ (10 mCi $mL^{-1}$) and 2 μL (37.3 nmol) of a solution of $InCl_3$ (18672.5 nmol $mL^{-1}$ in 0.05 M hydrochloric acid). The unradioactive solution of $InCl_3$ was used to maintain a fixed concentration of indium during the experiment. The volume of each sample was adjusted to 500 μL with 0.1 M sodium acetate, and the solutions were incubated at 37°C for 30 min. The final pH of each solution ranged from 5.5 to 5.8, with a final $^{111}$In concentration of 74.6 nmol $mL^{-1}$. The chelation yield was measured on a Phosphorimager apparatus (445SI) after thin-layer chromatography on cellulose plates (Merck 5552/0025) by elution with 0.1 M sodium acetate, pH 5.8: methanol (1:1).

**4.7.2. Complexation studies with $^{153}$Sm.** Stock solutions of each chelate (2, 0.2, 0.02, 0.002 mg $mL^{-1}$) were prepared in 0.1 M sodium acetate, pH 5.8. To form $^{153}$Sm chelating agent complexes, 1 μL (0.74 nmol) of $^{153}$Sm stock solution (140.5 mCi $mL^{-1}$) was added to a range of 1, 2, 5 and 50 equiv. of each chelating agent (EDTA, CDTA, **7a** and **7b**), before adjustment of the volume to 500 μL. The final pH of each solution ranged from 5.5 to 5.8, with a final $^{153}$Sm concentration of 1.5 nmol $mL^{-1}$.

After incubation at 37°C for 1 h, complexation was measured on a phosphoimager 445SI after thin-layer chromatography on cellulose plates (Merck 5552/0025) by elution with 0.1 M sodium acetate, pH 5.8: methanol (1:1).

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