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# Synthesis of Carboranyl Polyamines for DNA Targeting

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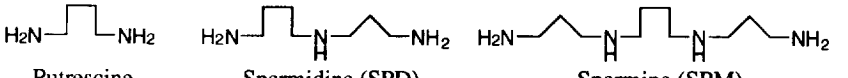
**Abstract:** Three groups of internal and terminal *N*-substituted carboranyl spermidines/spermines were synthesized as potential BNCT agents for the treatment of malignant tumors. Copyright © 1996 Elsevier Science Ltd

Boron neutron capture therapy (BNCT), a binary system, has the potential for treating brain tumors based on nuclear reaction of boron-10 with thermal neutrons.[1] The fission products of this reaction are high linear energy transfer (LET) particles whose size and energy confine them to those cells containing boron-10. The key problem is can boron compounds be designed that will selectively target tumor cell?

Various classes of boron compounds have been synthesized on the basis that these boron carriers might mimic their naturally occurring analogues and become selectively and differentially incorporated into tumor cells.[2] Polyamines: putrescine, spermidine (SPD) and spermine (SPM) (Figure 1) are an important class of naturally-

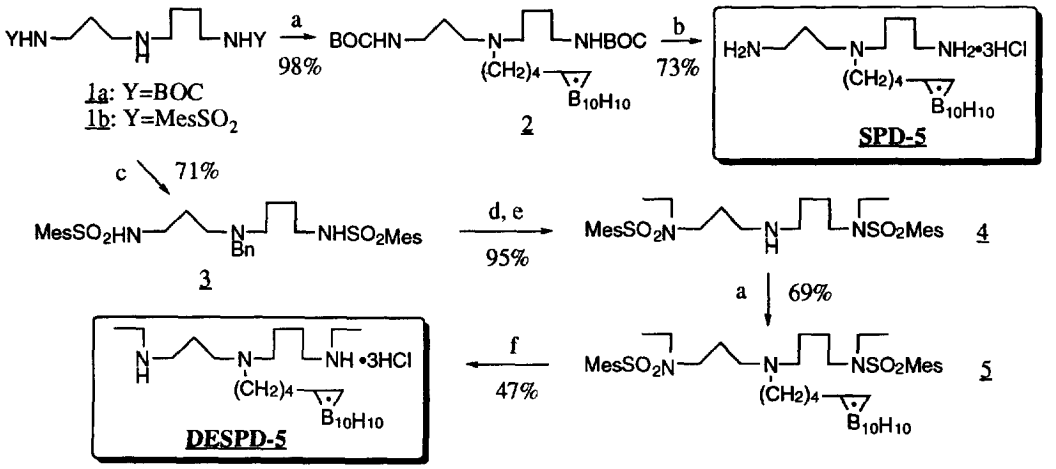
Figure 1.



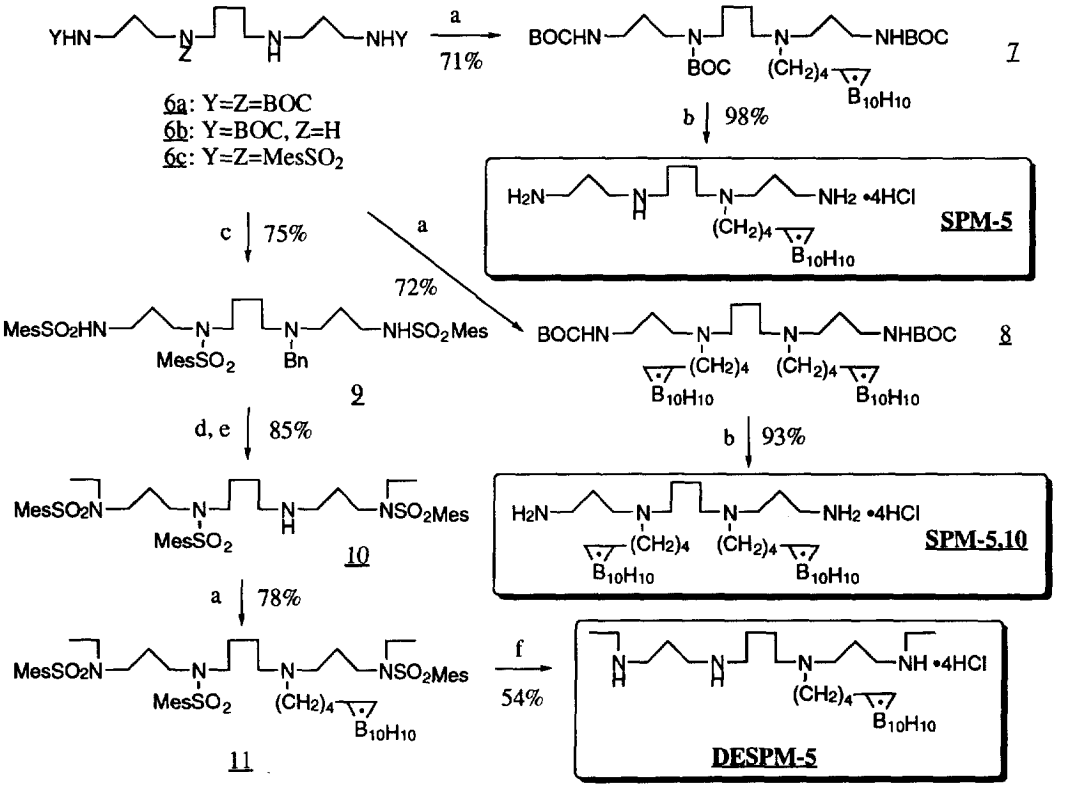

Putrescine Spermidine (SPD) Spermine (SPM)

occurring compounds. They are essential for cell growth and differentiation and elevated concentrations have been found especially in rapidly proliferating tumors cells.[3] Furthermore, cationic polyamines bind strongly to DNA through an electrostatic interaction[4] and incorporation of cancer chemotherapeutic agents into the polyamine scaffold has produced a more active cytoreductive compound than the parent chemotherapeutic agent.[5] The problem in the synthesis of carborane-containing polyamines is the basic chemical incompatibility of the carborane moiety in the presence of strong organic bases. How can such a structure be synthesized, isolated and purified? One approach has been described.[6] It necessitates that the amino function be masked and that this protecting group be removed under acidic conditions, generating the amine as a hydrochloride salt. In this approach, there is no chemical incompatibility.

Using this approach, we have synthesized three series of N-carboranyl containing polyamines starting with spermidine and spermine. The first series involved insertion of the boron group on an internal nitrogen of SPD and SPM. N-(4-Carboranylbutyl) derivatives of SPD/SPM, **SPD-5** and **SPM-5**, were synthesized by the alkylation of tert-butoxycarbonyl (BOC) protected SPD/SPM[7] with 4-carboranylbutyl iodide (CBB-I)[8] as shown in Schemes 1 and 2. Removal of the BOC group from **2** and **7** by 3N HCl (aq.)/Ethanol at 40-50 °C (Scheme 1 and 2) yielded **SPD-5** and **SPM-5**, respectively. In the case of spermine, there are two internal nitrogen atoms and therefore, there is the possibility of incorporating two boron moieties at positions $N^5$ and $N^{10}$. When compound **6b** was alkylated with CBB-I even in the presence of its excess (Scheme 2), **SPM-5,10** was the only product that could be isolated. Since secondary amines are sufficiently strong bases to degrade the ortho carborane cage to their nido-counterparts,[9] the trimethylsilyl (TMS) group was previously used[8a] to protect the




Scheme 1. a) $HCB_{10}H_{10}C(CH_2)_4I$, $K_2CO_3$/DMF, 60-70 °C; b) 3N HCl/MeOH, 40-50 °C; c) BnBr, $K_2CO_3$/DMF, 60-70 °C; d) NaH, EtI/DMF; e) Pd/C, $H_2$/MeOH; f) conc. HCl/EtOH, refluxing.

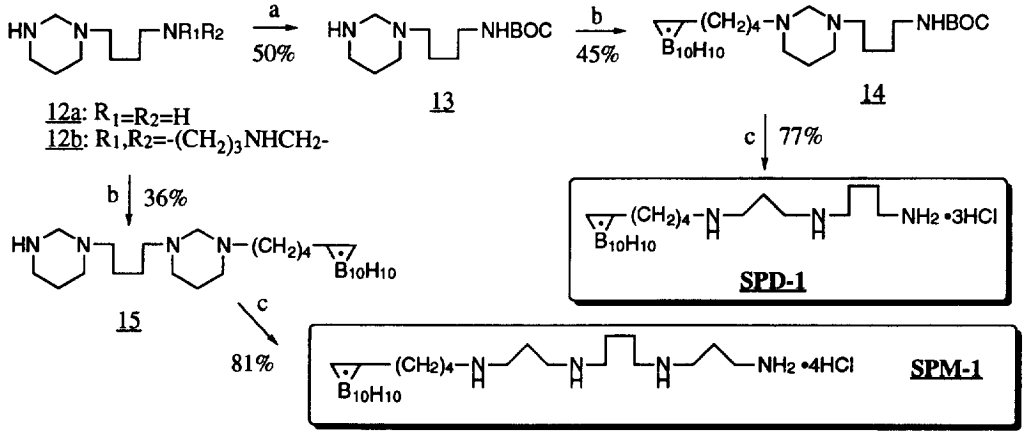



Scheme 2. a) $HCB_{10}H_{10}C(CH_2)_4I$, $K_2CO_3$/DMF, 60-70 °C; b) 3N HCl/MeOH, 40-50 °C; c) BnBr, $K_2CO_3$/DMF, 60-70 °C; d) NaH, EtI/DMF; e) Pd/C, $H_2$/MeOH; f) conc. HCl/EtOH, refluxing.

secondary amine of **1a** and reduce its nucleophilicity. However, attempts to synthesize **8** by this procedure gave extremely low yields even with prolonged reaction times.[9b] This may be due to degradation caused by the tertiary amines of **8**. For this reason, the direct alkylating procedure within a short reaction time (1h) was employed. In this case, **8** was formed in high yield (72%).

A second series of compounds, in which ethyl groups were attached on the terminal nitrogens of SPD/SPM was carried out in order to prevent toxic degradation products from being formed from primary amines.[10] Alkylation of the internal nitrogen yielded compounds analogous to the first series. Examples of such structures are **DESPD-5** and **DESPM-5**. Attempts at ethylating the carbamate groups of **1a** were unsuccessful, even when the $N^5$-position was masked by the carbobenzyloxy (Cbz) or the benzyl (Bn) groups. However, when the BOC group was replaced by a 2-mesitylenesulfonyl ($MesSO_2$) group and the internal NH group protected by Bn, the ethylation of **3** and **9** occurred in excellent yields (Scheme 1 and 2).[11] Debenzylation was carried out by catalytic hydrogenation and the free secondary amines, **4** and **10**, could then be alkylated with CBB-I. Subsequently, the $MesSO_2$ groups were removed and the target compounds **DESPD-5**, **DESPM-5**, were obtained.

For comparison with the internally *N*-alkylated SPD/SPM analogues, a third series of terminally *N*-alkylated SPD/SPM analogues was undertaken (Scheme 3). In this case, SPD/SPM were protected by forming hexahydropyrimidine ring(s) with formaldehyde.[12] The primary amine of **12a** was then masked with BOC (**13**) and subsequently reacted with CBB-I to give **14**. Without protection, **12b** reacted with CCB-I to give mono *N*-(4-carboranylbutylated) compound **15** with some bis(*N*-carboranylbutylated) as a by-product. The latter could be




Scheme 3. a) BOC-ON/THF, -40-25 °C; b) $HCB_{10}H_{10}C(CH_2)_4I$, $K_2CO_3$/DMF, 25 °C; c) 3N HCl/MeOH, 40-50 °C.

readily separated from **15** by chromatography. The yields were moderate (40%), possibly due to degradation by the strongly basic amino group(s) of hexahydopyrimidine. By deprotecting both the BOC group and the methylene group of hexahydropyrimidine ring(s) of **14**, and **15**, the target compounds, **SPD-1** and **SPM-1**, were obtained under the same conditions as used in forming of **SPD-5**.

Studies of *in vitro* cytotoxicity measurements and cellular uptake using rat F98 glioma cells, and polyamine displacement of ethidium bromide from calf thymus DNA for these compounds have shown that they retain the ability to displace ethidium bromide from calf thymus DNA; possess the ability for rapid uptake by F98 glioma cells; and have greater toxicity than SPD/SPM, especially those with terminal *N*-substituted (**SPD-1**, **SPM-1**) boron compounds.

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