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The synthesis of a carborane gadolinium–DTPA complex for boron neutron capture therapy

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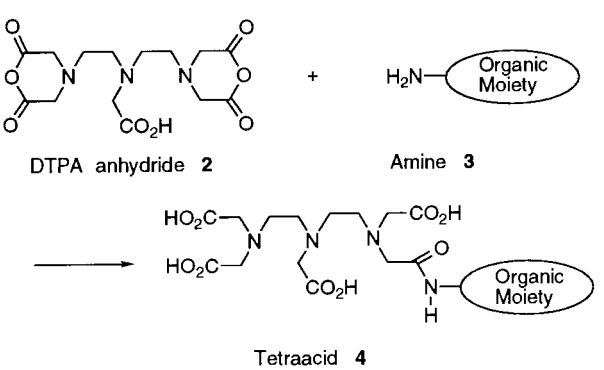
Abstract

Five-carboxylate DTPA derivatives (**5** and **10**) were synthesized via the palladium-catalyzed reaction of allyl ethyl carbonate **9** with diethylenetriamine-*N*-ethoxycarbonyl acetic-*N*,*N*′,*N*″,*N*″-tetraacetic acid hexaethyl ester **7**. This method can be applied to the synthesis of a Gd–carborane complex. The reaction of the hexaethyl ester **7** with carboranyl allyl carbonate **13a** proceeded very smoothly under $Pd(dba)_2$/2dppe catalyst (10 mol%) in THF at 50°C, giving the C–C bond formation product **14** in 74% yield. Hydrolysis of the ethyl esters in **14** was carried out with LiOH in aqueous methanol followed by treatment with diluted hydrochloric acid (1N) to afford the corresponding pentaacid **15** in 68% yield. Treatment of the carborane containing DTPA derivative **15** with gadolinium(III) chloride hexahydrate gave the desired Gd–DTPA carborane complex **16** in quantitative yield.

Keywords: Boron neutron capture therapy; Chelating reagent; Gadolinium; Carborane

1. Introduction

Diethylenetriaminepentaacetic acid (DTPA, **1**) is one of the most well-known chelating reagents for the production of stable complexes with various heavy metal ions [1]. A gadolinium–DTPA complex, which is commercially available under the trade name of 'Magnebist' and used in recent years as an MRI contrast medium, has attracted particularly high attention in the medical field [1b]. Bifunctional chelating agents based on DTPA are compounds that comprise both a powerful metal chelating group and a second functional group which can be a reactive moiety capable of forming covalent bonds with biological molecules or a hydrophobic aliphatic chain. A general method for coupling DTPA with the second functional group has included an amide bond formation reaction between DTPA anhydride **2** and amines **3**, which produces the tetraacid derivatives **4** (Scheme 1) [1]. During the reaction, one of the five carboxyl groups of DTPA is converted into an ester or an amide. Consequently, the carboxyl groups capable of coordinating to a metal ion are reduced in number to four [2]. Reduction of the number of carboxyl groups may result in a problem in that a metal ion is liberated



Scheme 1.

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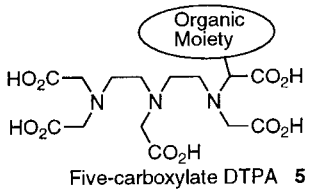


Fig. 1.

in vivo [3]. Accordingly, it is desirable to develop a method for preparing DTPA-bifunctional chelating agents in which a second functional group is attached to the DTPA carbon framework through a C–C bond (for example **5**, Fig. 1). A number of bifunctional chelating reagents based on EDTA (ethylenediaminetetraacetic acid) have been prepared from *p*-aminobenzyl-EDTA in which an amino functional group is bound to the EDTA chelating group through a C–C bond [3]. However, few DTPA derivatives having a second functional group at the carbon skeleton (such as **5**) have been synthesized.

On the other hand, neutron capture therapy is included in the radiotherapy of cancers [4]. In boron neutron capture therapy, mercaptoundecahydrodecaborate (BSH) and *p*-boronophenyl alanine (BPA) are used as a neutron capture agent in the treatment of brain tumor and malignant skin cancer [5]. The boron containing compounds are administered to the patient by means of intravenous injection or direct injection into the diseased part, and after a period of time, thermal neutrons are irradiated to the diseased part. For improving the therapeutic effect, the diseased part should be irradiated with thermal neutrons when the boron compound is accumulated at the tumor in the patient in the highest concentration. However, it is not practical or feasible to measure consecutively the boron concentration of the compound in each tissue in a body, which leads to reduction in the therapeutic effect. Boron MRI [6] and PET using ^{18}F-BPA-Fructose [7], which has been developed by Kabalka and co-workers, have a possibility to solve these problems. It occurred to us that if we synthesize a gadolinium containing carborane compound, we would be able to measure the boron concentration in each tissue by using the MRI contrasting effects of gadolinium.

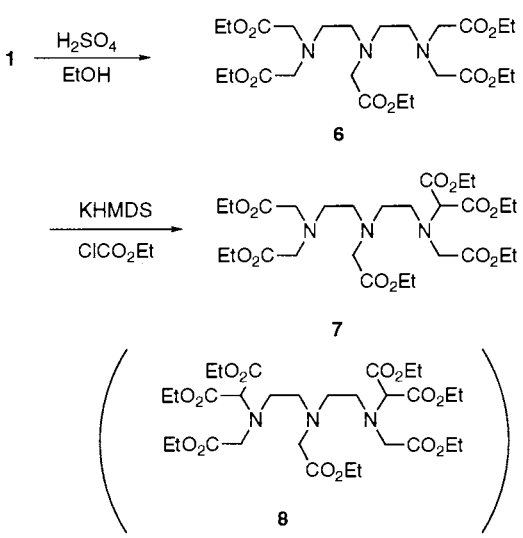
Herein we report a new synthetic method of five-carboxylate DTPA derivatives via a palladium catalyzed C–C bond formation reaction, and its application to the synthesis of a gadolinium–DTPA complex containing a carborane unit. Synthesis of this compound enables us to measure the accumulation of the boron carriers in a tumor tissue consecutively by means of MRI, since the compound linked to a gadolinium–DTPA complex has MRI contrasting nature [8,9].

2. Results and discussion

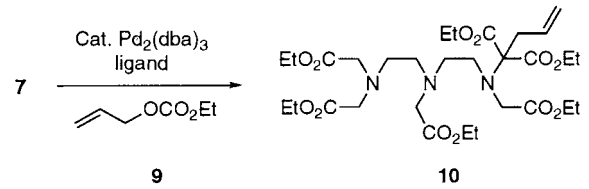
2.1. A synthetic method of five-carboxylate DTPA derivatives

The pentaethyl ester **6** was prepared in 79% yield by refluxing DTPA (**1**) in ethanol in the presence of sulfuric acid (Scheme 2). Carbanion formation at the α-position of the ester group of **6** was followed by trapping with various electrophiles. The reaction of carbanions, which were formed by the treatment of the pentaethyl ester **6** with NaH, KOMe, KOtBu, or *sec*-BuLi, with various electrophiles, such as acrolein, propargyl bromide, and ethyl chloroformate gave a complex mixture of products. The reaction of **6** with one equiv of KHMDS in THF at -78°C followed by trapping with excess amounts of ethyl chloroformate afforded the hexaethyl ester **7** in low yield along with **6** recovered ($>70\%$). The use of two equivalents KHMDS and three equivalents of ethyl chloroformate gave the mono-carboxylated product **7** in 53% yield without being accompanied with the di-carboxylated product **8** [10]. However, the use of three equivalents of KHMDS and three equivalents of ethyl chloroformate gave a mixture of **7** and **8**. Under these conditions, the carbanion of **6** did not react with other electrophiles such as acrolein, propargyl bromide, benzyl bromide, and butyl bromide.

It was considered that the carbon–carbon bond formation at the methyne carbon of the hexaethyl ester **7** might take place by the reaction of the carbanion of **7** with electrophiles . The use of rather strong bases such as NaH caused complex ester condensations. No reaction took place with weak bases, such as K_2CO_3 (suspension) in acetone. However, the palladium-catalyzed allylation reaction of **7** with allyl ethyl carbonate **9**



Scheme 2.



Scheme 3.

proceeded very smoothly giving the allylation product **10** in high yield (Scheme 3, [11]). The results are shown in Table 1. The use of palladium bis(dibenzylideneacetone) (dba) with Ph_3P and/or trimethylolpropane phosphate (tmpp) as a ligand gave **10** in lower yields along with the recovery of **7** (entries 1 and 2). Other palladium catalysts such as $Pd(PPh_3)_4$ and $PdCl_2(PPh_3)_2$ were not effective for this allylation reaction. The best result was obtained by using 1,2-bis(diphenylphosphino)ethane (dppe) as a ligand [12], which gave **10** in 80% yield without recovering **7** (entry 3). THF was the best solvent; the reaction of **7** with **9** in the presence of $Pd(dba)_2$/2dppe in CH_3CN did not give the desired product (entry 4). Since an allylic moiety has been attached as a second functional group of DTPA via C–C bond, biological molecules can be bound to a metal chelating group without losing one of five carboxylate groups.

2.2. Synthesis of carborane-containing Gd–DTPA complex

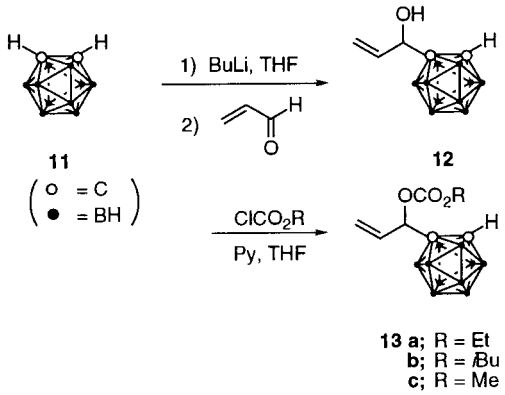
Much attention has been paid to ^{157}Gd-labelled DNA ligand as a Gd-carrier for neutron capture therapy [13]. Additionally *ortho*-carborane is known to be an important and useful structural unit for boron neutron capture therapy. Combination of ^{157}Gd and ^{10}B might enhance the efficiency of neutron capture therapy. Therefore, the synthetic method used to prepare all carboxylate free DTPA derivative was applied to the synthesis of a Gd–carborane complex [14].

Table 1
Palladium-catalyzed allylation of **7** with allyl ethyl carbonate **9**[a]

Entry	Ligand	Solvent	Crude mixture **7**:**10**	Yield of **10** (%)
1	PPh_3	THF	50:50	40
2	tmpp[b]	THF	50:50	42
3	dppe	THF	0:100	80
4	dppe	CH_3CN	100:0	0

[a] The reaction was carried out at r.t. in THF (1 mmol ml^{-1}) for 1 ~ 2 h under Ar with **7**: $Pd(dba)_2$: monophosphine (diphosphine) = 1: 0.1: 0.4 (0.2) as molar ratio.

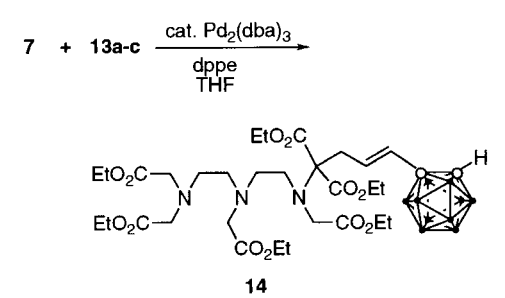
[b] tmpp = trimethylolpropane phosphate.



Scheme 4.

The preparation of 1-*ortho*-carboranyl-2-propenyl carbonate derivatives **13** is shown in Scheme 4. The reaction of 1-lithio-*ortho*-carborane, which was generated by treating *ortho*-carborane **11** with one equivalent BuLi in THF at $-78°C$, with acrolein gave allylic alcohol **12** in 89% yield. In this case, the disubstituted product was not obtained [15,16]. The treatment of **12** with ethyl chloroformate gave **13a** in 91% yield. Under the same condition, **13b** (81%) and **13c** (71%) were obtained from *iso*-butyl- and methyl chloroformate, respectively. The palladium-catalyzed coupling reaction of activated methyne **7** with allylic carbonates **13** is shown in Scheme 5 and Table 2. The reaction of one equivalent **7** with three equivalents **13a** proceeded very smoothly under $Pd(dba)_2$/2dppe catalyst (10 mol%) in THF at 50°C, giving **14** in 74% yield (entry 1). Excess **13a** was recovered, and can be used again as a starting material. The use of one equivalent **13a** gave **14** in lower yield. Other allyl carbonates such as *iso*-butyl allylcarbonate **13b** (entry 2) or methyl allylcarbonate **13c** (entry 3) gave **14** in lower yields (38 and 64%, respectively).

Hydrolysis of all ethyl esters of **14** was carried out with LiOH in aqueous methanol followed by treatment with dilute hydrochloric acid (1N) to afford the pentaacid **15** in 68% yield (Scheme 6). Sodium or potassium hydroxide did not work well. One equivalent of gadolinium(III) chloride hexahydrate was added to a methanol solution of the carborane containing DTPA



Scheme 5.

Table 2
Effect of leaving groups of allylic carbonates **13** on palladium-catalyzed reaction[a]

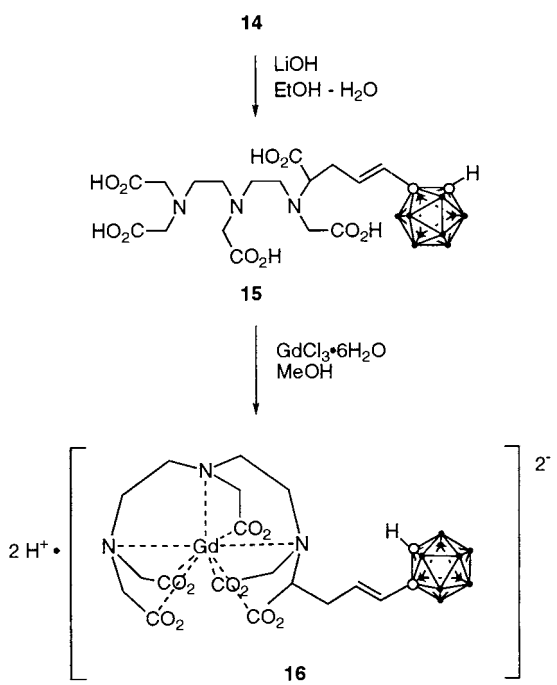
Entry	R	Carbonbate **13**	Yield of **14** (%)[b]
1	Et	**13a**	74
2	*i*Bu	**13b**	38
3	Me	**13c**	64

[a] A mixture of **7** (one equivalent), **13** (three equivalents), $Pd(dba)_2$ (0.1 equivalents), and dppe (0.2 equivalents) in THF was stirred at 50°C for 12 h under Ar.
[b] Isolated yield based on **7**.

derivative **15** and then the resultant mixture was treated with sodium carbonate to afford the desired Gd–carborane complex **16** in quantitative yield.

3. Conclusions

The key for the successful functionalization of DTPA hexaethyl ester **7** is the use of the palladium catalyzed allylation. Conventional carbanion based procedures led to self-condensation of the ester groups. Instead of simple allyl carbonate **9**, allyl carbonates having biologically active moieties (for example **13**) can be used or further manipulation from the allyl group of compound **10** may be possible. Consequently, we believe that all pentacarboxylate-free DTPA analogue **5** has the potential to become an attractive alternative for the previous amide-bonded tetraacid.



Scheme 6.

4. Experimental

Melting points were determined on an MRK No. 8026 and uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded on a Jeol GSX-270 spectrometer. The chemical shifts are reported in δ units relative to internal tetramethylsilane. IR spectra were recorded on a Shimadzu FTIR-8200A spectrometer. High-resolution mass spectra were recorded on a Jeol JMS-HX110. Most commercially supplied chemicals were distilled and stored over molecular sieves.

4.1. Preparation of pentaethyl ester of DTPA 6

To a solution of diethylenetriaminepentaacetic acid **1** (25 g, 63.5 mmol) in ethanol (500 ml), concentrated sulfuric acid (10 ml, 180 mmol) was added and the mixture was stirred under reflux for 20 h. The reaction mixture was cooled to r.t., concentrated, and diluted with methylene chloride (100 ml). Aqueous NaOH solution (10%) was added to the resulting mixture at 0°C to make the solution alkaline, and then the organic layer was separated, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated and purified by silica gel column chromatography (hexane: ethyl acetate = 2:3) to give **6** (26.88 g, 50.4 mmol, 78% yield) as a white solid: IR (KBr) 2979, 1735, 1029, 728 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.21–4.10 (m, 10H), 3.57 (s, 8H), 3.49 (s, 2H), 2.9–2.75 (m, 8H), 1.27 (t, $J = 7.5$ Hz, 12H), 1.26 (t, $J = 7.5$ Hz, 3H); ^{13}C-NMR ($CDCl_3$) δ 171.5, 171.2, 60.3, 60.1, 55.2, 52.7, 52.2, 14.2; Anal. Calcd. for $C_{24}H_{43}N_3O_{10}$: C, 54.02; H, 8.12; N 7.87. Found: C, 53.79; H, 7.88; N, 7.72.

4.2. Preparation of the hexaethyl ester 7

A mixture of a toluene solution of potassium bis(trimethylsilyl)amide (15 ml, 7.5 mmol) and THF (50 ml) was cooled to −78°C under Ar and **6** (2 g, 3.75 mmol) in THF (30 ml) was slowly added dropwise to the mixture over a period of 12 min. After the reaction mixture was stirred for 70 min at −78°C, ethyl chloroformate (1.22 g, 11.25 mmol) in THF (30 ml) was added dropwise over a period of 20 min and the mixture was further stirred for 50 min at −78°C. The reaction mixture was quenched with aqueous NH_4Cl solution (2N), extracted with ether, dried over anhydrous $MgSO_4$, and concentrated in vacuo. Purification by silica gel column chromatography (benzene: ethyl acetate = 2: 1) gave **7** as a syrup (1.2 g, 1.98 mmol, 78% yield): IR (Film) 2980, 1728, 1034, 728 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.48 (s, 1H), 4.27–4.06 (m, 12H), 3.67 (s, 2H), 3.56 (s, 4H), 3.48 (s, 2H), 2.97–2.73 (m, 8H), 1.33–1.2 (m, 18H)); ^{13}C-NMR ($CDCl_3$) δ 171.6, 171.3168.4, 168, 67.5, 61.4, 61.5, 60.4, 60.2, 55.2, 55.1, 53.5, 53.2, 52.7, 52.3, 51.5, 14.5; Anal. Calcd. for

$C_{27}H_{47}N_3O_{12}$: C, 53.54; H, 7.82; N 6.94. Found: C, 53.36; H, 7.51; N, 6.78.

4.3. Allylation of hexaethyl ester **7** with allyl ethyl carbonate **9**

A mixture of allyl ethyl carbonate **9** (259 mg, 2.23 mmol), $Pd(dba)_2$ (42.5 mg, 0.074 mmol), dppe (59 mg, 0.148 mmol) and **7** (450 mg, 0.74 mmol) in THF (5 ml) was refluxed for 3 h. THF was removed and the residue was purified by silica gel column chromatography with benzene/ethyl acetate (2:1) to give **10** (383.8 mg, 0.59 mmol, 80.3%) as a light pale oil. IR (Film): 3075w, 2982s, 1730s, 1639m, 1446s, 725m cm^{-1}; ^{1}H-NMR ($CDCl_3$): 5.95–5.78 (m, 1H), 5.15–5.01 (m, 2H), 4.25–4.07 (m, 12H), 3.57 (s, 2H), 3.55 (s, 4H,), 3.45 (s, 2H), 2.97–2.71 (m, 8H), 1.27 (t, $J = 7$ Hz, 18H) ppm; ^{13}C-NMR ($CDCl_3$): 171.8q, 171.5q, 171.3q, 169.6q, 132.8t, 118d, 75q, 61.3d, 60.4d, 60.3d, 60.2d, 55.5d, 55.3d, 54d, 52.9d, 52.8d, 52.4d, 50.4d, 38.9d, 14.2s ppm. Anal. Calcd. for $C_{30}H_{51}N_3O_{12}$: C 55.8, H 7.96, N 6.51; Found C 55.73, H 7.66, N 6.49.

4.4. Preparation of carborane derivatives **13**

A typical procedure for the synthesis of **13a** (R = ethyl group); To a mixture of 1-carboranyl-2-propenol **12** (1.20 g, 5.98 mmol), which was prepared by the addition of *ortho*-carborane to acrolein according to the literature procedure [15], and pyridine (1.4 ml) in CH_2Cl_2 (5 ml) was added ethyl chloroformate (1.95 g, 17.9 mmol) at 0°C. After being stirred for 3 h, the reaction mixture was poured into ice-water. The organic layer was extracted, dried over anhydrous $MgSO_4$, and concentrated in vacuo. Purification by silica gel column chromatography (hexane: ethyl acetate = 1:1) gave **13a** as a colorless liquid (1.48 g, 5.44 mmol, 91% yield): IR (Film) 3072, 2966, 2595, 1750, 1646, 1471, 1019, 720 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 5.83–5.68 (m, 1H), 5.52 (d, $J = 7.5$ Hz, 1H), 5.48–5.38 (m, 2H), 3.96 (dd, $J = 6.5$, 2.5 Hz, 1H), 3.95 (dd, $J = 6.5$, 2.5 Hz, 1H), 3.87 (s, 1H), 2.07–1.90 (m, 1H), 0.95 (d, $J = 6.5$ Hz, 6H); ^{13}C-NMR ($CDCl_3$) δ 153.5, 131.2, 121.7, 76.8, 75.1, 74.7, 59.2, 27.8, 18.9; Anal. Calcd. for $C_{10}H_{24}B_{10}O_3$: C, 39.98; H, 8.05. Found: C, 40.28; H, 7.75. **13b** (R = *iso*-butyl group): IR (Film) 3072, 2985, 2593, 1752, 1645, 1002 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 5.82–5.67 (m, 1H), 5.51 (d, $J = 7.5$ Hz, 1H), 5.48–5.38 (m, 2H), 4.23 (q, $J = 7.0$ Hz, 2H), 3.87 (s, 1H), 1.33 (t, $J = 7.0$ Hz, 3H); ^{13}C-NMR ($CDCl_3$) δ 153.3, 131.2, 121.9, 76.9, 74.7, 65.3, 59.3, 14.1; Anal. Calcd. for $C_8H_{20}B_{10}O_3$: C, 35.28; H, 7.40. Found: C, 35.08; H, 7.16. **13c** (R = methyl group): IR (KBr) 3080, 2970, 2590, 1720, 1650, 1440, 1250, 720 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 5.82–5.67 (m, 1H), 5.51 (d, $J = 7.5$ Hz, 1H), 5.48–5.40 (m, 2H), 3.83 (s, 3H), 3.58 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ 153.9, 131.0, 122.0, 77.0, 74.5, 59.2, 55.6; Anal. Calcd. for $C_7H_{18}B_{10}O_3$: C, 35.55; H, 7.02. Found: C, 32.6; H, 6.80.

4.5. Synthesis of **14**

A representative procedure for palladium-catalyzed allylation is as follows. A mixture of **7** (584 mg, 0.96 mmol), $Pd(dba)_2$ (55 mg, 0.096 mmol), dppe (77 mg, 0.19 mmol), and **13a** (579 mg, 2.89 mmol) was dissolved in THF (10 ml) and the mixture was stirred at 50°C for 12 h under Ar. After removal of THF, the reaction mixture was purified by silica gel column chromatography (hexane: ethyl acetate: methanol = 40: 20: 1) to give **14** (562 mg, 0.71 mmol, 74% yield). IR (Film): 3020s, 2984s, 2598s, 1735s, 1653w, 1371s, 4082s cm^{-1}; ^{1}H-NMR ($CDCl_3$): 6.17 (dt, $J = 7$, 15.5 Hz, 1H), 5.77 (d, J = 15.5 Hz,), 4.25–4.09 (m, 12H), 3.89 (s, 1H), 3.55 (s, 4H), 3.52 (s, 2H), 3.39 (s, 2H), 2.88–2.65 (m, 8H), 1.28 (t, $J = 7$ Hz, 18H) ppm; ^{13}C-NMR ($CDCl_3$): 171.8q, 171.4q, 171.2q, 169q, 133.8t, 127d, 74.9q, 73.7q, 61.7d, 61.2t, 60.6d, 60.5d, 60.3d, 55.5d, 55.3d, 53.9d, 53.8d, 52.9d, 52.2d, 50.9d, 14.2s ppm. Anal. Calcd. for $C_{32}H_{61}B_{10}N_3O_{12}$: C 48.78, H 7.8, N 5.33. Found: C 48.44, H 7.55, N 5.2.

4.6. Deprotection of hexaethyl ester **14**

A solution of $LiOH-H_2O$ (558 mg, 13.3 mmol) in EtOH (30 ml) was added to a solution of **14** (1.16 g, 1.47 mmol) in EtOH (5 ml) over a period of 30 min at r.t., and the mixture was stirred for 12 h. The reaction mixture was filtered through Celite and the filtrate was evaporated in vacuo. The resulting residue was then diluted with water (15 ml) and washed with ether to remove impurities insoluble in water. To the mixture was added an aqueous solution of HCl (10%, 4.5 g, 13.3 mmol) at 0°C. After the acidic solution was stirred for 20 min, the precipitate was collected, dissolved in MeOH (20 ml), and purified by HPLC with $MeOH-H_2O$ (5:2) as an eluent to give **15** (548 mg, 0.998 mmol, 68% yield) as a white solid: IR (KBr) 3411, 3014, 2592, 1726, 1632, 1396, 1222, 1018 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 6.17 (dt, $J = 15.5$, 7.0 Hz, 1H), 5.89 (d, $J = 15.5$ Hz, 1H), 4.62 (s, 1H), 4.06–3.88 (m, 1H), 3.62 (s, 4H), 3.53–3.08 (m, 12H), 2.65–2.40 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ 175.7, 174.5, 174.1, 170.4, 136.3, 127.7, 75.1, 65.3, 62.4, 56.1, 55.7, 53.9, 53.8, 53.0, 50.7, 50.3, 33.3; Anal. Calcd. for $C_{19}H_{37}B_{10}N_3O_{10}\cdot 1/2H_2O$: C, 39.04; H, 6.55; N, 7.19. Found: C, 38.96; H, 6.43; N, 7.05.

4.7. Carborane Gd-DTPA complex **16**

To a solution of **15** (215 mg, 0.374 mmol) in MeOH (5 ml) was added $GdCl_3\cdot 6H_2O$ (140 mg, 0.374 mmol) at r.t. and the reaction mixture was stirred for 5 h. To the

mixture was added Na_2CO_3 (31 mg, 0.374 mmol) and after being stirred for 30 min at r.t., the reaction mixture was diluted with MeOH (5 ml). Purification by HPLC with MeOH–H_2O (5: 2) as an eluent gave **16** (153 mg, 0.209 mmol) as a white solid: IR (KBr) 3375, 2980, 2592, 1596, 1405, 1094, 1021, 723 cm^{-1}; Anal. Calcd. for $C_{19}H_{33}B_{10}N_3O_{10}Gd \cdot 1/4H_2O$: C, 31.08; H, 4.74; N, 5.72. Found: C, 31.45; H, 4.77; N, 5.33.

References

[1] Recent examples: (a) Lanthanide–cyclodextrin complex; T.J.Wenzel, M.S. Bogyo, E.L. Lebeau, J. Am. Chem. Soc. 116 (1994) 4858. (b) Gadolinium complexes: P.F. Sieving, A.D. Watson, S.M. Rocklage, Bioconjugate Chem. 1 (1990) 65. (c) Terbium complex: M.P.Bailey, B.F. Rocks, C. Riley, Analyst 109 (1984) 1449. (d) Indium complexes: C.H. Paik, V.K. Sood, N. Le, J.A. Carrasquillo, J.C. Reynolds, R.D. Neumann, R.C. Rega, Nucl. Med. Biol. 19 (1992) 517. (e) Technetium complexes: Y. B. J. Aldenhoff, M. J. P. G. van Kroonenburg, S. V. M. Zimmy, P. P. C. A. Menheere, L. H. Koole, J. Chem. Soc. Chem. Commun. (1995) 523.

[2] X-ray structure analysis of the Gd-DTPA·H_2O exhibited a distorted capped square antiprism: H. Gries, H. Miklautz, Physiol. Chem. Phys. Med. NMR 16 (1984) 105.

[3] (a) S. V. Deshpanda, R. Subramanian, M. J. McCall, G. L. Denardo, C. F. Meares, J. Nuclear Med. 31 (1990) 218. (b) C. F. Meares, M. J. McCall, D. T. Reardan, D. A. Goodwin, C. I. Diamanti, M. Mctigue, Anal. Biochem. 142 (1984) 68. (c) C. F. Meares, D. A. Goodwin, J. Protein Chem. 3 (1984) 215.

[4] G.L. Locher, Am. J. Roentgeno. 36 (1936) 1.

[5] Review Papers: (a) Y. Yamamoto, Pure. Appl. Chem. 63 (1991) 423. (b) M. F. Hawthorne, Angew. Chem. Int. Ed. Engl. 32 (1993) 950. (c) R. F. Barth, A. H. Soloway, R. G. Fairchild, Cancer Research 50 (1990) 1061. (d) A. H. Soloway, W. Tjarks, B. A. Barnum, F.-G. Rong, R. F. Barth, I. M. Wyzlic, J. G. Wilson, Chem. Rev. 98 (1998) 1515.

[6] G. W. Kabalka, C. Tang, P. Bendel, J. Neuro-Oncol. 33 (1997) 153.

[7] G. W. Kabalka, G. T. Smith, J. P. Dyke, W. S. Reid, C. P. D. Longford, T. G. Roberts, N. K. Reddy, E. Buonocore, K. F. Hübner, J. Nucl. Med. 38 (1997) 1762.

[8] H. Nemoto, J. Cai, Y. Yamamoto, Tetrahedron Lett. 37 (1996) 539.

[9] Y. Yamamoto, J. Cai. H. Nemoto, H. Nakamura, F. Girard, K. Yoshida, H. Fukuda, in: B. Larsson, J. Crawford, R. Weinreich (Eds.), Advances in Neutron Capture Therapy, Plenum Press, New York, 1997, p. 436.

[10] In the case of using NaHMDS instead of KHMDS, the yield of **8** was increased. The structure of **8** was not clear, because the position, to which the second ester group attached, could not be determined.

[11] J. Tsuji, I. Shimizu, I. Mikami, Y. Ohashi, T. Sugiura, K. Takahashi, J. Org. Chem. 50 (1985) 1523.

[12] This choice of the catalyst combination gives often better results as reported in our recent papers; H. Nemoto, F.-G. Rong, Y. Yamamoto, J. Org. Chem. 55 (1990) 6065. H. Nemoto, J. Cai, Y. Yamamoto, J. Chem. Soc. Chem. Commun. (1994) 577.

[13] A. D. Whittaker, D. P. Kelly, M. Pardee, R. F. Martin, in: B. J. Allen, D. E. Moore, B. V. Harrington (Eds), Progress in Neutron Capture Therapy for Cancer; Plenum Press, New York, 1992, p. 231.

[14] (a) F. Girard, H. Nakamura, H. Fukuda, Y. Yamamoto, K, Yoshida, in: Y. Ishii et al. (Eds.), Recent Advances in Biomedical Imaging, Elsevier Science, Amsterdam, 1997, p. 201. (b) F. Girard, H. Fukuda, H. Nakamura, Y. Yamamoto, K. Yoshida, in B. Larsson, J. Crawford, R. Weinreich (Eds.), Advances in Neutron Capture Therapy, Plenum Press, New York, 1997, p. 271.

[15] Diluted condition was important for preparing monosubstituted carboranes; see J. Cai, H. Nemoto, H. Nakamura, B. Singaram, Y. Yamamoto, Chem. Lett. (1996) 791. H. Nakamura, K. Aoyagi, Y. Yamamoto, J. Org. Chem. 62 (1997) 780. H. Nakamura, K. Aoyagi, Y. Yamamoto, J. Am. Chem. Soc. 120 (1998) 1167.

[16] J. L. Mauer, F. Verchier, A. J. Seino, C. B. Knobler, M. F. Hawthorne, J. Org. Chem. 55 (1990) 838.