Pergamon

Tetrahedron Letters 39 (1998) 4489–4492

TETRAHEDRON
LETTERS

Synthesis of New Lipophilic *Ortho*-Dicarboranes

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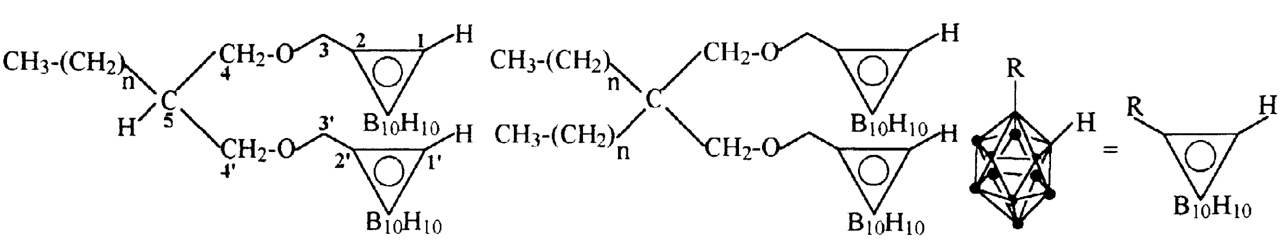
Received 17 February 1998; accepted 21 April 1998

Abstract: *The synthesis of several new lipoidal dicarborane compounds prepared by reaction of decaborane with several fatty mono- and bis-alkyl-1,3-diols is described.* © 1998 Elsevier Science Ltd. All rights reserved.

Boron Neutron Capture Therapy (BNCT) is a binary approach to cancer therapy based on the nuclear reaction of boron-10 with thermal neutrons [$^{10}B(n, \alpha)^{7}Li$]. Successful therapy using this attractive system requires the selective localisation of 10- 30 ppm ^{10}B in tumor cells. Because of these constraints, the synthesis of selective boron-rich molecules remains one of the most challenging areas of investigations in BNCT. The use of *nido*-decaborane(14) as starting material is persuasive since this relatively stable boron-rich compound can be readily functionalized to be linked to biological carriers or to their analogues[1,2]. Additionally these *closo*-carborane derivatives are hydrophobic, which is an advantage since lipophilic compounds are retained better in the tumor cells than hydrophilic ones.

We recently showed that a lipophilic anchorage of chelating agents into the phospholipid layer of lipoproteins (LDL) allowed the selective delivery of radionucleides into tumor cells, for diagnostic purposes[3]. Electron microscopic examination revealed the localization of the radioelement in the deep-seated cytoplasm[3]. In order to test this possible way to selectively deliver boron-rich compounds into cancerous cells, we synthesized polyhedral dicarboranes bearing long lipophilic chains.

In the present work several lipoidal *ortho*-dicarboranyl derivatives were synthesized to give compounds with different lipophilicities, by varying the length and the number of the alkyl tails, **1** or **2** (Scheme 1).



mono-1,3-dicarboranyl metoxypropane, **1** (**a, b**); dialkyl-1,3-dicarboranyl metoxypropane, **2** (**a, b**);
with n = 11 (**a**) or 15 (**b**)

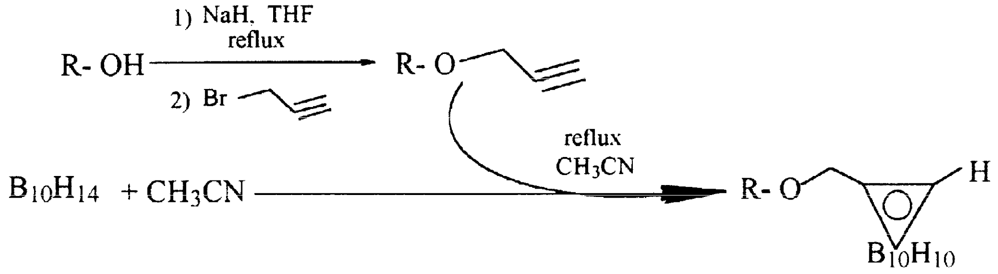
Carborane unit

Scheme 1

PII: S0040-4039(98)00870-3

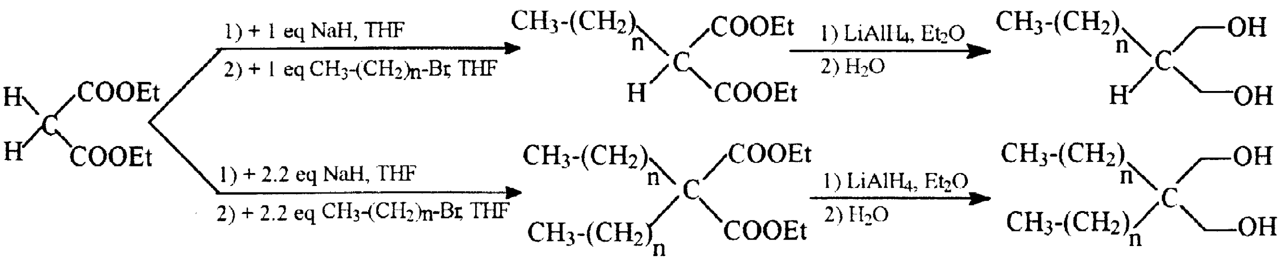
Ether linkages between the hydrophobic part and the icosahedral cages were chosen because they increase the polarity and the solubility of the product in biological media. These C-linked carboranyl compounds were prepared starting from two series of fatty alcohols, mono- or di-substituted-1,3-diols.

To obtain these boron carriers, the generally chosen way, described for the first time by Heying[4] or more recently by L. Schneiderova[5], proceeds in two steps (Scheme 2). First, the starting alcohol is converted into its acetylenic derivative. Then, the corresponding carborane is readily formed by reaction of the alkyne with *nido*-decaborane(14): $B_{10}H_{14}$, in the presence of a boiling Lewis base such as acetonitrile.



Scheme 2: Heying's general method.

Original 2-monoalkyl- or 2,2-bisalkyl-1,3-diols were synthesized starting from diethylmalonate. One equivalent of diethylmalonate was added to a solution of freshly distilled THF with one or two equivalent(s) of sodium hydride in suspension. After deprotonation by refluxing the mixture, alkylbromide was added. The hydrophobic character of the resulting malonate diester depended on the added quantity of bromide. It gave a mono-alkyl ester malonate, **3**, or a di-alkyl ester malonate, **4**, depending on the number of bromide equivalents used. Both were then reduced in dry ether with lithium aluminium hydride (Scheme 3) and purified by a silica gel column flash chromatography with toluene to give alkylpropane-1,3-diol, 5, or dialkylpropane-1,3-diol, **6**. The hydrophobic character may be modulated by the length of the alkyl bromide used (n = 11 (**a**) or 15 (**b**)).



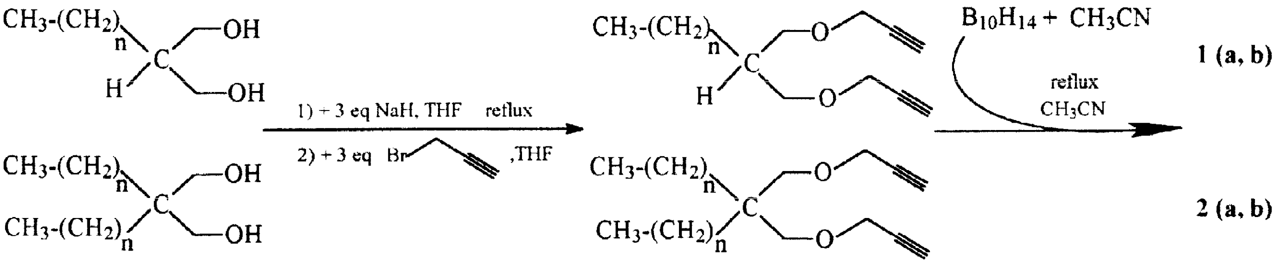
Diethyl malonate,

diethyl n-alkylmalonate, **3 (a, b)** or
diethyl n-dialkylmalonate, **4 (a, b)**

alkylpropane-1,3-diol, **5 (a, b)** or
dialkylpropane-1,3-diol, **6 (a, b)**.

Scheme 3

The corresponding dicarboranyl ethers were obtained by propargylation of these diols, followed by condensation with *nido*-decaborane(14) as described by T. L. Heying[4] (Scheme 4). As the triple bond may be subject to steric hinderance (especially for 2,2-disubstituted-1,3-diols), conversion of the diacetylenic compounds into the corresponding biscarboranes was achieved with an excess of $B_{10}H_{14}$. Decaborane(14) was refluxed under a nitrogen atmosphere in dry acetonitrile for six hours and the fatty acetylenic molecule was added. The reaction was run *in situ* for two days under refluxing at 70 °C, in order to increase the yield of the desired monoalkyl-1,3-dicarboranyl metoxypropane, **1** (**a** or **b**), or dialkyl-1,3-dicarboranyl metoxypropane, **2** (**a** or **b**) (25%).



alkylpropane-1,3-diol, **5 (a, b)** or
dialkylpropane-1,3-diol, **6 (a, b)**

alkyl-1,3-dipropargyloxypropane, **7 (a, b)** or
dialkyl-1,3-dipropargyloxypropane, **8 (a, b)**.

Scheme 4

The bonding between lipophilic and carborane units was confirmed by the ^{1}H NMR, ^{13}C NMR, $^{11}B\{^{1}H\}$ NMR, IR spectra and by mass spectroscopy (DCI/ NH_3) analysis[6].

In summary, we have described the synthesis of novel, lipophilic boron-rich compounds. The biological evaluation of these new *ortho*-dicarborane clusters will be explored together with physical aspects concerning the probability of lethal reactions in tumor cells.

References and Notes

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6. Atom numbering is given in Scheme 1. The numbering of carbon atoms in the alkyl chains starts from [6] for the CH$_2$ α-linked to the quaternary atom [5]. It ends with the terminal CH$_3$ group. Chemical shifts for ^{1}H NMR (250 MHz) and ^{13}C NMR (63 MHz) were referenced to SiMe$_4$ (0.00 ppm) and measured to the residual CDCl$_3$ proton; coupling constants J in Hz. Chemical shift values for ^{11}B spectra (80 MHz, CDCl$_3$) were referenced to external BF$_3$.OEt$_2$ (0.00 ppm).

1a: NaH (30 mmol) and dodecyl bromide (20 mmol) were added to diethylmalonate (20 mmol) in THF. 17 mmol of isolated **3a** were reduced with LiAlH$_4$ (85 mmol) in dry Et$_2$O and hydrolysed with water in excess. Purified **5a** (5 mmol) was deprotonated with NaH (15 mmol) and addition of propargyl bromide (15 mmol) in THF. B$_{10}$H$_{14}$ (3.1 mmol) was refluxed in CH$_3$CN (10 ml) with **7a** (1.5 mmol) and chromatographied to give **1a**. DCI/ NH$_3$, m/z 574 ([M+ NH$_4$]$^+$) calculated for C$_{21}$H$_{56}$O$_2$B$_{20}$. IR (KBr): 3080 cm^{-1}(C-H, carboranyl); 2920, 2880 (C-H, alkyl); 2580 (B-H); 1270 (B-H); 1100 (C-O-C, ether); 720 (C-H, alkyl). ^{1}H NMR: 0.88 (t, J = 6.6, 3H, [CH$_3$]); 1-3 (br.m, 20 H, [B-H]); 1.27 (s, 22H, H-[6 to 16]); 1.80 (m, 1H, H-[5]); 3.39 (d, J = 5.53, 4H, H-[4], H-[4']); 3.83 (s, 4H, H-[3], H-[3']). ^{13}C NMR: 14.14 ([CH$_3$]); 22.70, 26.86, 28.18, 29.36, 29.49, 29.59, 29.65, 29.72, 31.92 ([6 to 16]); 38.94 ([5]); 57.67 ([1, 1']); 71.99 ([4, 4']), 72.19 [(3, 3']); 72.66 ([2, 2']). ^{11}B{^{1}H} NMR: -0.44; -6.55; -10.54; -12.12; -14.79.

1b: DCI/ NH$_3$, m/z 630 ([M+ NH$_4$]$^+$) calculated for C$_{25}$H$_{64}$O$_2$B$_{20}$. IR (KBr): 3080 cm^{-1}(C-H, carboranyl); 2920, 2880 (C-H, alkyl); 2580 (B-H); 1270 (B-H); 1100 (C-O-C, ether); 720 (C-H, alkyl). ^{1}H NMR: 0.88 (t, J = 6.9, 3H, [CH$_3$]); 1-3 (br.m, 20 H, [B-H]); 1.27 (s, 30H, H-[6 to 20]); 1.82 (m, 1H, H-[5]); 3.39 (d, J = 6.55, 4H, H-[4], H-[4']); 3.81 (s, 4H, H-[3], H-[3']). ^{13}C NMR: 14.15 ([CH$_3$]); 22.71, 26.87, 28.18, 29.38, 29.49, 29.60, 29.71, 31.94 ([6 to 20]); 38.95 ([5]); 57.67 ([1, 1']); 71.99 ([4, 4']); 72.21 ([3, 3']); 72.64 ([2, 2']). ^{11}B{^{1}H} NMR: -0.73; -6.51; -8.81; -12.03; -14.56; -15.32.

2a: DCI/ NH$_3$, m/z 743 ([M+ NH$_4$]$^+$) calculated for C$_{33}$H$_{80}$O$_2$B$_{20}$. IR (KBr): 3080 cm^{-1}(C-H, carboranyl); 2920, 2880 (C-H, alkyl); 2590 (B-H); 1260 (B-H); 1120 (C-O-C, ether); 720 (C-H, alkyl). ^{13}C NMR: 14.82 ([CH$_3$, CH$_3$']); 23.39, 26.61, 27.54, 28.84, 30.06, 30.36, 31.01, 32.08, 32.61 ([6 to 16], [6' to 16']); 42.23 ([5]); 58.36 ([1, 1']); 72.87 ([4, 4']); 73.32 ([2, 2']); 74.92 ([3, 3']).

2b: DCI/ NH$_3$, m/z 845 ([M+ NH$_4$]$^+$) calculated for C$_{41}$H$_{96}$O$_2$B$_{20}$. IR (KBr): 3080 cm^{-1}(C-H, carboranyl); 2920, 2880 (C-H, alkyl); 2590 (B-H); 1260 (B-H); 1120 (C-O-C, ether); 720 (C-H, alkyl). ^{13}C NMR: 14.35 ([CH$_3$, CH$_3$']); 23.12, 23.16, 29.90, 30.14, 30.20, 30.27, 30.51, 30.89, 31.75, 32.14 ([6 to 20], [6' to 20']); 41.65 ([5]); 58.79 ([1, 1']); 72.64 ([4, 4']); 73.08 ([2, 2']); 74.29 ([3, 3']).