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Synthesis of New Building Blocks for Boron-Rich Oligomers in Boron Neutron Capture Therapy (BNCT). I.

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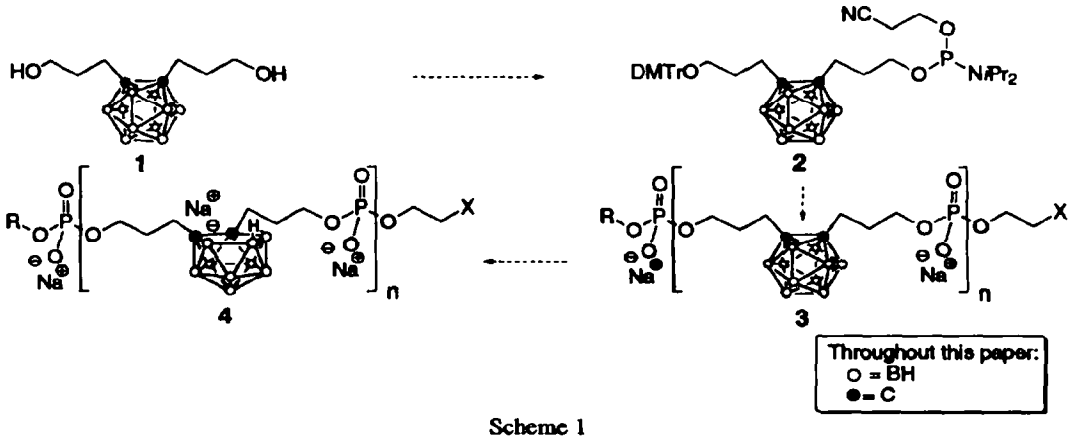
Abstract: The synthesis of carborane-containing subunits for use in the construction of boronated oligophosphates via solid phase synthesis is described.

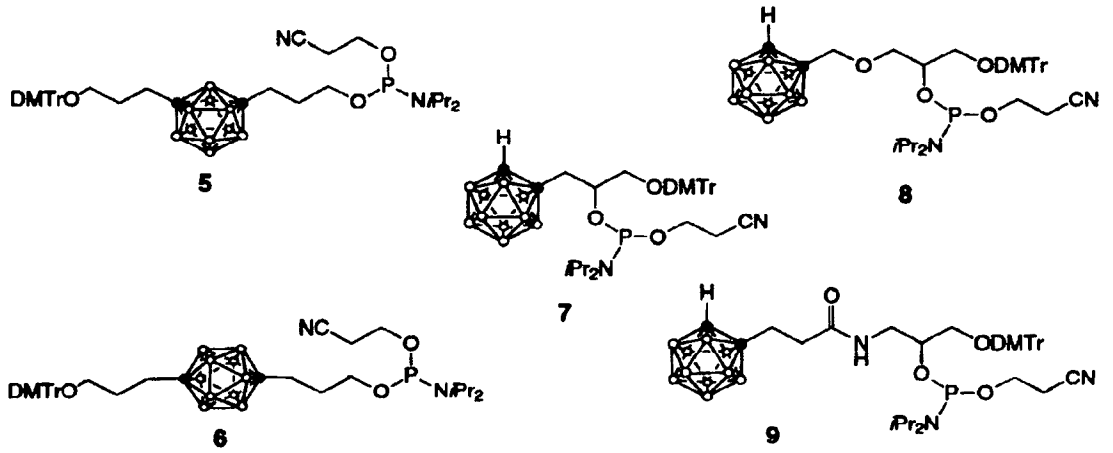
Boron neutron capture therapy (BNCT) is a binary approach to cancer therapy based upon the capture of thermal neutrons by ^{10}B, which results in the emission of extremely cytotoxic α-particles and ^{7}Li nuclei. It has been calculated that effective therapy will require the selective localization of 10-30 ppm ^{10}B in tumor cells. Numerous systems for the selective delivery of boron-rich macromolecules are under investigation including tumor-targeting antibodies, bioregulatory peptides and sex hormones.[1]

Recently, we described a method that permits the rapid and efficient synthesis of homogeneous boron-rich oligomeric phosphate diesters such as **3** (Scheme 1) using automated DNA synthesizers.[2] This method allows the construction of boron-rich macromolecules having an enormous latitude with respect to composition, sequence and size while allowing functionalization of the oligophosphates with a variety of reactive groups at defined locations. Oligomers **3** and **4** were synthesized starting from the the carborane-containing diol **1**, which was converted to monomer **2** by protection of one hydroxyl group with the dimethoxytrityl group followed by activation of the other hydroxyl group with a phosphoramidite functionality. Although oligomers such as **3** are already water soluble, their hydrophilicity can be further enhanced by converting the *closo* carborane cages into anionic *nido* derivatives, thereby affording oligomers such as **4**.



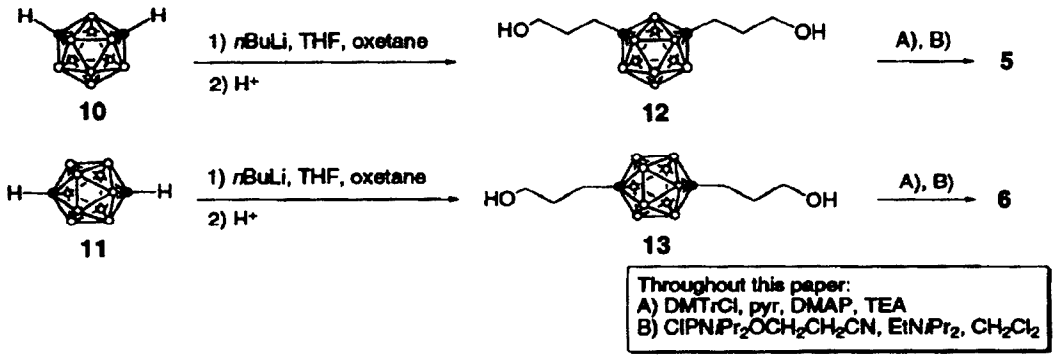
Scheme 1

In order to study and ultimately optimize the chemical and biological properties of those boron-rich oligophosphates we have synthesized several new monomers (**5-9**, Scheme 2) with different structural features. The syntheses of these compounds are presented herein.[3]



Scheme 2

The *meta*- and *para*- carborane analogs of **2**, compounds **5** and **6**, respectively, were synthesized in a straightforward manner. The parent unsubstituted *meta*- and *para*- carboranes **10** and **11** were converted into the corresponding dipropanols **12** and **13**, monoprotected as the dimethoxytrityl ethers, and activated as phosphoramidites **5** and **6** at the remaining hydroxyl group (Scheme 3).

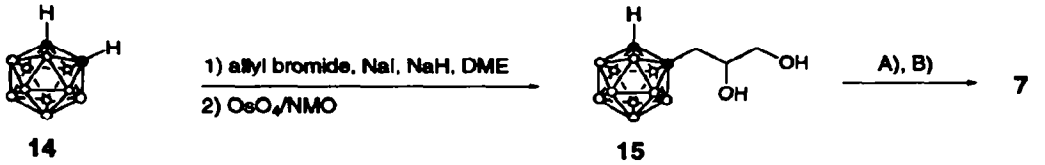


Scheme 3

The three carborane isomers not only present distinctly different geometric features, but also undergo conversion from the neutral *closo* structures to the corresponding *nido* derivatives at substantially different rates (*ortho*>>*meta*>>*para*).[4] This provides us with a mechanism to eventually control the overall charge distrubution and hydrophilicity of oligophosphates derived from combinations of these monomers.

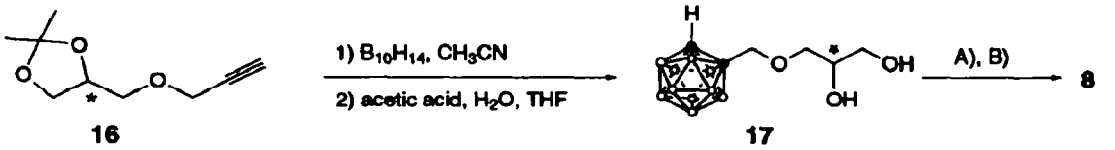
Monomers **7**, **8** and **9** were designed to take advantage of the selectivity of the dimethoxytrityl protection reaction for primary over secondary alcohols, avoiding the "statistical" protection reaction employed in the synthesis of monomers **2**, **5** and **6**. These monomers also afford oligomers in which the carborane substituent is not a structural part of the oligophosphate backbone.

Allyl carborane, which was obtained in 60% yield from *ortho* carborane **14**, NaH, NaI and allyl bromide after 10h stirring at room temperature,[5] was oxidized to diol **15** with OsO_4/NMO in 66% yield. Reaction of this diol with dimethoxytrityl chloride followed by 2-cyanoethyl-N,N-diisopropyl-chlorophosphoramidite gave compound **7** in 80% overall yield for the last two steps (Scheme 4).



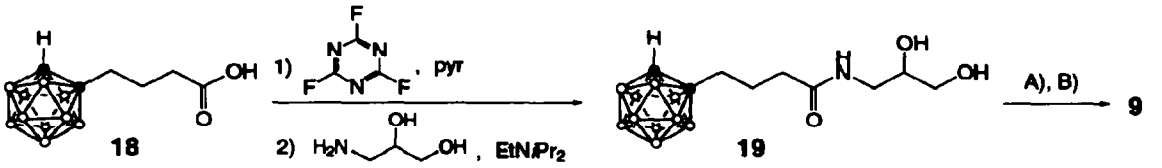
Scheme 4

A slightly modified approach was taken in the synthesis of compound **8**. Solketal was reacted with propargyl bromide to give alkyne **16**.[6] Reaction of this compound with $B_{10}H_{14}$[7] followed by cleavage of the ketal gave the diol **17** as a pale yellow oil in 20% overall yield. Stepwise functionalization of the hydroxyl groups yielded **8** as a white foam (Scheme 5). In the same manner (*R*)-**8** and (*S*)-**8** were obtained from commercially available (*R*)- and (*S*)-solketal, thereby providing access to studies relating the influence of the chiral center to the secondary structure of the corresponding oligomers.



Scheme 5

For the synthesis of compound **9**, carboranyl butanoic acid[8] **18** was activated as the acyl fluoride in pyridine/CH_2Cl_2 and reacted with 3-amino-1,2-propanediol to give the amide **19** in 72% yield. This type of activation proved to be superior to the use of DCC (37-47% yield). The phosphoramidite **9** was then obtained in two steps from **19** as a white foam in reasonable yields (Scheme 6).



Scheme 6

Oligophosphates have been synthesized from each of the monomers presented herein. We are currently exploring the relationships between structural features of the monomers and the chemical and biological properties of oligomers derived from these building blocks.

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2. Kane, R. R., Drechsel, K., Hawthorne, M. F. *J. Am. Chem. Soc.* **1993**, *115*, 8853.
3. Full experimental details for the synthesis of the compounds described herein can be obtained from the authors. Analytical data for compounds **16** and **8** are given below as examples.
   16 : ^{1}*H NMR (360MHz, CDCl$_3$)*: δ = 3.53-3.62 (m, 3H), 3.71 (dd, 1H, J=11.3Hz, J=3.8Hz), 3.85-3.91 (m, 3H), 3.95 (s, 1H) ppm. ^{13}*C NMR (90MHz, CDCl$_3$)*: δ = 73.17, 72.67, 70.51, 63.47, 57.77, 53.42 ppm. ^{11}*B NMR (160MHz, CH$_2$Cl$_2$)*: δ = -3.49, -5.40, -9.73, -12.10, -13.28, -13.66 ppm. *IR (neat)*: 3754-3135 (br), 2594 (s) cm^{-1}.
   8: ^{1}*H NMR (360MHz, CDCl$_3$)*: δ = 1.07 (s, 3H), 1.09 (s, 3H), 1,14 (s, 3H), 1,18 (s, 2H), 2,43 (t, 2H, J=6.4Hz), 2.60 (t., 2H, J= 6.2Hz), 3.08-3.19 (m, 2H), 3.48-3.93 (m, 4H), 3,77 (s, 6H), 3.78 (s, 1H), 3.95-4.08 (m, 1H), 6.80 (d, 4H, J=8.7Hz), 7.29 (d, 4H, J=8.7Hz), 6.81-7.42 (m, 5H) ppm. ^{13}*C NMR (90MHz, CDCl$_3$)*: δ = 158.46, 144.67, 135.88, 135.80, 130.22, 129.94, 128.09, 128.05, 127.75, 126.82, 117.62, 113.03, 86.01, 72.68, 72.46, 72.28, 72.17, 63.37, 58.17, 5797, 57.75, 55.17, 43.22, 43.12, 42.98, 24.67, 24.62, 24.55, 20.36, 20.20 ppm. ^{11}*B NMR (160 Hz, CH$_2$Cl$_2$)*: δ = -3.374, 5.089, -9.321, -11.78, -12.98 ppm. ^{31}*P NMR (145MHz, CDCl$_3$)*: δ = 149.27, 149.15 ppm. *HI RES FAB-MS* : exp.: m/e = 752.4741 [M$^-$]; obs: m/e 752.4728; Δ=1.7 ppm.
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