

Synthesis of Gadolinium (\pm)-10-(1-Hydroxypropan-2-yl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyltriacetate *via* Tribenzyl 1,4,7,10-Tetraazacyclododecane-1,4,7-tricarboxylate

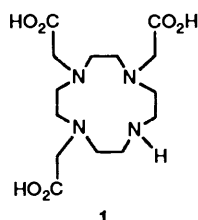
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The synthesis of monogadolinium 10-(1-hydroxypropan-2-yl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyltriacetate **12** has been achieved through a multistep sequence. The key step in the synthesis was the reaction of the previously unknown tribenzyl 1,4,7,10-tetraazacyclododecane-1,4,7-tricarboxylate **6** with ethyl 2-(trifluoromethylsulphonyloxy)propionate **4** to give **7**. Reduction of **7** with $\text{LiBH}_4/9\text{-OMe-BBN}$, followed by hydrogenolysis of the protecting groups (*Z* groups) yielded 2-(1,4,7,10-tetraazacyclododec-1-yl)propanol **10**. The monosubstituted macrocycle **10** was alkylated with bromoacetic acid and then complexed with gadolinium oxide to yield the title compound.

Metal chelates have found increasing use as diagnostic and therapeutic agents in medicine.¹ Recently, we have reported the synthesis of a variety of nonionic gadolinium chelates useful as contrast agents in Magnetic Resonance Imaging (MRI).² These chelates are derived from the core ligand 1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane, **1**, (DO3A).



In continuation of our efforts in this area, we have been interested in preparing ligands with sterically hindered side arms. The gadolinium chelates from these ligands might be expected to show altered biodistribution as a function of lipophilicity. One target was the 10-(1-hydroxypropan-2-yl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyltriacetic acid **11**. Here we describe the synthesis of **11** and its gadolinium chelate **12**.

Results and Discussion

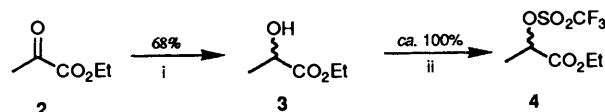
Our approach to the synthesis of **11** involved the preparation of 2-(1,4,7,10-tetraazacyclododecyl)propanol **10**, followed by alkylation with bromoacetic acid (Scheme 2). Required for this approach was the availability of a protected macrocycle that would allow for monoalkylation with the required side chain. Although tri-*N*-tosyl macrocycle was available from our earlier work,² we selected the previously unreported tribenzyl 1,4,7,10-tetraazacyclododecane-1,4,7-tricarboxylate **6** since the *N*-benzyloxycarbonyl (*Z* group) is more readily removed.³

Tri-*Z*-macrocycle **6** was prepared in an unoptimized yield of ca. 50% by treating 1,4,7,10-tetraazacyclododecane **5** with 3.2 equiv. of benzyl chloroformate in methylene dichloride in the presence of triethylamine. The major side product in this reaction was the corresponding tetrasubstituted macrocycle which was removed by flash chromatography.

Introduction of the sterically demanding 1-hydroxypropan-2-yl side chain onto **6** proved to be difficult. Reaction of **6** with α -halogeno propionic acids (esters) or ethyl α -tolylsulphonyloxypropionate provided the desired compound in poor yield under a variety of conditions. Effenberger has demonstrated the

use of triflate esters of α -hydroxy carboxylic acids as reactive electrophiles for the alkylation of secondary amines.⁴ Following this approach, the 1-hydroxypropan-2-yl chain was introduced into **6**.

Racemic 2-(trifluoromethylsulphonyloxy)ethyl propionate **4** was prepared from ethyl pyruvate **2** in two steps (Scheme 1).

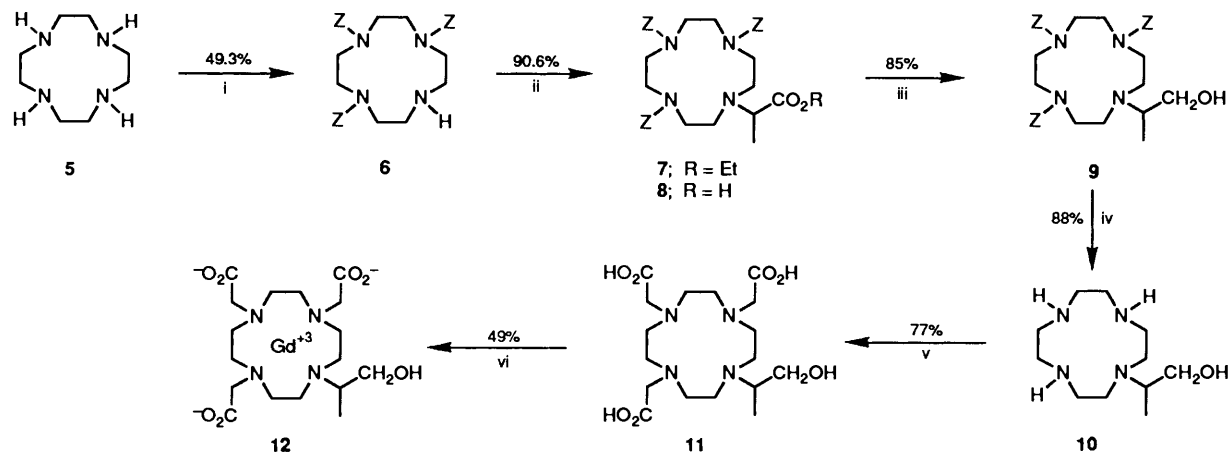


Scheme 1 Reagents and conditions: i, Pt/C, H_2 , 50 psi; ii, Triflic anhydride, Py, CH_2Cl_2

Catalytic reduction of **2** (Pt/C, EtOH) provided ethyl 2-hydroxypropionate **3** in 68% isolated yield. Reaction of **3** with triflic anhydride and pyridine in CH_2Cl_2 furnished **4** in almost quantitative yield. Alkylation of **6** with **4** in acetonitrile- Na_2CO_3 proceeded smoothly to provide the key compound **7** in 90.6% yield. Reduction of **7** into **9** was initially achieved *via* ester saponification followed by diborane reduction. However, on scale-up, the diborane reduction of **8** was complicated by the formation of a number of impurities. A variety of methods were therefore explored to reduce **7** directly to **9** without affecting the *Z* groups. The method of choice involved treatment of a THF solution of **7** with 1.4 equiv. of LiBH_4 in the presence of 9-methoxy-9-borabicyclo[3.3.1]nonane (9-OMe-BBN) as catalyst⁵ at reflux and these conditions provided **9** in 85% yield. Removal of the protecting groups of **9** was readily accomplished by hydrogenolysis (Pd/C) and the monosubstituted macrocycle **10** was isolated in 88% yield.

Alkylation of **10** with bromoacetic acid proceeded in a straightforward manner. Excess of reagent was removed from the crude product by ion-exchange chromatography (Dowex 50W-X8). Further purification of the product was achieved by chromatography on IRA 900C (hydroxy form) and poly(4-vinylpyridine) (PVP) resins. The target ligand **11** was isolated in 77% yield. Complexation of **11** with Gd_2O_3 was achieved following the procedure previously described.² The resulting gadolinium complex was purified by crystallization to give the target compound **12** in 49% yield. Compound **12** has been evaluated for use as a contrast agent in MRI and compared with gadolinium chelates previously reported.² The results of these biological studies as well as physical chemical measurements will be reported separately.

In summary, the work described in this paper demonstrates



Scheme 2 Reagents: i, $\text{ClCO}_2\text{CH}_2\text{Ph}$, CH_2Cl_2 , Et_3N ; ii, **4**, CH_3CN , Na_2CO_3 ; iii, LiBH_4 , 9-OMe-BBN, THF; iv, Pd/C, H_2 ; v, $\text{BrCH}_2\text{CO}_2\text{H}$, NaOH, H_2O ; vi, Gd_2O_3 , H_2O

the utility of tri-Z macrocycle **6** to achieve exclusive monoalkylation.⁶ Also demonstrated was the use of **4** for the introduction of a sterically hindered side chain into a tetraaza macrocyclic system.

Experimental

All compounds described are racemic. Reagents were obtained from either Aldrich Chemical Company or Fisher Scientific and used as received. Solvents were purified and dried by standard methods. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-360 spectrometer. Unless otherwise indicated, NMR spectra were recorded as dilute solutions in $[\text{D}_3]\text{chloroform}$ with tetramethylsilane as an internal standard. All J values are in Hz. Elemental analyses, mass spectra, and IR spectra were obtained from the respective departments within the Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, New Jersey. Mass spectra were recorded under chemical ionization conditions unless otherwise indicated. Column chromatography was done using 'Baker' silical gel for flash chromatography. Analytical TLC was performed on ANALTECH Silica Gel GF plates (250 microns). Drying refers to the use of sodium sulphate (Na_2SO_4). Anhydrous reactions were carried out under an atmosphere of argon or nitrogen. The phrase 'work-up' refers to the procedure when the organic layer was separated, dried over Na_2SO_4 , and the solvent was evaporated under reduced pressure.

HPLC columns were obtained from either Waters Chromatography Division, or Phenomenex. The ligand **11** was assayed by two methods. (1) *Copper-based method*. Column: 25 cm \times 4.6 mm ID, PLRP-S, average particle diameter of 5 μ ; Mobile phase: 1% acetonitrile: 99% 50 mmol dm^{-3} , pH 4.0 ammonium phosphate buffer; Detection: λ 290 nm UV; Flow rate: 0.5 $\text{cm}^3 \text{min}^{-1}$. One or two drops of the solution to be analysed was mixed with copper(II) chloride (0.0235 mol dm^{-3} aqueous solution; 1 cm^3) and held for 15 min. The solution was then diluted with enough mobile phase to obtain a pale blue solution.

(2) *PAC-5 method*. Column: 25 cm \times 4.6 mm ID, 5 Amino-Cyano (PAC-5); Mobile phase: 10% acetonitrile: 90% 50 mmol dm^{-3} , pH 4.0 ammonium phosphate buffer; Detection: λ 220 nm UV; Flow rate: 1.0 $\text{cm}^3 \text{min}^{-1}$. The solution or isolated solid was dissolved in the mobile phase before injection to give a solution concentration of ca. 5 mg cm^{-3} for **11** and 15 mg cm^{-3} for **12**. Compound **12** was also assayed by a fluorescence method (3):⁷ Column: 5C 18 Nucleosil; Mobile phase: 50 mmol dm^{-3} Tris acetate, 10 mmol dm^{-3} Na_2EDTA , pH 7.0 buffer (98:2 v/v); Fluorescence: λ 280 nm (excitation) and λ 316 nm (emission);

Flow rate: 1 $\text{cm}^3 \text{min}^{-1}$. An approximate concentration of 2–3 mg cm^{-3} in the mobile phase was used. This method was also used for the detection of any free gadolinium(III) present in compound **12**.

1,4,7,10-Tetraazacyclododecane **5** was purchased from Parish Chemical Company, Orem, Utah. Alternatively, **5** may be prepared by one of several literature methods.^{8–10} Gadolinium oxide (99.99%) was obtained from Molycorp, Inc., White Plains, New York. Amberlite IRA 900C (hydroxy form) was obtained from Rohm and Hass, Philadelphia. Poly(4-vinylpyridine) (PVP) resin was obtained from Reilly Industries, Inc., Indianapolis, Indiana. All resins were conditioned according to the manufacturer's recommendations prior to use. Distilled deionized water was obtained from a Millipore Super Q purification (10 M Ω cm) and used to minimize trace metal contamination of the ligands and complexes.

Tribenzyl 1,4,7,10-Tetraazacyclododecane-1,4,7-tricarboxylate 6.—Into a 2 dm^3 round bottomed flask containing **5** (35 g, 0.203 mol) in CH_2Cl_2 (750 cm^3) was added triethylamine (Et_3N) (131.6 g, 1.3 mol) and the solution was cooled to 5 $^\circ\text{C}$. To this solution was added benzyl chloroformate (110.9 g, 0.65 mol) over a 3 h period. The solution was then stirred at 5 $^\circ\text{C}$ for 48 h. At the end of this time, the reaction mixture was warmed to room temperature and transferred to a separating funnel. The organic layer was separated and washed successively with 10% aqueous HCl (2 \times 250 cm^3), 10% aqueous NaOH (1 \times 250 cm^3), water (1 \times 250 cm^3) and saturated brine (1 \times 250 cm^3). Work-up of the organic layer furnished an orange brown oil (146 g), which was divided into equal portions. Each of these was then preadsorbed onto neutral alumina (250 g, Woelm, activity I) and then put on a bed of neutral alumina (1300 g) contained in a 2 dm^3 sintered glass funnel. The bed was washed with approximately 2 bed volumes each of 20, 40, 60 and 80% EtOAc in hexane. The purity of each fraction was evaluated by TLC (60% EtOAc–hexane, R_f = 0.24) and the pure fractions were combined and concentrated to yield the *title compound 6* (57.6 g, 49.3%) as a viscous liquid; δ_{H} 7.2 (15 H, m, ArH), 5.0 [6 H, m, (ArCH₂O₂C)₃], 3.7, 3.5, 3.3, 2.2 [16 H, br m, N(CH₂CH₂)₄N] and 1.0 (1 H, br s, NH); δ_{C} 156.0, 155.6, 136.7, 136.4, 128.2, 128.1, 127.7, 127.5, 127.3, 66.7, 66.4, 50.8, 49.1, 48.9, 48.7, 48.4 and 45.2; m/z 575 (M + H)⁺ (Found: C, 66.75; H, 6.7; N, 9.65. C₃₂H₃₈N₄O₆ requires C, 66.88; H, 6.66; N, 9.75%).

Ethyl 2-Hydroxypropionate 3.—To a solution of ethyl pyruvate **2** (30 g, 0.26 mol) in ethyl alcohol (300 cm^3), was added 5% Pd/C catalyst (3.5 g) and the mixture was agitated in an

atmosphere of hydrogen (Paar shaker, 50 psi). After 16 h, the catalyst was filtered off and washed with EtOH (100 cm³). The filtrate and the alcohol wash were combined and concentrated on a rotary evaporator. The resulting liquid was vacuum distilled to give **3** (21 g, 68%) as a colourless liquid, b.p. 70–74 °C/55 mmHg; δ_{H} 4.22 (3 H, m, CO₂CH₂ and CHOH), 1.38 (3 H, d, *J* 7, CHCH₃) and 1.26 (3 H, t, *J* 7, CH₂CH₃).

Ethyl 2-(Trifluoromethylsulphonyloxy)propionate 4.—Into a 250 cm³ 3-neck round bottom flask equipped with a thermometer, addition funnel and a mechanical stirrer was placed pyridine (2.89 g, 0.036 mol) and CH₂Cl₂ (80 cm³) and the solution was cooled to –20 °C. With vigorous agitation, triflic anhydride (9.82 g, 0.035 mol) was slowly added to the solution while the reaction temperature was maintained at –20 °C. After *ca.* 15 min, a solution of **2** (4.11 g, 0.035 mol) in CH₂Cl₂ (40 cm³) was added and cooling was continued at –20 °C. After 30 min, the cooling bath was replaced by a water bath (20 °C) and the solution was stirred at ambient temperature for 1 h. At the end of this time the reaction mixture was filtered through a bed of silica gel and the silica gel was washed with CH₂Cl₂ (50 cm³). The filtrate and washings were combined and concentrated on a rotary evaporator while the bath temperature was kept at 20–25 °C to give **4** (8.7 g, *ca.* 100%) as a colourless liquid; $\nu_{\text{max}}/\text{cm}^{-1}$ 1750, 1405, 1130, 1070, 1005 and 940; δ_{H} 5.21 (1 H, q, *J* 7, CH₃CH), 4.30 (2 H, q, *J* 6.9, CO₂CH₂), 1.72 (3 H, d, *J* 6.8, CHCH₃) and 1.32 (3 H, t, *J* 6.8, CH₂CH₃). The NMR spectrum of **4** was identical with that reported for the (*S*)-isomer¹¹ and the compound was used in the next step without further purification.

Tribenzyl 10-[1-(Ethoxycarbonyl)ethyl]-1,4,7,10-tetraazacyclododecane-1,4,7-tricarboxylate 7.—Into a 3-neck 2 dm³ flask containing **6** (60 g, 0.104 mol) and Na₂CO₃ (13.84 g, 0.131 mol) in MeCN (700 cm³) was slowly added a solution of **4** (32.65 g, 0.131 mol) in MeCN (70 cm³). After the mixture had been stirred at ambient temperature for 16 h, it was filtered and the filtrate was concentrated on a rotary evaporator. The liquid product obtained was purified by flash chromatography (40% EtOAc–hexane) to yield **7** (63.5 g, 90.6%) as a pale yellow liquid; $\nu_{\text{max}}/\text{cm}^{-1}$ 1704 br, 1416 and 1003; δ_{H} 7.30 (15 H, br s, ArH), 5.20–4.85 (6 H, br m, CH₂Ar), 4.10 (2 H, br q, CO₂CH₂), 3.75 (1 H, br q, CHCH₃), 3.60–2.50 [16 H, br m, N(CH₂CH₂)₄N], 1.22 (3 H, t, *J* 7, CH₂CH₃) and 1.18 (3 H, br s, CHCH₃); δ_{C} 172.1, 156.2, 155.8, 136.3, 136.1, 127.9, 127.7, 127.5, 127.4, 127.3, 66.5, 66.3, 59.7, 56.1, 50.1, 49.6, 49.0, 48.6, 47.9, 13.8 and 13.0; m/z 675 (M + H)⁺ (Found: C, 66.05; H, 6.9; N, 8.25. C₃₇H₄₆N₄O₈ requires C, 65.85; H, 6.87; N, 8.31%).

Tribenzyl 10-(1-Hydroxypropan-2-yl)-1,4,7,10-tetraazacyclododecane-1,4,7-tricarboxylate 9.—Into a 3-neck 2 dm³ flask was added as solution of **7** (56 g, 0.083 mol) in THF (800 cm³) and the solution was cooled to 0–5 °C. To this was added dropwise a solution of LiBH₄ in THF (2 mol dm⁻³; 58.15 cm³, 0.116 mol), followed by a solution of 9-OMe-BBN in hexane (1 mol dm⁻³; 8.3 cm³, 0.0083 mol). After the addition was complete, the reaction mixture was brought to room temperature and then heated and agitated at reflux for 16 h. After this time, the flask was immersed in an ice bath and NaOH (3 mol dm⁻³; 39 cm³) was added cautiously (H₂ evolution). After being stirred for 0.5 h, the clear THF solution was decanted and the precipitate was stirred with THF (100 cm³) and decanted. Silica gel (*ca.* 100 g) was added to the combined THF solutions and the slurry was stirred until the effervescence had ceased (15 min). The mixture was filtered and the silica gel was washed with additional THF (100 cm³). The THF solutions were combined and concentrated under reduced pressure to yield a gummy product which was purified by flash chromatography (70% EtOAc–hexane). Com-

pound **9** (52.5 g, 85%), was obtained as a glassy solid; $\nu_{\text{max}}/\text{cm}^{-1}$ 3478br and 1699br; δ_{H} 7.35 (15 H, br s, ArH), 5.20–4.85 (6 H, m, CH₂Ar), 3.80–2.20 [20 H, br m, CH₂OH, CHCH₃, N(CH₂CH₂)₄N] and 0.82 (3 H, br d, CHCH₃); δ_{C} 156.5, 155.8, 136.3, 136.2, 128.1, 127.8, 127.7, 127.6, 127.5, 66.8, 66.6, 63.7, 54.8, 48.1, 47.8 and 8.7; m/z 633 (M + H)⁺ (Found: C, 66.4; H, 7.15; N, 8.8. C₃₅H₄₄N₄O₇ requires C, 66.43; H, 7.01; N, 8.86%).

2-(1,4,7,10-Tetraazacyclododec-1-yl)propanol 10.—To a solution of **9** (475 mg, 0.75 mmol) dissolved in absolute EtOH (100 cm³) placed in a 250-cm³ round bottom flask was added 10% Pd/C catalyst (50 mg). After purging the system with nitrogen, hydrogen gas was bubbled into the solution through a sparge tube for 16 h. At the end of this time, the catalyst was filtered off and washed with EtOH (25 cm³). The filtrate and washings were combined, passed through a 0.22-micron filter and then concentrated under reduced pressure. The product obtained was further dried *in vacuo* at 50 °C for 72 h to give **10** (152 mg, 88%) as a thick liquid; $\nu_{\text{max}}/\text{cm}^{-1}$ 3386 (s br); δ_{H} 3.43 (1 H, dd, *J* 10.8 and 9, CH_AHOH), 3.34 (1 H, dd, *J* 11.1 and 5.4, CH_BOH), 3.00–2.30 [20 H, m, CH₂OH, CHCH₃, N(CH₂CH₂)₄N] and 0.85 (3 H, d, *J* 6.9, CHCH₃); δ_{C} 63.9, 56.2, 47.6, 47.5, 46.3, 45.9 and 9.6; m/z 231 (M + H)⁺ (Found: C, 55.65; H, 11.5; N, 23.0; H₂O, 3.62. C₁₁H₂₆N₄O·0.48H₂O requires C, 55.28; H, 11.37; N, 23.44).

10-(1-Hydroxypropan-2-yl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyltriacetic Acid 11.—To a solution of bromoacetic acid (49.39 g, 0.355 mol) in deionized water (103 cm³) at 0 °C was added NaOH (31.28 g, 0.782 mol) in water (137 cm³). After the mixture had been stirred for 5 min, compound **10** (19 g, 0.083 mol) dissolved in deionized water (45 cm³) was added and the solution was heated at 70 °C for 4–5 h. At the end of this time, the reaction mixture was cooled in an ice–water bath, the pH was adjusted to 2.0 with HCl, and the solution was applied to a column of Dowex 50W-X8 (50–100 mesh, H⁺, 2 dm³). After washing the column with deionized water (6 dm³), the compound was eluted with NH₄OH (1 mol dm⁻³; 5 dm³), followed by NH₄OH (2 mol dm⁻³; 2 dm³). Several fractions (500 cm³) were collected and assayed by HPLC method (1). The appropriate fractions were combined and concentrated to dryness. To remove excess of ammonia, the resulting solid was dissolved in deionized water and reconcentrated to dryness. This process was repeated several times to obtain crude **11** as a pale yellow solid (25.7 g, 77%). This material was used in the next step without further purification.

For analytical purposes, the crude **11** obtained above was further purified according to the following procedure.

The compound (*ca.* 3.6 g) was dissolved in a minimum amount of deionized water and the solution was loaded onto a column of IRA 900C (hydroxy form, 120 cm³). After washing with 4 bed volumes of deionized water, the column was eluted with H₂SO₄ (1 mol dm⁻³; 100 cm³), followed by 2 bed volumes of deionized water. Several fractions (50 cm³) were collected and analysed by HPLC method (1). The appropriate fractions were combined and the solution was passed slowly through a column of poly(4-vinylpyridine) (PVP) (200 cm³). Several fractions (50 cm³), were collected. The PVP column was further eluted with 2 bed volumes of deionized water and fraction collecting continued. All the fractions were assayed by HPLC method (1) and checked by BaCl₂ for the absence of sulphate ion. The appropriate fractions were combined and concentrated to dryness on a rotary evaporator to yield **11** (2.1 g) as a pale yellow solid. Approximate retention time by HPLC method (1): 26 min; approximate retention time by HPLC method (2): 14.30 min; $\nu_{\text{max}}/\text{cm}^{-1}$ 3395s br, 2970, 2849, 1632, 1395, 1227, 1162, 1087 and 1050; δ_{H} (in D₂O, CH₃CN as internal standard) 3.80–2.70 (26 H, m, (CH₂CO₂H)₃, CH₂OH, CHCH₃, N(CH₂CH₂)₄N] and 1.02

(3 H, br s, CHCH₃); δ_{C} (in D₂O, CH₃CN as internal standard) 174.5, 172.5, 61.2, 56.1, 55.9, 55.6, 51.8, 50.9, 50.5, 49.4, 48.6, 47.9, 46.9 and 44.7; m/z 405 (M + H)⁺ (Found: C, 50.35; H, 8.15; N, 13.45; H₂O, 0.51%. C₁₇H₃₂N₄O₇·0.12H₂O requires C, 50.23; H, 7.99; N, 13.78).

Gadolinium 10-(1-Hydroxypropan-2-yl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyltriacetate 12.—To **11** (25.1 g, 0.062 mol), dissolved in deionized water (450 cm³) was added Gd₂O₃ (12.36 g, 0.034 mol), and the mixture was heated at reflux for 14 h. The absence of **11** was assessed by HPLC method (1) and formation of **12** was followed by HPLC method (3). When the reaction was complete, the suspension was filtered through a Millipore Zeta pad followed by a Millipore 5.0- μm disposable filter unit and the filtrate was concentrated on a rotary evaporator. The solid obtained was dissolved in deionized water (90 cm³) (a slight heating was necessary) and the resulting solution was added under slow agitation to propan-2-ol (1800 cm³). After ca. 16 h, the crystal slurry was centrifuged. The solid obtained was recrystallized once and dried in a vacuum oven at 50 °C for 6 h to give **12** (17 g, 49%) as a white solid, m.p. > 200 °C. Approximate retention time by HPLC method (2): 7.4 min; approximate retention time by HPLC method (3): 9.4 min; detection limit: 0.1 mg cm⁻³; $\nu_{\text{max}}/\text{cm}^{-1}$ 3420br, 2978, 2864, 1612, 1386, 1323, 1085 and 935; m/z (FAB) 557 to 562 (M + H)⁺ [the characteristic isotope pattern for a molecule containing one gadolinium atom is evident in the mass spectrum] (Found: C, 36.45; H, 5.3; N, 9.8; H₂O 0.96%. C₁₇H₂₉N₄O₇Gd·0.30H₂O requires C, 36.19; H, 5.29; N, 9.93%).

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