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Synthesis of Gadolinium (±)-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 $LiBH_4$/9-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.

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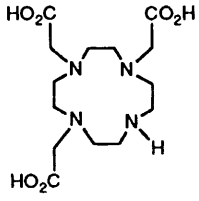
Metal chelates have found increasing use as diagnostic and therapeutic agents in medicine.[1] Recently, we have reported the synthesis of a variety of nonionic gadolinium chelates useful as contrast agents in Magnetic Resonance Imaging (MRI).[2] These chelates are derived from the core ligand 1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane,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



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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**.

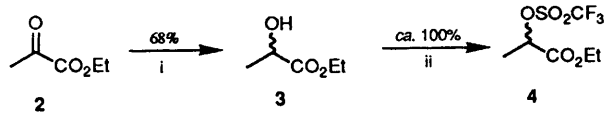
Results and Discussion

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).



2 **3** **4**

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-hydroxypropionato **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 catalyst[5] 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

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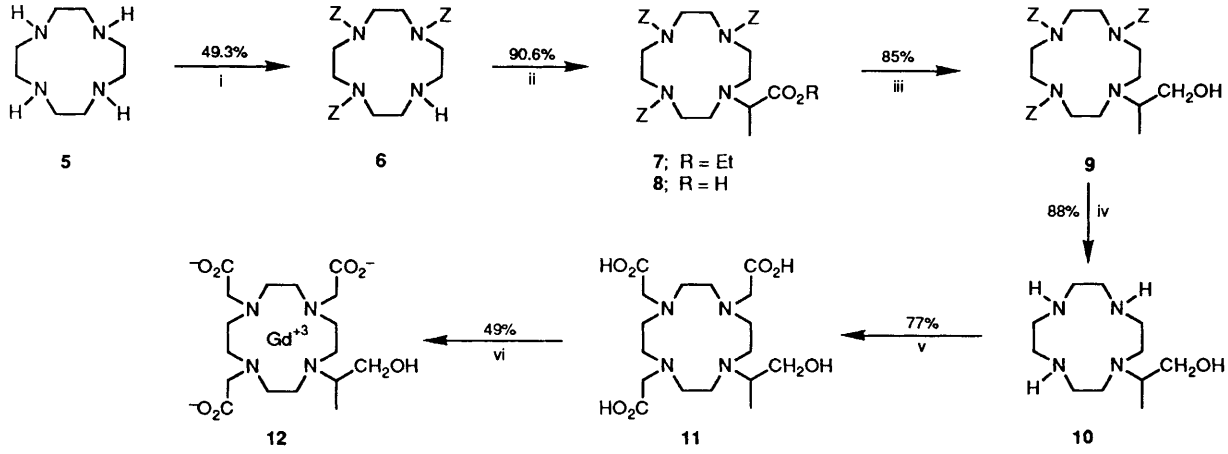

Scheme 2 *Reagents:* i, $ClCO_2CH_2Ph$, CH_2Cl_2, Et_3N; ii, **4**, CH_3CN, Na_2CO_3; iii, $LiBH_4$, 9-OMe-BBN, THF; iv, Pd/C, H_2; v, $BrCH_2CO_2H$, NaOH, H_2O; vi, Gd_2O_3, H_2O

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 [$^2H_3$]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 × 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 cm^3 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 × 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 cm^3 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 cm^3 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 MΩ 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 °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 °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 × 250 cm^3), 10% aqueous NaOH (1 × 250 cm^3), water (1 × 250 cm^3) and saturated brine (1 × 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, Ar*H*), 5.0 [6 H, m, (ArC$H_2O_2C)_3$], 3.7, 3.5, 3.3, 2.2 [16 H, br m, N($CH_2CH_2)_4$N] 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. $C_{32}H_{38}N_4O_6$ 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

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atmosphere of hydrogen (Paar shaker, 50 psi). After 16 h, the catalyst was filtered off and washed with EtOH (100 cm^3). 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, CO_2CH_2 and $CHOH$), 1.38 (3 H, d, J 7, $CHCH_3$) and 1.26 (3 H, t, J 7, CH_2CH_3).

Ethyl 2-(*Trifluoromethylsulphonyloxy*)*propionate* **4**.—Into a 250 cm^3 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 CH_2Cl_2 (80 cm^3) 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 CH_2Cl_2 (40 cm^3) 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 CH_2Cl_2 (50 cm^3). 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; ν_{max}/cm^{-1} 1750, 1405, 1130, 1070, 1005 and 940; δ_H 5.21 (1 H, q, J 7, CH_3CH), 4.30 (2 H, q, J 6.9, CO_2CH_2), 1.72 (3 H, d, J 6.8, $CHCH_3$) and 1.32 (3 H, t, J 6.8, CH_2CH_3). The NMR spectrum of **4** was identical with that reported for the (*S*)-isomer[11] 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 dm^3 flask containing **6** (60 g, 0.104 mol) and Na_2CO_3 (13.84 g, 0.131 mol) in MeCN (700 cm^3) was slowly added a solution of **4** (32.65 g, 0.131 mol) in MeCN (70 cm^3). 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; ν_{max}/cm^{-1} 1704 br, 1416 and 1003; δ_H 7.30 (15 H, br s, ArH), 5.20–4.85 (6 H, br m, CH_2Ar), 4.10 (2 H, br q, CO_2CH_2), 3.75 (1 H, br q, $CHCH_3$), 3.60–2.50 [16 H, br m, $N(CH_2CH_2)_4N$)], 1.22 (3 H, t, J 7, CH_2CH_3) and 1.18 (3 H, br s, $CHCH_3$); 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. $C_{37}H_{46}N_4O_8$ 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 dm^3 flask was added as solution of **7** (56 g, 0.083 mol) in THF (800 cm^3) and the solution was cooled to 0–5 °C. To this was added dropwise a solution of $LiBH_4$ in THF (2 mol dm^{-3}; 58.15 cm^3, 0.116 mol), followed by a solution of 9-OMe-BBN in hexane (1 mol dm^{-3}; 8.3 cm^3, 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 cm^3) was added cautiously (H_2 evolution). After being stirred for 0.5 h, the clear THF solution was decanted and the precipitate was stirred with THF (100 cm^3) 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 cm^3). The THF solutions were combined and concentrated under reduced pressure to yield a gummy product which was purified by flash chromatography (70% ETOAc–hexane). Compound **9** (52.5 g, 85%), was obtained as a glassy solid; ν_{max}/cm^{-1} 3478br and 1699br; δ_H 7.35 (15 H, br s, ArH), 5.20–4.85 (6 H, m, CH_2Ar), 3.80–2.20 [20 H, br m, CH_2OH, $CHCH_3$, $N(CH_2CH_2)_4N$] and 0.82 (3 H, br d, $CHCH_3$); 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. $C_{35}H_{44}N_4O_7$ 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 cm^3) placed in a 250-cm^3 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 cm^3). 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; ν_{max}/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, CHH_BOH), 3.00–2.30 [20 H, m, CH_2OH, $CHCH_3$, $N(CH_2CH_2)_4N$] and 0.85 (3 H, d, J 6.9, $CHCH_3$); 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; H_2O, 3.62. $C_{11}H_{26}N_4O{\cdot}0.48H_2O$ 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 cm^3) at 0 °C was added NaOH (31.28 g, 0.782 mol) in water (137 cm^3). After the mixture had been stirred for 5 min, compound **10** (19 g, 0.083 mol) dissolved in deionized water (45 cm^3) 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 dm^3). After washing the column with deionized water (6 dm^3), the compound was eluted with NH_4OH (1 mol dm^{-3}; 5 dm^3), followed by NH_4OH (2 mol dm^{-3}; 2 dm^3). Several fractions (500 cm^3) 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 cm^3). After washing with 4 bed volumes of deionized water, the column was eluted with H_2SO_4 (1 mol dm^{-3}; 100 cm^3), followed by 2 bed volumes of deionized water. Several fractions (50 cm^3) 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 cm^3). Several fractions (50 cm^3), 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 $BaCl_2$ 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; ν_{max}/cm^{-1} 3395s br, 2970, 2849, 1632, 1395, 1227, 1162, 1087 and 1050; δ_H(in D_2O, CH_3CN as internal standard) 3.80–2.70 (26 H, m, $(CH_2CO_2H)_3$, CH_2OH, $CHCH_3$, $N(CH_2CH_2)_4N$] and 1.02

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(3 H, br s, $CHCH_3$); δ_C(in D_2O, CH_3CN 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; H_2O, 0.51%. $C_{17}H_{32}N_4O_7 \cdot 0.12H_2O$ 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 cm^3) was added Gd_2O_3 (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 cm^3) (a slight heating was necessary) and the resulting solution was added under slow agitation to propan-2-ol (1800 cm^3). 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}; ν_{max}/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; H_2O 0.96%. $C_{17}H_{29}N_4O_7Gd \cdot 0.30H_2O$ requires C, 36.19; H, 5.29; N, 9.93%).

Acknowledgements

The authors thank Dr. D. Sieh and Ms. K. Varrichio for HPLC analysis, Dr. G. C. Di Donato and his associates for mass spectral data, Dr. M. H. Huang and his co-workers for IR spectra, and Mr. T. McCormick and his associates for elemental analyses. The authors also thank Drs. R. Ranganathan and S. Kang for fruitful discussions.

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Paper 1/02854E
Received 13*th June* 1991
Accepted 26*th July* 1991

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