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Synthesis of 2-[2-(3-Aminopropyl)-1,2-dicarba-*closo*-dodecaboran(12)-1-ylmethoxy]-1,3-propanediol, a Hydrophilically Substituted Aminoalkyl-*o*-carborane

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A 1,2-dicarba-*closo*-dodecaborane(12) derivative, containing a hydrophilic diol group and an amino group, 2-[2-(3-aminopropyl)-1,2-dicarba-*closo*-dodecaboran(12)-1-ylmethoxy]-1,3-propanediol (**1a**), has been synthesised from the dibenzyl ether of 2-[1,2-dicarba-*closo*-dodecaboran(12)-1-ylmethoxy]-1,3-propanediol (**5**) by alkylation on the unsubstituted carbon atom of the *o*-carborane cage with oxetane followed by bromination with CBr_4–Ph_3P to give 2-[2-(3-bromopropyl)-1,2-dicarba-*closo*-dodecaboran(12)-1-ylmethoxy]-1,3-dibenzyloxypropane (**3**). The amine function was introduced by ion-pair alkylation, in water–dichloromethane, of the Gabriel reagent dibenzyl iminodicarboxylate with the bromide **3**. Hydrogenolysis of the doubly protected amino diol **4** gave the amino diol **1a** with $pK_a = 8.5$.

The water solubility of the amine hydrochloride **1b** and the free amine **1a** are 22 g l^{-1} and 0.7 g l^{-1}, respectively.

There is much current interest in the syntheses of boron compounds with potential use in boron neutron capture therapy against cancer, BNCT.[1–3] This therapy utilises the cytotoxic effect from the neutron capture reaction [$^{10}B(n,\alpha)^7Li$]. The boron compounds can be delivered selectively to the tumour cells, either by use of targeting strategies or *per se*.

We are focusing on the possibility of using epidermal growth factor, EGF, for the delivery of toxic agents and boron compounds to tumour cells.[4–6] Some gliomas, breast cancers, and squamous carcinomas have receptor amplification for EGF. EGF-conjugates loaded with toxic agents are presently studied at our laboratories, on cultured human malignant glioma, U343MGaC12:6 cells.

We have been synthesising amines[7] and amino acids[8,9] containing the boron rich *o*-carborane cage. The amine function of these compounds allows conjugation to EGF via a suitable spacer such as dextran.

For several years there has been a great deal of interest in making water-soluble carboranes for use in biological experiments. Different methods of solubilizing the very lipophilic *o*-carborane have been described. Hawthorne and co-workers have reported a series of *O*-glycosylcarboranes obtained by reaction of ω-hydroxyalkylcarboranes with esterified carbohydrates in the presence of Lewis acid catalysts.[10] Hawthorne *et al.* reacted lithiated *o*-carboranes with isopropylidene ketal protected aldehydic sugars, including glyceraldehyde, to give hydroxyalkylated carboranes.[11] Yamamoto *et al.* have developed a method for palladium-catalysed allylation of carboranes under neutral conditions. Oxidation of the allylated products gave 1,2-diols.[12] Degradation of the *o*-carborane cage to the corresponding negatively charged *nido*-carborane, has been used by Hawthorne and co-workers to solubilize carboranylamino acids and peptides.[13,14] The four methods mentioned all give stereochemically heterogenous products. This stereochemical problem has been avoided in the diol **5a** and the tetraol **6a**, recently described by Yamamoto.[15] In a previous paper we reported the synthesis of some ω-aminoalkyl-*o*-carboranes.[7] Here we describe the preparation of the hydrophilically substituted amine, 2-[2-(3-aminopropyl)-1,2-dicarba-*closo*-dodecaboran(12)-1-ylmethoxy]-1,3-propanediol **1a** derived from the diol **5a**.

Biological experiments concerning binding and toxicity of **1a** to cultured human glioma and mouse melanoma cells have been reported elsewhere.[16]

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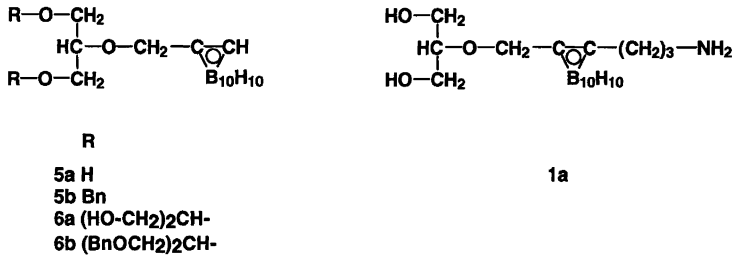
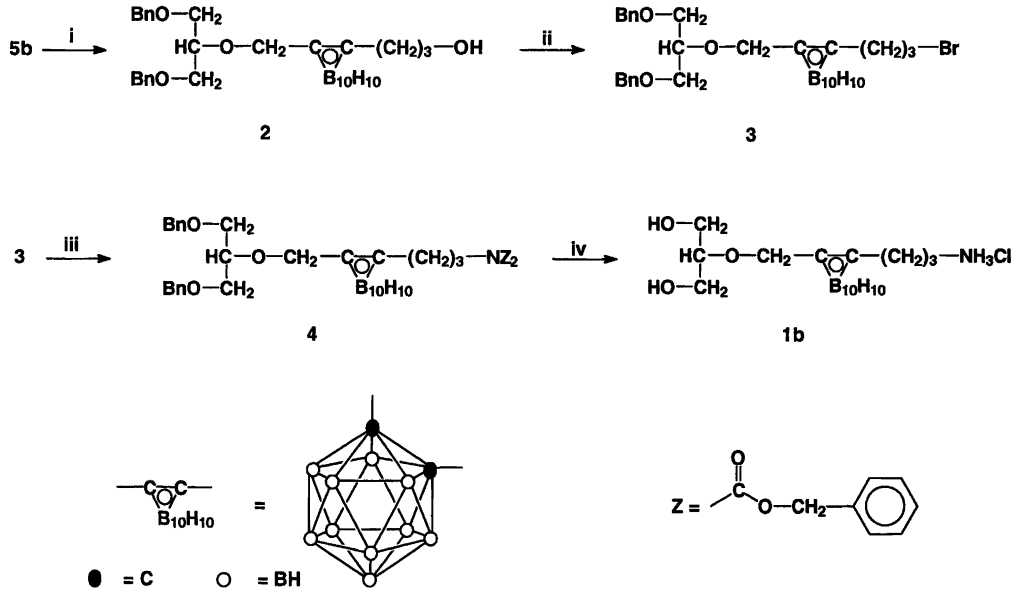


Scheme 1.



Scheme 2. i, 1.1 M BuLi, oxetane, THF, 0 °C–reflux; ii, 1.25 equiv. CBr_4, 1.5 equiv. PPh_3, CH_2Cl_2, 0 °C; iii, 1 equiv. $QHSO_4$, 2 equiv. 2 M NaOH, 1 equiv. HNZ_2, CH_2Cl_2, 40 °C; iv, H_2–Pd, abs. EtOH, r.t.

Results and discussion

Initially we tried to attach a hydrophilic substituent to 3-aminopropyl-*o*-carborane via 1-(3-*N,N*-di-*tert*-butyloxycarbonylaminopropyl)-*o*-carborane previously synthesised in this laboratory.[7] Attempts to react this protected amine with electrophiles, such as methyl iodide, via the anion formed by removal of the acidic CH-hydrogen atom of the cage, failed with either butyllithium or LDA as base. Palladium-catalysed allylation[12] at the CH-carbon atom of the cage also failed. No reaction was observed with allyl ethyl carbonate using $Pd_2{\cdot}(DBA)_3{\cdot}CHCl_3$[†] and DPPE* as the ligand.

In our final approach, the *o*-carborane was functionalised with a hydrophilic group before the introduction of the aminoalkyl function. The synthesis of the diolamine **1a** along these lines, starting with the dibenzyl ether **5b** of 2-[1,2-dicarba-*closo*-dodecaboran(12)-1-ylmethoxy]-1,3-propanediol **5a**,[15] is shown in Scheme 2.

The protected diol **5b** was *C*-alkylated on the cage by reaction with butyllithium in THF, followed by oxetane to give the hydroxypropyl-substituted *o*-carborane **2**. The product was purified by flash column chromatography to give **2** in 71% yield as an oil. Attempts to react the protected tetraol **6b**, in a similar way, failed, probably because of steric hindrance.

Bromination[17] of the alcohol **2** with carbon tetrabromide and triphenylphosphine in dichloromethane at 0 °C for 10 min gave **3** in 81% yield.

The classical Gabriel method using phthalimide cannot be used to convert the bromide **3** into the corresponding amine as the standard basic deprotection conditions degrade the *o*-carborane cage to the corresponding *nido*-compound. Instead we used the Gabriel reagent dibenzyl iminodicarboxylate (HNZ_2).[18] Alkylation of HNZ_2 with the bromide **3**, using the phase-transfer alkylation technique described by Brändström,[19] gave the protected amino diol **4** in 88% yield. This method, previously used by us in the alkylation of di-*tert*-butyl iminodicarboxylate [$HN(BOC)_2$], avoids the anhydrous conditions generally used in alkylation of Gabriel reagents.[20]

The alcohol and amine protecting groups in **4** were chosen in order to be removable in one step by hydrogenolysis using Pd as the catalyst. Using this method the crystalline amine hydrochloride **1b** was obtained in 88%

† Tri(dibenzylideneacetone)dipalladium–chloroform.
* The bidentate ligand 1,2-bis(diphenylphosphino)ethane.

yield. The overall yield of the hydrochloride **1b** was 45% in four steps. The product was obtained as the hydrochloride because the palladium catalyst was generated *in situ* from $Pd(OH)_2$ on carbon with an excess of concentrated hydrochloric acid. Addition of base to **1b** gave the free amine **1a**.

The amine hydrochloride **1b** had a solubility of 22 g l^{-1} in water, whereas the solubility of the free amine was found to be 0.70 g l^{-1} in water. The pK_a was ca. 8.5, determined by graphical analysis of a titration curve of the free amine titrated with 0.011 M hydrochloric acid.

Experimental

General details. THF was distilled from the sodium–benzophenone ketyl radical and CH_2Cl_2 was distilled from CaH_2. The ^1H, ^{13}C and ^{11}B NMR spectra were recorded in $CDCl_3$ or CD_3OD on a Varian Unity-400 spectrometer operating at 400, 100.6 and 128.3 MHz respectively or on a Varian XL-300 spectrometer operating at 300, 75.4 and 96.2 MHz respectively. Boron trifluoride–diethyl ether was used as an external standard for the boron spectra. The IR spectra were obtained using a Perkin-Elmer 1600 FT-IR spectrometer. Mass spectra were recorded on a ZAB instrument. Elemental analyses were performed by *Analytische Laboratorien*, Engelskirchen, Germany. Merck Silica Gel 60 (230–400 mesh) and Merck Silica Gel 60 F_{254} were used for flash column chromatography[21] and TLC respectively. Melting points are uncorrected and were obtained using a Büchi capillary melting point apparatus or a Leitz hot-stage microscope. 'Q^+' is used for the tetrabutylammonium ion and 'cb' is used for the *o*-carborane cage. The solubility was determined by analysing an evaporated saturated aqueous solution of the amine by NMR spectroscopy, by dissolving it in deuteriated methanol with a weighed amount of internal standard, in this case mesitylene.

2-[2-(3-Hydroxypropyl)-1,2-dicarba-closo-*dodecaboran(12)-1-ylmethoxy]-1,3-dibenzyloxypropane (***2***).* To an ice-cold solution of 2-[1,2-dicarba-*closo*-dodecaboran(12)-1-ylmethoxy]-1,3-dibenzyloxypropane (**5b**), (3.20 g, 7.45 mmol) in dry THF (100 ml) under N_2, was added dropwise a solution of 1.1 M butyllithium (7.0 ml, 7.6 mmol) in hexane over 60 min. The resulting solution was stirred for 3 h at 0°C. Oxetane (0.505 ml, 7.45 mmol) was then added dropwise over 30 min. The solution was heated under reflux for 17 h, and then the reaction was quenched with 2 M HCl (15 ml). The solution was concentrated *in vacuo* and the water phase was extracted with diethyl ether (3 × 20 ml). The combined extracts were washed with brine (3 × 15 ml) and were dried over sodium sulphate. Concentration gave the crude product (3.83 g) which was purified by flash column chromatography on silica gel using pentane–diethyl ether (2:1) as the eluent, $R_f = 0.18$, to give **3** as an oil containing some impurities. Yield 2.57 g (71%). Anal. Found: C 57.89, H 7.79. Calc. for $C_{23}H_{38}B_{10}O_4$: C 56.77, H 7.87. ^1H NMR ($CDCl_3$): δ 7.34 (m, 10 H, arom), 4.51 (s, 4 H, 2 × PhCH_2), 4.17 (s, 2 H, cb-CH_2-O), 3.75 (m, A-part of an AB_2C_2 system, 1 H, CH_2CHCH_2), 3.57 (m, B-part of an AB_2C_2 system, 2 H, -CH_2CH-), 3.55 (m, C-part of an AB_2C_2 system, 2 H, -CH_2CH-), 3.33 (t, $J = 5.6$ Hz, 2 H, CH_2OH), 2.28 (m, 2 H, cb-CH_2CH$_2$), 1.68 (m, 2 H, $CH_2CH_2CH_2$). ^{13}C NMR ($CDCl_3$): δ 137.5 (arom), 128.5 (arom), 127.9 (arom), 127.7 (arom), 79.0 (CH_2CHCH_2), 78.3 (cb *C*-1), 77.8 (cb *C*-2), 73.5 (PhCH_2), 70.5 (cb-CH_2), 70.4 (CH_2CHCH_2), 61.2 (CH_2OH), 32.4 (cb-CH_2-), 31.4 (-CH_2CH$_2$OH). ^{11}B NMR ($CDCl_3$): δ −4.6 (2 B), −11.2 (8 B). IR (NaCl plates): 3420 (s), 3088 (w), 3064 (w), 3030 (m), 2869 (s), 2856 (s), 1734 (w), 1496 (m), 1454 (s), 1366 (s), 1206 (m), 1102 (s), 1027 (s), 911 (m), 738 (s), 699 (s) cm^{-1}. FAB-MS (*m/z*): obs. 486 within the expected boron cluster envelope, calc. for $(M - H)^-$ 486.

2-[2-(3-Bromopropyl)-1,2-dicarba-closo-*dodecaboran(12)-1-ylmethoxy]-1,3-dibenzyloxypropane (***3***).* To an ice-cold solution of 2-[2-(3-hydroxypropyl)-1,2-dicarba-*closo*-dodecaboran(12)-1-ylmethoxy]-1,3-dibenzyloxypropane (**2**), (2.46 g, 5.05 mmol) and carbon tetrabromide (2.40 g, 7.22 mmol) in dry dichloromethane (20 ml) was added dropwise a solution of triphenylphosphine (2.27 g, 8.65 mmol) in dichloromethane (8 ml). The resulting solution was stirred for 10 min and concentrated. The residue was stirred with dry diethyl ether (20 ml). After filtration and concentration of the filtrate, the crude product was purified by flash column chromatography on silica gel, with pentane–diethyl ether (4:1) as the eluent to give **3** ($R_f = 0.34$). Yield 2.19 g (81%). Anal. $C_{23}H_{37}B_{10}BrO_3$: C, H, B. ^1H NMR ($CDCl_3$): δ 7.34 (m, 10 H, arom), 4.52 (s, 4 H, PhCH_2), 4.21 (s, 2 H, cb-CH_2), 3.78 (m, A-part of an AB_2C_2 system, 1 H, CH_2CHCH_2), 3.58 (m, B-part of an AB_2C_2 system, -CH_2CH-), 3.56 (m, C-part of an AB_2C_2 system, 2 H, -CH_2CH-), 3.18 (t, $J = 6.2$ Hz, 2 H, CH_2Br), 2.32 (m, 2 H, cb-CH_2CH$_2$), 2.01 (m, 2 H, $CH_2CH_2CH_2$). ^{13}C NMR ($CDCl_3$): δ 137.8 (arom), 128.4 (arom), 127.8 (arom), 127.7 (arom), 79.2 (CH_2CHCH_2), 78.5 (cb *C*-1), 76.7 (cb *C*-2), 73.5 (PhCH_2), 70.6 (cb-CH_2), 70.5 (CH_2CHCH_2), 33.3 (cb-CH_2-), 32.0 (-CH_2CH_2Br), 32.0 (-CH_2CH$_2$Br). ^{11}B NMR ($CDCl_3$): δ −4.6 (2 B), −11.4 (8 B). IR (NaCl plates): 3063 (m), 3030 (m), 2911 (m), 2863 (s), 2586 (s), 1496 (m), 1453 (s), 1366 (m), 1348 (m), 1330 (w), 1303 (m), 1261 (s), 1206 (m), 1106 (s), 1028 (m), 985 (m), 910 (m), 737 (s), 698 (s) cm^{-1}. FAB-MS (*m/z*): obs. 549 within the expected boron cluster envelope, calc. for M^- 549.

*2-[2-(3-*N,N*-Dibenzyloxycarbonylaminopropyl)-1,2-dicarba*-closo-*dodecaboran(12)-1-ylmethoxy]-1,3-dibenzyloxypropane (***4***).* To a stirred mixture of $QHSO_4$ (681 mg, 2.01 mmol) and NaOH (2.05 ml of 2.00 M, 4.1 mmol) was added dibenzyl iminodicarboxylate (574 mg, 1.77 mmol) in dichloromethane (10 ml) and this was followed by the dropwise addition of 2-[2-(3-bromopropyl)-

1,2-dicarba-*closo*-dodecaboran(12)-1-ylmethoxy]-1,3-dibenzyloxypropane (**3**) (975 mg, 1.77 mmol) in dichloromethane (7 ml). The resulting solution was heated under reflux for 2 h, cooled to room temperature, and then water (5 ml) was added. The aqueous phase was extracted with dichloromethane (20 ml). The combined organic phases were washed with water (5 ml), dried over sodium sulphate and concentrated. The residue was stirred with dry diethyl ether (20 ml) in order to precipitate the QBr, the precipitate was extracted with dry diethyl ether (2 × 20 ml) and the combined extracts were concentrated. The crude product was purified by flash column chromatography on silica gel (100 g) with toluene–acetonitrile 92.5:7.5 as the solvent to give **4** (R_f = 0.37). Yield: 1.18 g (88%). Anal. $C_{39}H_{51}B_{10}NO_7$: C, H, N, B. ^{1}H NMR ($CDCl_3$): δ 7.33 (m, 20 H, arom), 5.22 (s, 4 H, ZCH_2), 4.49 (s, 4 H, $PhCH_2$), 4.11 (s, 2 H, cb-CH_2), 3.70 (m, A-part of an AB_2C_2 system, 1 H, CH_2CHCH_2), 3.51 (m, B-part of an AB_2C_2 system, -CH_2CH-), 3.50 (m, C-part of an AB_2C_2 system, 2 H, -CH_2CH-), 3.47 (t, J = 7.6 Hz, 2 H, CH_2N), 2.12 (m, 2 H, cb-CH_2CH_2), 1.77 (m, 2 H, $CH_2CH_2CH_2$). ^{13}C NMR ($CDCl_3$): δ 152.3 (C=O), 137.9 (arom), 135.2 (arom), 128.5 (br, arom), 127.7 (br, arom), 79.3 (CH_2CHCH_2), 78.6 (cb C-1), 73.6 (cb C-2), 73.5 ($PhCH_2$), 70.7 (cb-CH_2), 70.6 (CH_2CHCH_2), 68.8 (ZCH_2), 45.9 (CH_2N), 32.0 (C-CH_2CH_2-), 28.8 ($CH_2CH_2CH_2$). ^{11}B NMR ($CDCl_3$): δ −4.6 (2 B), −11.4 (8 B). IR (NaCl plates): 3064 (w), 3032 (m), 2865 (m), 2584 (s), 1793 (m), 1752 (s), 1724 (s), 1698 (s), 1497 (m), 1454 (s), 1406 (m), 1385 (s), 1353 (s), 1329 (s), 1281 (s), 1241 (m), 1190 (s), 1122 (s), 1104 (s), 1028 (m), 956 (m), 910 (m), 740 (s), 697 (s) cm^{-1}. FAB-MS (*m/z*): obs. 754 within the expected boron cluster envelope, calc. for M^- 754.

2-[2-(3-Aminopropyl)-1,2-dicarba-closo-*dodecaboran(12)-1-ylmethoxy]-1,3-propanediol hydrochloride* (**1b**). 2-[2-(3-*N,N*-Dibenzyloxycarbonylaminopropyl)-1,2-dicarba-*closo*-dodecaboran(12)-1-ylmethoxy]-1,3-dibenzyloxypropane (**4**) (272 mg, 0.361 mmol) was hydrogenated in absolute ethanol (10 ml) containing 12 M HCl (2 drops), in the presence of palladium hydroxide on carbon (52 mg) for 22 h. The reaction mixture was filtered through Celite and concentrated *in vacuo* to give crude **1b** (128 mg). The crude product was purified by precipitation from a methanol solution with diethyl ether to give **1b** (108 mg, 0.316 mmol) in 88% yield. M.p. 161–164°C. pK_a = 8.5. Anal. $C_9H_{28}B_{10}ClNO_3$: C, H, N, B. ^{1}H NMR (CD_3OD): δ 4.33 (s, 2 H, OH_2CC), 3.71 (m, A-part of an A_2B_2C system, 2 H, HOCH_2CH-), 3.63 (m, B-part of an A_2B_2C system, 2 H, HOCH_2CH-), 3.55 (m, C-part of an A_2B_2C system, 1 H, $HOCH_2CH$-), 2.99 (t, 2 H, J = 7.2 Hz, 2 H, CH_2N), 2.50 (m, 2 H, CCH_2-), 1.98 (m, 2 H, $CH_2CH_2CH_2$). ^{13}C NMR (CD_3OD): δ 83.8 ($HOCH_2CH$-), 80.6 (cb-C1), 78.4 (cb-C2), 71.5 (OH_2CC), 62.7 ($HOCH_2CH$-), 40.0 (CH_2N), 32.7 (CCH_2CH_2), 28.6 ($CH_2CH_2CH_2$). ^{11}B NMR (CD_3OD): δ −2.6 (2 B), −9.4 (8 B). IR (KBr disc): 3260 (s), 3063 (s), 2994 (s), 2956 (s), 2935 (s), 2880 (s), 2756 (m), 2634 (s), 2622 (s), 2595 (s), 2571 (s), 1628 (m), 1503 (s), 1446 (m), 1424 (w), 1395 (w), 1383 (w), 1348 (m), 1318 (w), 1298 (w), 1168 (m), 1142 (m), 1121 (s), 1104 (m), 1079 (s), 1071 (s), 1057 (s), 1026 (m), 1014 (s), 642 (m) cm^{-1}. FAB-MS (*m/z*): obs. 341 within the expected boron cluster envelope, calc. for $(M-H)^-$ 341.

2-[2-(3-Aminopropyl)-1,2-dicarba-closo-*dodecaboran(12)-1-ylmethoxy]-1,3-propanediol* (**1a**). 2-[2-(3-Aminopropyl)-1,2-dicarba-*closo*-dodecaboran(12)-1-ylmethoxy]-1,3-propanediol hydrochloride (**1b**) (116 mg, 0.34 mmol) was partly dissolved in water (4 ml) and was mixed with saturated Na_2CO_3 (4 ml). The aqueous phase was extracted with diethyl ether (3 × 5 ml). The combined extracts were washed with brine (3 × 5 ml) and then dried over sodium sulphate. Concentration gave the free amine **1a** (92 mg, 0.30 mmol) in 89% yield. The product was used without further purification.

^{1}H NMR ($CDCl_3$): δ 4.26 (s, 2 H, OH_2CC), 3.69 (m, A-part of an A_2B_2C system, 2 H, HOCH_2CH-), 3.61 (m, B-part of an A_2B_2C system, 2 H, HOCH_2CH-), 3.50 (m, C-part of an A_2B_2C system, 1 H, $HOCH_2CH$-), 2.77 (t, 2 H, J = 5.6 Hz, 2 H, CH_2N), 2.44 (m, 2 H, CCH_2-), 1.72 (m, 2 H, $CH_2CH_2CH_2$).

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