Synthesis of *o*-carborane derivatives containing the tri(ethylene glycol) group

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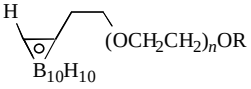
A general approach to the preparation of carborane derivatives containing the hydrophilic ethylene glycol fragment was developed.

The derivatization of the carborane cage $C_2B_{10}H_{12}$ can be performed because two carbon atoms are accessible to organic reactions. Thus, the cage can be incorporated into biologically active moieties. However, the high lipophilicity of the carborane cage often leads to low water solubility of the final compounds. Sufficient solubility in water is very important for potential applications to the boron nuclear capture therapy of cancer. To increase the water solubility, the *o*-carborane cage can be degraded to the corresponding anionic [*nido*-7,8-$C_2B_9H_{11}$]$^-$ species. This method was used to prepare dicarbaundecaborate derivatives of porphyrines,[1] thioureas[2] and amino acids.[3] The water solubility can also be increased by the attachment of hydrophilic substituents. For example, a number of carboranyl carbohydrates have been synthesised recently.[4–6] Yamamoto and co-workers[7] have developed a method of polyol cascade synthesis, which was used for the preparation of hydrophilically substituted carboranyl amino acids,[8,9] amines,[9–11] netropsin and distamycin A analogues.[12]

The aim of this work was to develop the preparation of the poly(ethylene glycol)-containing *o*-carborane with one CH group free for modification:

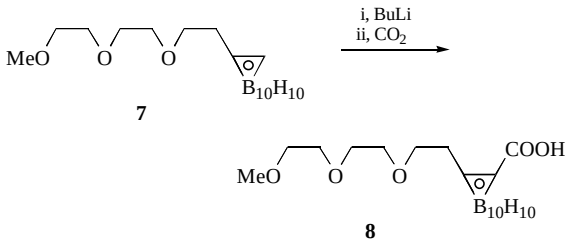


1

Compound **2** can be easily converted into iodide **4** in two steps with a total yield of 92%.[13] Compound **4** reacted with lithium trimethylsilylacetylenide to give trimethylsilylacetylenide **5** (Scheme 1).† Compound **5** was treated with tetrabutylammonium fluoride to remove the Me_3Si group and give novel acetylene **6** in a total yield of 86% (from **4**). Note that this method for the preparation of polyglyme acetylenes is novel and very convenient. Previously,[19] the synthesis of 4-(2-methoxyethoxy)-but-1-yne by the interaction of propargyl bromide and 2-methoxyethoxymethyl chloride in 74% yield was described.[14] Compound **6** reacted with decaborane in acetonitrile to give carborane **7** in a rather good yield (52%).

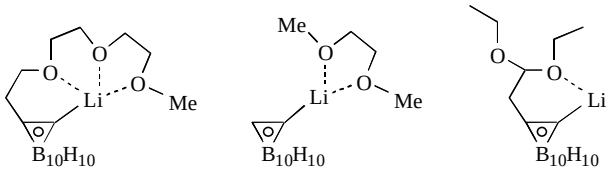
An attempt to prepare **7** by the interaction of a dilithiated carborane with iodide **4** resulted, as expected, in a mixture of **7**, the disubstituted derivative and the unsubstituted carborane in the 2:1:1 ratio.

The modification of **7** was studied by the example of lithiation followed by carboxylation.‡



7 **8**

Note that carboranyl lithium derivative of **7** was almost insoluble in a THF–hexane mixture, as compared with other carboranyllithium derivatives. This may be explained by the formation of intramolecular complex **9**. The formation of similar complexes (like **10** or **11**) was also proposed earlier.[15,16]



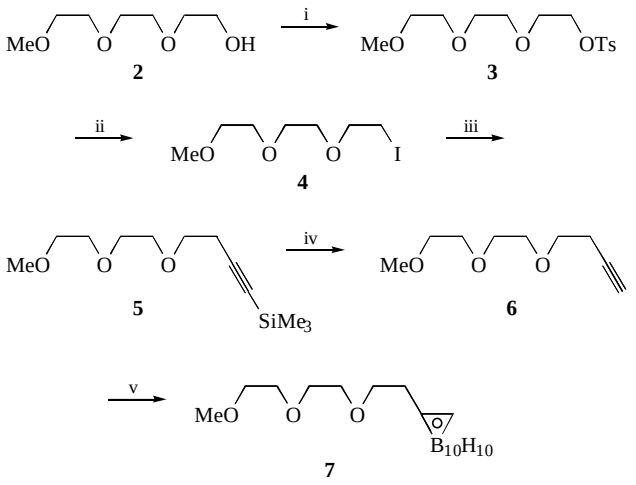
9 **10** **11**

† *Materials and equipment*. Commercial chemicals of reagent grade were used. THF was distilled from Na/benzophenone. Sublimated decaborane was used. Compound **4** was prepared according the described method.[13] ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX-400 spectrometer at 400.13 and 100.33 MHz, respectively. ^{11}B NMR spectra were recorded on a Bruker AC-200 spectrometer at 64.21 MHz. Chemical shifts were measured with respect to external standards (TMS and $BF_3{\cdot}Et_2O$). Mass spectra were measured on a Kratos MS-890 (80 eV) spectrometer. Melting points were measured in sealed capillaries and not corrected.

1-Trimethylsilyl-5,8,11-trioxadodec-1-yne **5**. A 1.6 M BuLi solution in hexane (45.6 ml, 0.073 mol) was added to a cooled (–50 °C) solution of trimethylsilylacetylene (10.3 ml, 0.073 mol) in dry THF (50 ml), and the resulting mixture was stirred at –50 °C for 1 h. Next, it was warmed to –20 °C, and a solution of 10 g (0.0365 mol) of iodide **4** was added dropwise. The mixture was stirred at room temperature and then added to 150 ml of a saturated NaCl solution. The mixture was extracted with diethyl ether (5×50 ml), and the ether fractions were combined and dried with Na_2SO_4. After removing the solvent, the residue was distilled *in vacuo* to give 8.1 g of compound **5** (90%), bp 61 °C (10^{-3} Torr). ^{1}H NMR ($CDCl_3$) δ: 0.11 (s, 9H, Si–Me), 2.49 (t, 2H, CH_2–C≡C), 3.35 (s, 3H, OMe), 3.53 and 3.61 (A_2B_2, 4H, MeO–CH_2CH_2), 3.56 (t, 2H, CH_2CH_2–C≡C), 3.61 (m, 4H, CH_2O–CH_2CH_2–OCH_2). Found (%): C, 58.98; H, 9.77. Calc. for $C_{12}H_{24}O_3Si$ (%): C, 58.97, H, 9.90.

5,8,11-Trioxadodec-1-yne **6**. A solution of 8 g (0.033 mol) of **5** and of 8 g of $Bu_4NF{\cdot}H_2O$ in 50 ml of THF was stirred at room temperature for 18 h. Next, it was added to 150 ml of a saturated NaCl solution. The mixture was extracted with diethyl ether (5×50 ml), and the ether fractions were combined and dried with Na_2SO_4. The removal of the solvents and distillation *in vacuo* gave 4.9 g (95.2%) of **6**, bp 96–98 °C (3 Torr). ^{1}H NMR ($CDCl_3$) δ: 1.9 (t, 1H, HC≡, J_{HCCCH_2} 2.6 Hz), 2.42 (td, 2H, HC≡C–CH_2, J_{HCCCH_2} 2.6 Hz), 3.3 (s, 3H, OMe), 3.5–3.65 (m, 10H, CH_2O). ^{13}C NMR ($CDCl_3$) δ: 20.13 (CH_2–C≡CH), 59.27 (OMe), 68.62 (HC≡), 69.63, 69.71, 70.69, 70.91, 72.31 (CH_2O), 81.58 (C≡CH). Found (%): C, 62.53; H, 9.74. Calc. for $C_9H_{16}O_3$ (%): C, 62.77; H, 9.36.

‡ *1-Carboxy-2-(3',6',9'-trioxadecyl)-1,2-dicarba*-closo-*dodecaborane* **8**. To a solution of **7** (4.2 g, 0.015 mol) in 50 ml of dry THF cooled to –30 °C 10 ml (0.015 mol) of 1.6 M BuLi in hexane was added, and the resulting mixture was stirred at –30 °C for 1 h. A white precipitate was formed. The mixture was warmed to room temperature and added to an excess of solid CO_2. Next, 50 ml of a saturated $NaHCO_3$ solution was added, and the resulting mixture was extracted twice with diethyl ether (40 ml) and twice with hexane (40 ml). The separated aqueous layer was acidified to pH 1–2, and the white precipitate of **8** was filtered off and dried *in vacuo* to give 4.8 g (94%), mp 127–129 °C. ^{1}H NMR ($CDCl_3$) δ: 0.96–3.42 (m, 10H, BH), 2.76 (t, 2H, CH_2–C_{arb}), 3.40 (s, 3H, OMe), 3.5–3.6 (m, 10H, CH_2O), 7.69 (s, 1H, COOH). ^{13}C NMR ($CDCl_3$) δ: 35.75 (CH_2–C_{arb}), 58.80 (OMe), 69.24, 69.45, 69.61, 69.78, 71.53, (CH_2O), 78.46 (CCH_2), 161.40 (C=O), *C*–COOH unresolved. MS, *m*/*z*: 334 (M^+). Found (%): C, 35.17; H, 7.50. Calc. for $C_{10}H_{26}B_{10}O_5$ (%): C, 35.92; H, 7.84.



Scheme 1 i, TsCl–pyridine, CH_2Cl_2; ii, NaI/acetonitrile, reflux, iii, LiC≡CTMS, THF; iv, $(NBu_4)F_{aq}$, THF; v, $B_{10}H_{14}$, acetonitrile, reflux.

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1-(3',6',9'-Trioxadecyl)-1,2-dicarba-closo-*dodecaborane* **7**. To a boiling solution of decaborane (4 g, 0.033 mol) in 50 ml of dry acetonitrile 4.6 g (0.033 mol) of **6** in 20 ml of acetonitrile was added, and the mixture was refluxed until the evolution of hydrogen stopped (about 5 h). Next, the mixture was cooled, the solvent was evaporated, and the residue was extracted with hot hexane (4×40 ml). The hexane extracts were combined, and hexane was evaporated; the residue was crystallised from diethyl ether–hexane (1:1) to give 4.2 g (52%) of pure **7**, mp 145–147 °C. ^{1}H NMR ($CDCl_3$) δ: 1.00–3.44 (m, 10H, B–H), 2.51 (t, 2H, CH_2–$C_{arb.}$), 3.37 (s, 3H, OMe), 3.5–3.7 (m, 10H, CH_2O), 4.17 (br. s, 1H, CH–$C_{arb.}$). ^{13}C NMR ($CDCl_3$) δ: 38.22 (CH_2–$C_{arb.}$), 59.96 (CH–$C_{arb.}$), 61.24 (OMe), 69.34, 70.90, 71.11, 71.39, 72.78 (CH_2O), 74.39 [$C(C_{arb.})$–CH_2]. MS, *m*/*z*: 290 (M^+). Found (%): C, 36.84; H, 9.36. Calc. for $C_9H_{26}B_{10}O_3$ (%): C, 37.22; H, 9.02.

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