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Synthesis of Boronated Phenanthridinium Derivatives for Potential Use in Boron Neutron Capture Therapy (BNCT)

Hadi Ghaneolhosseini, Werner Tjarks, and Stefan Sjöberg*.

Department of Organic Chemistry, Uppsala University, Box 531, S-751 21 Uppsala, Sweden.

Abstract: 3,8-Diamino-5-[3-(12-(3-aminopropyl)-*p*-carborane-1-yl)propyl]-6-phenyl phenanthridinium chloride hydrochloride (**13**) has been synthesised by reacting 3,8-diacetamido-6-phenylphenanthridine (**9**) with 1-(3-*N,N*-dibenzyloxycarbonylaminopropyl)-12-(3-iodopropyl)-1,12-dicarba-*closo*-dodecaborane (**8a**) in nitrobenzene at 120°C for 4 days and subsequent removal of the protective groups using 33% HBr/AcOH. Conversion to the chloride hydrochloride was accomplished by the action of hydrochloric acid on the pseudo-base of **13**. © 1997 Elsevier Science Ltd.

INTRODUCTION

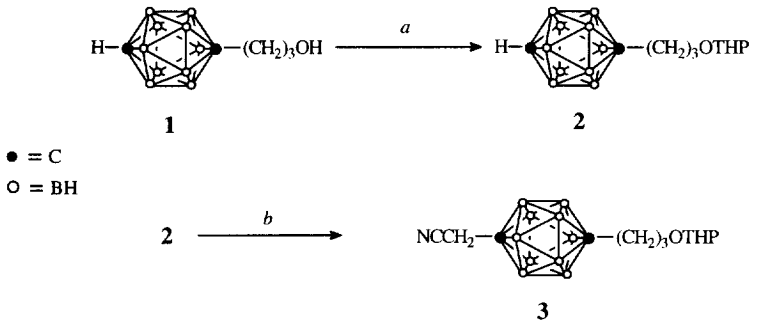
An interesting approach to the treatment of cancer is Boron Neutron Capture Therapy (BNCT) which utilises the capability of the non-radioactive ^{10}B-nuclide to capture relatively harmless thermal neutrons. This capture reaction [^{10}B(^{1}n,^{4}He)^{7}Li] generates strongly cell toxic ^{4}He and ^{7}Li ions possessing ranges of less than 10 μm in biological tissue. Therefore, *in situ* neutron irradiation of boron-loaded substances, localised predominantly in tumour cells, could result in selective tumour destruction with limited damage to surrounding healthy tissue.[1] It is anticipated that the lethal boron neutron capture reaction is especially effective when it occurs in close vicinity of tumour cell DNA.[2] Boron-containing DNA intercalator may be suitable agents for DNA specific boron delivery.

Early work in our laboratories focused on the synthesis of phenathridinium derivatives with *para*- and *nido*-carboranylpropyl groups at N-5 or *para*- and *nido*-carboranylethyl groups at C-6 of the phenanthridine ring structure.[3] The results from biological tests revealed that these compounds not only accumulated in cell nuclei but also to a great extent in other cell constituents. The presence of a highly lipophilic *p*-carborane cage and the overall neutral charge of *nido*-compounds render these molecules only sparingly water-soluble These characteristics contribute to significant interactions with non-DNA constituents of the cell, especially lipophilic membranes.[4] In order to increase the hydrophilicity and decrease the non-specific cell-binding, a phenanthridinium derivative (**13**) containing an aminoalkyl group attached to C-12 of the *para*-carborane cluster, located at N-5 position of the phenanthridine ring structure was prepared. The synthesis of this compound as well as interesting unsuccessful synthetic approaches to this and similar compounds are described herein.

RESULTS AND DISCUSSION

Our initial synthetic approach for the synthesis of phenanthridinium derivatives such as **13** with an aminoalkyl group at C-12 of the carborane cage is displayed in **Scheme 1**. Protection of the hydroxyl function

of compound **1**[5] using dihydropyran was carried out according to a previously described procedure.[6]The resulting protected alcohol **2**[Ψ] was obtained in 83% yield. The reaction of **2** with butyl lithium and subsequently iodoacetonitile afforded disubstituted *p*-carborane **3** in only 6% yield. This may be contributed to the acidic nature of the methylenic protons of iodoacetonitrile. The lithium salt of **2**, generated by the addition of butyl lithium, seems to abstract promptly a proton from this methylene group and reverts back to the neutral form (90 % recovery of **2**). The synthesis of **3** by phase transfer alkylation of **2** with acrylonitrile in the presence of "triton B[7]" (40% aqueous trimethylbenzylammonium hydroxide) was also attempted without success. It was intended to convert **3** to the corresponding iodo derivative according the procedure described in **Scheme 2** after removal of the tetrahydropyranyl protective group. Reaction of this iodo derivative with 3,8-diacetamido-6-phenylphenanthridine (**9**) in analogy to the method displayed in **Scheme 3** followed by reduction of the nitrile function and removal of the acetyl protective group from the 3,8-amino functions should then yield the aminoethyl analogue of target compound **13**. However, the low yield for **3** discouraged us to follow this synthetic route.

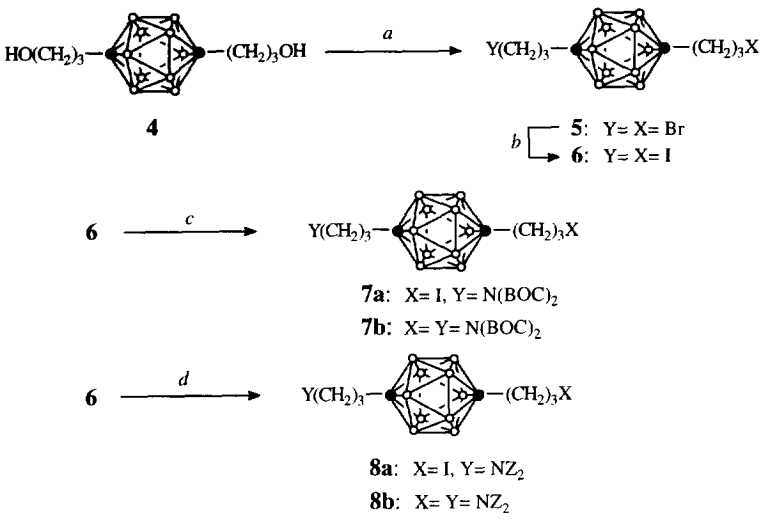


Reagents and conditions: a: 2,3 dihydropyran, *p*-toluenesulphonic acid, ether, reflux, 24hr.; *b*: butyl lithium, THF, iodoacetonitrile.

Scheme 1.

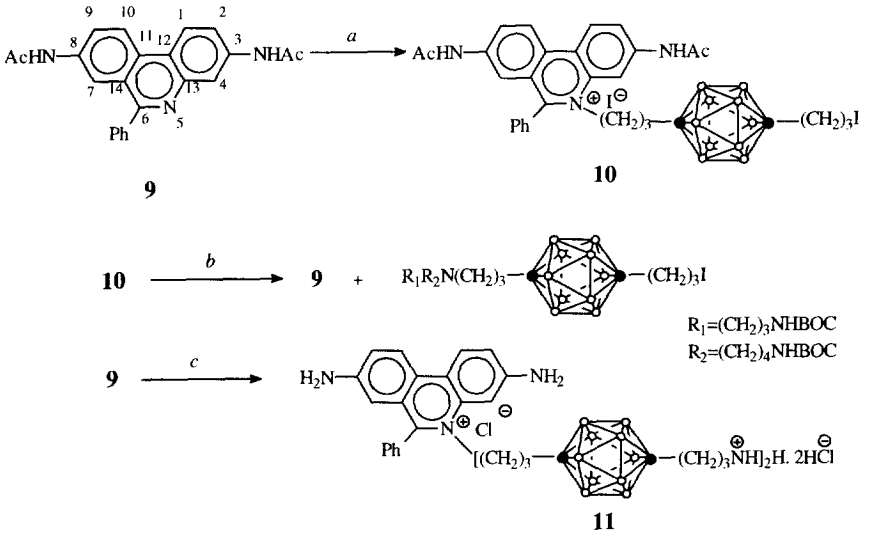
Our next approaches to introduce water-solubilising aminoalkyl substituents to carboranyl phenanthridinium derivatives involved disubstituted *p*-carborane derivatives **6**, **7a**, and **8a** shown in **Scheme 2**. Bromination of **4**[8] using carbon tetrabromide and triphenylphosphine in dichloromethane at 0°C afforded **5** in 85% yield. Compound **6** was obtained from **5** by Finkelstein reaction with sodium iodide in acetone. The yield was 97%. Phase transfer alkylation[9] of **6** was carried out by reacting one equivalent of either di-*tert*-butyliminocarboxylate [HN(BOC)2] or *N,N*-dibenzylimidodicarbonate [HNZ2] with one equivalent tetrabutyl ammonium hydrogensulfate, and two equivalents of 2M aqueous sodium hydroxide in dichloromethane. Purification of the crude products by column chromatography gave compound **7a** in 45% and **8a** in 41% yield respectively. The disubstituted compound **7b** isolated in 17% yield while we could not isolate **8b** under these conditions. A longer reaction time would cause the removal of one Z-protective group from **8a**.

The alkylation of 3,8-diacetamido-6-phenylphenanthridine (**9**)[10](**Scheme 3**) with a twofold excess of the diiodide **6** in nitrobenzene for 48 hr at 120-130°C afforded **10** in 24% yield. When **10** was reacted with a secondary alkylamine in DMF at 150°C to introduce amino groups, the quaternary nitrogen in the phenanthridinium moiety acted as a better leaving group than iodide. Also,^{1}H NMR spectroscopy showed that an oligomerised product, **11**, was produced when **9** was reacted with a twofold excess of **7a** in nitrobenzene for 48 hr at 120-130°C followed by the deprotection of amino groups in acidic milieu to introduce the aminoalkyl group. The oligomerisation is probably due to an instability of BOC-groups at the high reaction temperature (**Scheme 3**).



reagents and conditions: *a*: CBr_4, PPh_3, CH_2Cl_2, 0-25°C; *b*: NaI, acetone, 24hr, reflux, *c*: $(C_4H_9)NHSO_4$, 2M NaOH, $HN(BOC)_2$, CH_2Cl_2, reflux, 2hr; *d*: $(C_4H_9)NHSO_4$, 2M NaOH, HNZ_2, CH_2Cl_2, reflux, 5hr.

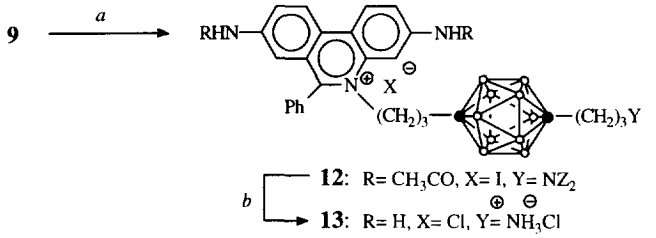
Scheme 2.



Reagents and conditions: *a*: **6**, nitrobenzene, 120°C, 48hr; *b*: HNR_1R_2, DMF, 150°C, 48hr; *c*: *i*) **7a**, nitrobenzene, 120°C, 48hr; *ii*) 10% HCl/MeOH, reflux, 2hr.

Scheme 3.

Finally, alkylation of **9** with **8a** (**Scheme 4**) in nitrobenzene for 4 days at 120°C afforded compound **12**. Removal of Z- and acetyl protective groups by 33% HBr/HOAc at RT afforded a bromide salt which was then successively converted into target compound **13** in 45% yield via the corresponding pseudo base according to a procedure described previously by Tjarks at al.[3].



Reagents and conditions: *a*: **8a**, nitrobenzene, 120°C, 4 days; *b*: *i*) 33% HBr/HOAc, RT, 2hr; *ii*) aqueous NaOH, pH= 14; *iii*) 10% HCl/MeOH, reflux, 2hr.

Scheme 4.

Compound **13** proved to be water soluble. Preliminary biological experiments *in vitro* indicated DNA intercalation without additional binding to cellular membranes. Although having potentially DNA localising capacity, it cannot be expected that boron-containing DNA intercalator, neither hydrophilic nor lipophilic, show any tumor-selectivity *per se*.. Special "tumour-delivery" systems may have to be employed for these agents. Our starategy for this is to use a two-step targeting principle which is outlined by Gedda *et al.*[11]

EXPERIMENTAL SECTION

General Details.

The ^{1}H, ^{13}C, ^{11}B NMR spectra were recorded in $CDCl_3$ (7.26 ppm, ^{1}H, 77.0 ppm, ^{13}C) or CD_3OD (3.35 ppm, ^{1}H, 49,0 ppm, ^{13}C) on a Varian XL-300/400 spectrometer operating at 300, 75.4, 96.2/ 400, 100.6 and 128.3 MHz, respectively. Boron fluoride etherate was used as external standard for the boron spectra. The IR spectra were obtained on a Perkin-Elmer 1600 FT-IR spectrometer. FAB-Mass spectra were recorded on a SX/SX 102A (JEOL) mass spectrometer. Elemental analyses were performed by Analytische Laboratrien, Lindlar, GERMANY. For column chromatography Merck Silica Gel 60 (230-400 mesh) was used. Merck Silica 60 F_{254} gel plates were used for TLC. Melting points are uncorrected and were obtained using a Buchi capillary melting point apparatus.

1,12-Bis(3-bromopropyl)-p-carborane (5).

A solution of 1,12-bis(3-hydroxypropyl)-*p*-carborane (**4**) (5.0g 19.2 mmol,1eq.) and carbon tetrabromide (15.93g, 48 mmol, 2.5 eq) in anhydrous methylene chloride (200 mL) was cooled to 0°C. To this mixture triphenylphosphine (15.11g, 57.6 mmol, 3 eq.) in anhydrous CH_2Cl_2 (100 mL) was added dropwise. The resulting solution was stirred for 2 hr at RT and then concentrated *in vacuo*. The residue was stirred with 100 mL of anhydrous ether for 30 min, filtered through silica and concentrated. The crude product was purified by

column chromatography using pentane as eluent to give 6.34g of **5** (R_f =0.36) in 85% yield. An analytical sample was obtained by recrystallisation from pentane. Mp :97-98°C. Anal. Calcd for $C_8H_{22}B_{10}Br_2$: C, 24.90; H, 5.70. Found: C, 25.20; H, 5.61. ^{1}H NMR($CDCl_3$): δ 3.21 (t, 4H, α-CH_2); 1.77 (m, 4H, γ-CH_2)M; 1.70 (m, 4H, β-CH_2). ^{13}C NMR($CDCl_3$): δ 78.1 (C in cage); 36.2 (α-CH_2); 32.1 (γ-CH_2); 32.0 (β-CH_2). ^{11}B NMR($CDCl_3$): δ -12.99 IR (KBr disk): 2965, 2600, 2359, 1448, 1261, 730 cm^{-1}.

*1,12-Bis(3-iodopropyl)-p-carborane (**6**).*

1,12-Bis(3-bromopropyl)-p-carborane (**5**) (6.11g, 15.8 mmol, 1 eq.) and sodium iodide (14.24g, 95 mmol, 6 eq.) were dissolved in acetone (200 mL). The solution was refluxed for 24 hr. Concentration of the reaction mixture afforded a yellow residue which was extracted with diethyl ether (3×50 mL), rinsed with water (3×20 mL) and brine (40 mL), dried over $MgSO_4$, and filtered. The filtrate was then concentrated *in vacuo*. The crude product was then purified by column chromatography using pentane to give 7.36g of **6** (R_f =0.46) in 97% yield. The analytical sample was achieved by recrystallisation from pentane. Mp :68-69°C. Anal. Calcd for $C_8H_{22}B_{10}I_2$: C,20.0; H, 4.6. Found: C, 20.19; H, 4.51. ^{1}H NMR($CDCl_3$): δ2.97 (t, 4H, α-CH_2); 1.72 (m, 4H, γ-CH_2); 1.64 (m, 4H, β-CH_2). ^{13}C NMR($CDCl_3$): δ 77.85 (C in cage); 38.4 (α-CH_2); 32.8 (γ-CH_2); 4.5 (β-CH_2). ^{11}B-NMR($CDCl_3$): δ -13.02. IR (KBr disk): 2965, 2592, 1451, 1288, 1170, 730 cm^{-1}.

*12- (3-Iodopropyl)- N,N-Di- tert-butyloxycarbonyl- 1-(3-aminopropyl)-p-carborane (**7a**) and N,N -Di- tert-butyloxycarbonyl-1,12-bis(3-aminopropyl)-p-carborane (**7b**).*

A solution of tetrabutylammonium hydrogen sulfate, $QHSO_4$, (0.141g, 0.415 mmol), aqueous sodium hydroxide 2.00 M (0.42 mL) and methylene chloride (10 mL) was stirred at 25°C. Di-*tert*-butyliminodicarboxylate, $HN(BOC)_2$, (0.091g, 0.415 mmol), dissolved in CH_2Cl_2 (3 mL), was then added at ambient temperature. After stirring for 30 min, compound **6** (0.20g, 0.415 mmol) dissolved in methylene chloride (5 mL) was added dropwise and the reaction mixture was refluxed for 2 hr. It was cooled to RT and the layers separated. The aqueous phase was extracted with methylene chloride (3×5 mL) and the combined organic layer was concentrated *in vacuo*. The residue was stirred with diethyl ether (25 mL) for 30 min in order to precipitate QI. The precipitate was filtered, washed with diethyl ether and the filtrate was dried over sodium sulfate. Evaporation of the solvent gave the crude products which were purified by column chromatography on silica using pentane/ether (4:1) giving **7a** (R_f = 0.7) in 45% (0.107g) and **7b** (R_f= 0.25) in 17% yield (0.047g) respectively. The analytical samples were prepared by recrystallisation from pentane. Data for compound **7a** are as follows: Mp: 85°C. Anal. Calcd for $C_{18}H_{40}B_{10}INO_4$: C, 37.96; H, 7.08; N, 2.46. Found: C, 38.18; H, 6.96; N, 2.40. ^{1}H NMR($CDCl_3$): δ 3.58 (t, 2H, CH_2N); 2.97 (t, 2H CH_2I); 1.71 (m, 2H, CH_2); 1.65 (m, 2H, CH_2), 1.60 (m, 2H, CH_2); 1.41 (m, 2H, CH_2). ^{13}C NMR($CDCl_3$): δ 152.4 (CO); 82.32 (*tert* C); 78.83 (C in cage); 77.69 (C in cage); 45.45 (CH_2N); 38.40 (CH_2I); 35.01 ($C_{cage}CH_2$); 32.81 ($C_{cage}CH_2$); 28.91 (CH_2CH_2N); 28.06 (CH_3); 4.33 (CH_2CH_2I). ^{11}B NMR(CDCl3): δ -13.04. IR (KBr disk): 2972, 2610, 1775, 1696, 1477, 1371, 1149, 558 cm^{-1}.

Data for compound **7b** are as follows: Mp: 146°C. Anal. Calcd for $C_{28}H_{58}B_{10}N_2O_4$: C,51.0; H, 8.90; N,4.30. Found: C, 51.24; H, 8.86; N, 4.36. HR: MS (NBA, FAB^+): Calcd for $C_{28}H_{58}N_2O_8{}^{11}B_{10}Na$: 683.4990, Found: 683.5064. ^{1}H NMR($CDCl_3$): δ 3.78 (t,4H, CH_2N); 1.62 (m, 4H, CH_2C_{cage}); 1.43 (m, 4H, CH_2). ^{13}C NMR($CDCl_3$): δ152.4 (CO); 82.32 (*tert.* C); 78.56 (C in cage); 45.48 (CH_2N); 35.00 (CH_2C_{cage}); 28.93 (CH_2); 28.06 (CH_3). ^{11}B NMR($CDCl_3$): δ -13.05. IR (KBr disk): 2975, 2607, 1776, 1372, 1283,1105 cm^{-1}.

*12-(3-Iodopropyl)-N,N-Dibenzyloxycarbonyl-1-(3-aminopropyl)-p-carborane(**8a**).*

Compound **8a** was synthesized as described for **7a** except it was refluxed for 5 hr and HNZ_2 has been used as protected amine. The crude product was purified by column chromatography using ether/pentane (1:3) as mobile phase giving **8a** (R_f =0.33) in 41% yield. An analytical sample was obtained by recrystallisation from pentane. Mp: 63°C. Anal. Calcd for $C_{24}H_{36}B_{10}INO_4$: C, 45.2; H, 5.70; N, 2.20. Found: C, 45.86; H, 5.88; N, 2.30. HR: MS (NBA, FAB^+): Calcd for $C_{24}H_{37}NO_4{}^{11}B_{10}I$: 640.2735, Found: 640.2728. ^1H NMR($CDCl_3$): δ 7.36 (m, 5H, arom.); 5.21 (s, 2H, CH_2Ph); 3.51 (t, 2H, CH_2N); 2.98 (t, 2H, CH_2I); 1.72 (m, 2H, CH_2C_{cage}); 1.65 (m, 2H, CH_2C_{cage}); 1.55 (m, 2H, CH_2CH_2N); 1.42 (m, 2H, CH_2CH_2I). ^{13}C NMR($CDCl_3$): δ 153.2 (CO), 135.14 (arom.); 128.61 (arom.); 128.42 (arom.); 128.26 (arom.); 78.54 (C in cage); 77.70 (C in cage); 68.70 (CH_2Ph); 45.88 (CH_2N); 38.38 (CH_2I); 34.71 (CH_2C_{cage}), 32.80 (CH_2C_{cage}); 28.73 (CH_2CH_2N); 4.33 (CH_2CH_2I). ^{11}B NMR($CDCl_3$): δ -13.07. IR (KBr disk): 3067, 2955, 2604, 1716, 1498, 1398, 1296, 1190, 581 cm^{-1}.

3, 8-Diamino-5-[3-(12-(3-aminopropyl)- p-carborane-1-yl) propyl]-6-phenyl phenanthridinium chloride hydrochloride (13).

3,8-Diacetamido-6-phenylphenanthridine (**9**) (0.30g, 0.812 mmol) and **8a** (2.5g, 3.92 mmol) were dissolved in nitrobenzene (2 mL) and stirred for 4 days at 120°C under nitrogen atmosphere. The reaction mixture was cooled to RT, diethylether (10 mL) and subsequently n-hexane (35 mL) were added to precipitate out product and unreacted starting material . The precipitates were filtered and washed with hexane. The resulting filtrate which contained mostly **8a** was concentrated. **8a** was recovered from this residue by column chromatography on silica with pentane as the mobile phase. The crude product **12** and unreacted starting material were then dissolved in methanol/CH_2Cl_2 and co-evaporated with silica gel to apply to a short silica gel column using CH_2Cl_2/MeOH (6:1) as the eluent. Partially purified compound **12** was deprotected by stirring with 33% HBr in acetic acid according to Berger at al.[12] for 2 hr at RT. Diethyl ether (100 mL) was added to precipitate the amine hydrogen bromide. For ease of purification , this hydrobromide was converted into the hydrochloride through a pseudo-base intermediate by dissolving the bromide in methanol and adding a NaOH-solution (pH=14). The resulting pseudo-base intermediate was extracted from the aqueous phase with CH_2Cl_2 (3x50 mL), dried over K_2CO_3, and concentrated. The residue was refluxed in 10% HCl in MeOH[10] for 2 hr. The solvent was then evaporated and the crude product was purified by column chromatography using a gradient of CH_2Cl_2/MeOH with increasing amount of methanol (95:5; 90:10; 80:20; 75:25) to obtain the amine hydrogen chloride **13** (R_f=0.25 in CH_2Cl_2/MeOH (75:25)) in 45% yield (0.22g, 0.367 mmol). A tetraphenylborate salt was obtained by dissolving **13** in water and adding aqueous sodium tetraphenylborate (1.2eq.). Bright rose color crystals were precipitated out and filtered off. The crude product was purified by flash chromatography on silica gel using CH_3CN/CH_2Cl_2 (1:1), (R_f=0.05-0.2). The bright red colored fractions were concentrated to dryness, dissolved in minimum amount of dichloromethane, and the product was precipitated by cautious addition of pentane on the top of the CH_2Cl_2 layer. The precipitate was filtered off, washed with pentane and dried *in vacuo*. An analytical sample was obtained from this tetraphenylborate salt. Mp (with sublimation): 140°C. Anal. Calcd for $C_{75}H_{80}B_{12}N_4$: C, 77.2; H, 6.91; N, 4.80. Found: C, 76.92; H, 6.84; N, 4.63. HR: MS (NBA, FAB^+): Calcd for $C_{27}H_{39}N_4{}^{11}B_{10}$: 529.4144, Found: 529.4136. ^1H NMR(CD_3COCD_3): δ 8.63 (d, 1H, H-1, $J_{1\text{-}2}$= 9.3 Hz); 8.57 (d, 1H, H-10, $J_{10\text{-}9}$= 9.3 Hz); 7.77 (m, 5H, Ph); 7.64 (dd, 1H, H-9, J = 9.1 and 2.1 Hz); 7.43 (dd, 1H, H-2, J = 9.1 and 2.1 Hz); 7.35 (m, 17H, BPh_4 and H-4); 6.90 (m, 16H, BPh_4); 6.78 (m, 8H, BPh_4); 6.46 (ds, 1H, H-7, J = 2.1 Hz); 5.81 (s, 2H, NH_2); 5.48 (s, 2H, NH_2); 4.35 (t, 2H, CH_2N-5); 3.56 (t, 2H, CH_2N); 1.90 (m, 2H, CH_2); 1.80 (m, 2H, CH_2); 1.60 (m, 4H, CH_2). ^{13}C NMR(CD_3COCD_3): δ 165.83 (B-C, BPh_4); 165.18 (B-C, BPh_4); 164.52 (B-C, BPh_4); 163.87 (B-C,BPh_4); 160.27 (C-6); 152.00 (C-3); 148.99 (C-8); 136.94 (BPh_4); 135.74 (C-13); 133.08 (C-11); 131.77 (C-9); 130.31 (Ph); 129.20 (Ph); 129.11 (Ph); 129.03 (Ph); 126.50 (C-14); 125.95 (BPh_4); 125.90 (BPh_4); 125.63 (C-10); 123.45 (C-1); 122.20 (BPh_4); 120.98 (C-2); 119.05 (C-12); 109.85 (C-7); 99.36 (C-4); 78.5 (C in cage); 57.10 (CH_2N-5); 53.52 (CH_2N); 47.72 (CH_2C_{cage}); 34.78 (CH_2CH_2N-5); 28.07 (CH_2CH_2N). ^{11}B

NMR(CD_3COCD_3): δ -5.66 (BPh_4); -12.05 (BH in cage). IR (KBr disk): 3464, 3366, 3214, 2998, 2599, 2343, 1629, 1578, 1490,1260, 735, 706 cm^{-1}.

ACKNOWLEDGEMENT

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REFERENCES AND NOTES

1. Carlsson, J.; Sjöberg, S. and Larsson, B.; Present status of boron neutron capture therapy. *Acta Oncol.*,**1992**,31, 803-814.
2. Hartman, T.; Carlsson, J.; *J. Radiother. Oncol.*; **1994**, 31, 61-75.
3. Tjarks, W.; Ghaneolhosseini, H.; Sjöberg, S.; *Tetrahedron Lett.*, **1996**, 37, 6905-6908.
4. Gedda, L.; Silvander, M.; Sjöberg, S.; Tjarks, W.; Carlsson, J.; submitted *Anti-Cancer Drug Design* , **1997**.
5. Malmquist, J.; Sjoberg, S.; *Tetrahedron*, **1996**, 52, 9207-9218.
6. Pagnette, Leo A.; Scott, M. K.; *J. Am. Chem. Soc.*, **1972**, 94, 6751-6758.
7. Kalinin, V. N.; Zurlova, O. M.; Zakharkin, L. I.; *J. Organometallic Chem.*, **1979**, 166, C37-C38.
8. Drechsel, K.; Lee, C. S.; Leung, E. W.; Hawthorne, M. F.; *Tetrahedron Letters*, **1994**, 35, 6217-6220.
9. Brändström, A.; Junggren, U.; *Tetrahedron Letters*, **1972**, 473.
10. Gaugain, B.; Barbet, J.; Oberlin, R.; *Biochemistry*,**1978**, 17, 5071-5078.
11. Gedda, L., Silvander, M., Sjöberg, S., Tjarks, W. and Carlsson, J.; Proceedings from the Seventh International Symposium on Neutron Capture Therapy for Cancer. **1997** in press.
12. Ben-Ishai, D.; Berger, A.; *J. Org. Chem.*, **1952**, 17, 1564-1570.

Ψ. Compounds **2**, **3**, **10**, and **11** were only analysed by ^{1}H NMR because the synthetic routes involving these compounds did not lead to target agents.

Compound **2**: ^{1}H NMR($CDCl_3$): δ 4.47 (t, 1H, THP); 3.77 (m, 2H, THP); 3.53 (m, 2H, THP); 3.45 (m, 2H, α-CH_2); 3.20 (m, 2H, THP); 2.62 (s, 1H, HCcage); 1.70 (m, 2H, γ-CH_2); 1.50 (m, 2H, β-CH_2); 1.43 (m, 2H, THP).; Compound **3**: ^{1}H NMR($CDCl_3$): δ 4.44 (t, 1H, THP); 3.75 (m, 2H, THP); 3.53 (m, 2H, THP); 3.45 (m, 2H, α-CH_2); 3.20 (m, 2H, THP); 1.62 (m,2H, γ-CH_2); 1.57 (m, 2H, β-CH_2); 1.50 (s, 2H, CH_2CN); 1.38 (m, 2H, THP).; Compound **10** : ^{1}H NMR(CD_3OD): δ 9.20 (s, 1H, H-7); 9.08 (d, H, H-1); 9.03 (d, 1H, H-10); 8.45 (d, 1H, H-9); 8.10 (s, 1H, H-4); 7.95 (d, 1H, H-2); 7.80 (m, 5H, Ph); 4,55 (t, 2H, CH_2N-5), 3.10 (t, 2H, CH_2I); 2.30 (s, 3H, CH_3); 2.10 (s, 3H, CH_3), 2.0-1.40 (m, 8H, CH_2).

Compound **11**: ^{1}H NMR(CD_3OD): δ 8.66 (d, 1H, H-1); 8.60 (d, 1H, H-10); 7.70 (m, 6H, Ph and H-9); 7.40 (d,1H, H-2); 7.20 (s, 1H, H-4); 6.50 (s,1H, H-7); 4.40 (t, 2H, CH_2N-5); 2.75 (m, 6H, CH_2N); 1.80-1.40 (m, 16H, CH_2).

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