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Water-soluble phosphonium salts containing 1,12-dicarba-*closo*-dodecaborane(12)

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ABSTRACT

The preparation of new water-soluble phosphonium salts containing 1,12-dodeca-*closo*-dodecaborane(12) (*closo*-1,12-carborane) for potential use as tumor-targeting agents in Boron Neutron Capture Therapy (BNCT) is described.

Delocalized lipophilic compounds (DLCs) such as the mitochondrial dye Rhodamine 123, and the phosphonium salts tetraphenylphosphonium (TPP) chloride, and triphenylmethylphosphonium (TPMP) iodide are known to accumulate selectively in cancer cells.[1–7] The salts display remarkable tumor selectivity as they are able to easily traverse the lipophilic mitochondrial membrane of a tumor cell as its membrane potential is ca. 60 mV higher than that of a healthy cell.[8] The in vivo uptake and retention studies of ^{11}C-labeled TPMP iodide in canine brain tumor have been determined by means of Positron Emission Tomography (PET) imaging. The salt was quickly taken up by the tumor with high selectivity (achieving a tumor/healthy tissue ratio of 48:1) and it was retained for a significant time (75 min).[9] The selectivity of TPMP for tumors over healthy tissue is approximately one order of magnitude greater than the boronated agents currently used in Boron Neutron Capture Therapy (BNCT), an experimental therapy which is primarily used in the treatment of high-grade gliomas.[10–13] These results clearly indicate that boron-containing analogues of TPMP could potentially be employed as boron-delivery agents in BNCT with a very high degree of tumor selectivity.

To the best of our knowledge, only a few boron-containing DLCs have been reported to date. For example, the 1,12-dicarba-*closo*-dodecaborane(12) (*closo*-1,12-carborane) analogue of dequalinium chloride has been described.[14] This salt was found to have similar tumor uptake and retention properties to Rhodamine 123 and TPP chloride, and it was also found to accumulate selectively in human epidermoid carcinoma and rat glioma in vitro.[14] Methyldiphenyl(1-carboranyl)phosphonium salts containing *closo*-1,2-, 1,7-, and 1,12-carborane (**1**) have also been described,[13] and these are the first boronated analogues of TPMP. Very recently, *closo*-1,2- and 1,7-carborane DLC derivatives of TPP were reported by Tsibouklis et al.[15] In the case of the TPP phosphonium salt **2**, the anionic boron entity (i.e., *nido*-7,8-carborane) is not covalently attached to the cation. Rather, it is acting as the counter-ion and so the exact mechanism of boron delivery and tumor selectivity for tumor cells is unclear. In vitro boron uptake studies involving human prostate epithelial carcinoma demonstrated that these DLC boron derivatives achieved a reasonable (up to 4.2:1) cancer to healthy tissue selectivity, as well as a high uptake of boron (ca. 10^{11} boron atoms cell^{-1}) despite the absence of any covalent link between the lipophilic phosphonium cation and the boron entity. Nile Blue DLC derivatives (where the *closo*-carborane moiety is covalently linked to the structure) demonstrated similar results (3.1:1 and 2.2:1 for *closo*-1,2- and 1,7-carborane, respectively)[15] and thus it appears that a covalent link between the phosphonium moiety and the boron moiety may not be necessary for the selective delivery of boron to tumor sites (Fig. 1).

A delicate balance between the lipophilicity and hydrophilicity of mitochondrial-targeting agents is required in order to optimize

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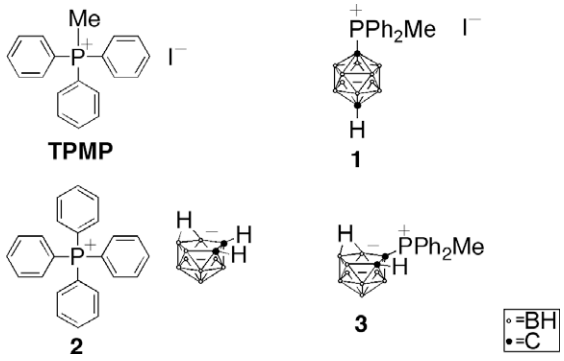
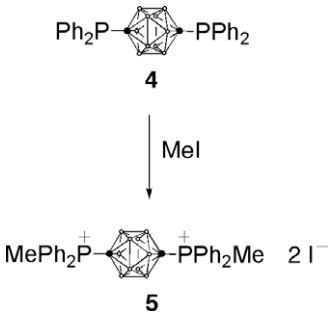


Figure 1. Phosphonium salts TPMP, **1**, and **2**, and the zwitterion **3**.



Scheme 1. Preparation of diphosphonium salt **5**.

their tumor selectivity.[3] Unlike the anionic *nido*-carborane cages, uncharged *closo*-carboranes have been shown to be as lipophilic as adamantane[16] and an enhancement of their hydrophilicity is usually required if they are to be exploited in biological systems. In general, the hydrophilicity of *closo*-carboranes can be increased by the installation of water-solubilizing groups at one or both of the cage carbon atoms, for example, carborane–carbohydrate conjugates, or a cascade polyol in the *closo*-1,7-carborane derivative of 1-aminocyclobutanecarboxylic acid (ACBC).[17] Indeed, we have previously employed a related strategy to the latter and reported the first example of a water-soluble platinum(II) complex containing a *closo*-carborane which was functionalized with a glycerol moiety.[18] An alternative approach to enhancing the hydrophilicity of *closo*-carboranes is to increase their overall charge. Hawthorne and co-workers have shown that in boron-functionalized alkylphosphonium-*closo*-carborane salts, the presence of cationic charges greatly improves their water solubility.[19] It was also demonstrated that the position of these charges relative to one another as well as relative to the *closo*-carborane cage dipole plays an important role in the overall aqueous solubility of the salts.

A recent study reported by our group has described TPMP carborane analogues which have one phenyl group replaced by a *closo*-1,2-, 1,7-, or 1,12-carborane.[13] The phosphonium salts containing either *closo*-1,2- or 1,7-carborane undergo a facile deboronation reaction in polar solvents to afford the corresponding 7,8- or 7,9-*nido*-carborane phosphonium zwitterions, respectively (e.g., **3**). A similar reaction was observed by Kalinin et al. where 1-(*closo*-1,2-carboranyl)methylpyridinium triflate was found to deboronate in aqueous pyridine to form the corresponding 1-(*nido*-7,8-carboranyl)methylpyridinium zwitterion.[20] In contrast, the *closo*-1,12-carborane derivative **1** was not found to deboronate readily and the phosphonium cation retained its overall charge.[13] Indeed, it is well established that *closo*-1,12-carborane is the least susceptible to cage deboronation when compared to its other isomers.[21–23] Preliminary in vitro cytotoxicity screening of **1** against the SF268 (human glioblastoma) cell line demonstrated a low toxicity compared with the analogous TPMP and dosing may not be limited by any inherent toxicity associated with the compound in future biological studies.[13]

Herein we describe two distinct strategies for the synthesis of water-soluble TPMP analogues containing *closo*-1,12-carborane. One route makes use of a water-solubilizing glycol chain. The other involves an increase in the cationic charge of the phosphonium salts.

An initial strategy was to prepare an analogue of **1** with two phosphonium centers. Treatment of the diphosphine **4**[24] with an excess of iodomethane in THF solution yielded the diphosphonium salt **5** in excellent yield and purity (Scheme 1) and it was characterized by means of multinuclear (^{1}H, ^{11}B, ^{13}C, and ^{31}P) NMR spectroscopy, microanalysis, and ESI-MS. The ^{1}H NMR spectrum of **5** contains a ^{31}P-coupled doublet at 3.31 ppm ($^{2}J_{PH}$ = 13.3 Hz) corresponding to the newly installed methyl group, which was confirmed by a ^{1}H{^{31}P} NMR experiment. The ^{31}P{^{1}H} NMR spectrum contains a singlet at 27.8 ppm, which is shifted downfield from the starting material ($\Delta\delta$ = 5 ppm) confirming a phosphonium center. The ESI mass spectrum contains the expected isotopic distribution of peaks at *m/z* 271 ($[M-2I]^{2+}$) as well as at *m/z* 344, which corresponds to the monocationic $MePh_2P^{+}$–$C_2B_{10}H_{10}$ fragment.

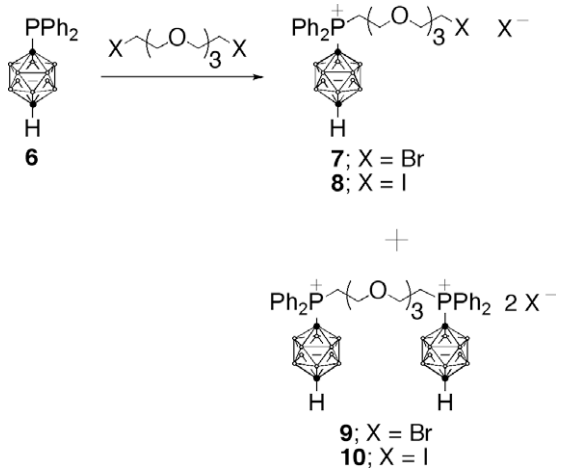
Distinct changes in the NMR spectra of **5** in polar solvents such as D_2O and DMF-d_7 were observed over a period of a few hours at room temperature, which prompted an investigation into the nature of the degradation products. A solution of **5** in EtOH was heated under reflux for three days and the isolated material was purified by recrystallization from MeOH to afford large colorless crystals, which were confirmed to be $[PMe_2Ph_2]I$ by NMR spectroscopy, ESI-MS, and microanalysis. The mechanism for this unusual transformation has yet to be resolved but the fate of the *closo*-carborane cage was investigated further. There exists strong evidence that deboronation of the 1,12-carborane cage occurs prior to cleavage of the P–C_{cage} bond, most likely during the first step of the transformation process. Indeed, the ^{11}B{^{1}H} NMR spectrum of the reaction mixture displayed resonances which were shifted significantly upfield (−8 to −40 ppm) from the region typically associated with that of *closo*-carboranes (2 to −15 ppm), a characteristic feature of *nido*-carboranes.[25–27] In addition, the high-resolution ESI-MS of the mixture exhibited a strong molecular ion peak at *m/z* 532.31687 corresponding to the monocationic species $[(PPh_2Me)_2$–$C_2B_9H_{10}]^{+}$ (Calcd for $C_{28}H_{36}B_9P_2$: 532.31793). Both the NMR and ESI-MS data are consistent with cage deboronation prior to cleavage to afford the monocationic phosphonium species by-product. It is well established that electron-withdrawing substituents positioned α- to the isomeric *closo*-1,2-carborane cage can lead to spontaneous degradation of the cage under mild conditions in polar solvents such as EtOH and DMSO.[28,29] This is particularly applicable to the *closo*-1,12-carborane cage in **5**, which is bonded directly to highly electron-withdrawing phosphonium centers at *both* of its carbon atoms thus resulting in an enhanced susceptibility to nucleophilic attack and subsequent deboronation by either a solvent molecule or perhaps the iodide counter-ion. To the best of our knowledge, these results demonstrate the first definitive example of a deboronation reaction involving a *closo*-1,12-carborane at room temperature. Previously reported preparations of *nido*-2,9-carborane employ much harsher conditions. For example, Hawthorne and Busby prepared *nido*-2,9-carborane in high yield by heating *closo*-1,12-carborane, KOH and 18-crown-6 ether in benzene solution for 42 h at 100 °C.[23] Similarly, Plesek and Hermanek,[30] and Fox et al.[21] have prepared *nido*-2,9-carborane in situ by treating *closo*-1,12-carborane with KOH in solution at high temperature.

The preparation of a hydrophilic, bromo- or iodo-alkyl phosphonium derivative of **1** would allow for further functionalization of the molecule by nucleophilic substitution of the halogen, for

example, by the use of $^{18}F^-$ for in vivo PET imaging studies.[31] Numerous attempts at the preparation of a short-chain, haloalkyl phosphonium species did not result in the formation of clean products in our hands, with many side-reactions predominating or, more commonly, an inseparable mixture of products being obtained. For example, phosphine **6** was treated with bromoiodomethane in THF solution at both ambient temperature and under reflux conditions. Both the bromomethylated and iodomethylated phosphonium salts were formed as expected but despite numerous attempts, the isolation of pure products from the reaction mixture proved to be fruitless. In contrast, the treatment of **6** with 1,2-dibromoethane, bromomethyltosylate, or bromoethyltosylate did not lead to the formation of any isolable phosphonium products. This unexpected result is most likely attributed to the strongly electron-withdrawing nature of the *closo*-carborane moiety, which would dramatically diminish the nucleophilicity of the phosphorus atom.[32–34]

The alkylation of **6** was ultimately achieved by using an excess of tetraethyleneglycol dibromide in DMF solution under an inert atmosphere at 120 °C. The product **7** was fully characterized by means of multinuclear (^{1}H, ^{11}B, ^{13}C, and ^{31}P) NMR spectroscopy, ESI-MS, and microanalysis. As expected, as there was only one electron-withdrawing group present in the *closo*-carborane, degradation of the product in polar solutions at room temperature was not observed (cf. **5**). Similarly, the alkylation of **6** using tetraethyleneglycol diiodide was successfully achieved to afford **8**. Confirmation of the structures of **7** and **8** was obtained by ^{1}H NMR spectroscopy. For example, in **7** the three signals corresponding to the tetraethyleneglycol dihalide precursor were replaced by eight distinct signals of which there were two ^{31}P-coupled resonances corresponding to the PCH_2CH_2O component (3.92 ppm, $^3J_{PH}$ = 12.1 Hz and 3.64 ppm, $^2J_{PH}$ = 22.4 Hz). In the ^{31}P{^{1}H} NMR spectrum of **7**, a sharp singlet was present at 31.7 ppm, which was shifted downfield from that of the starting material ($\Delta\delta$ = 9 ppm). In the ^{11}B{^{1}H} spectrum of **7**, the two broad singlets arising from the two distinct ^{11}B environments corresponding to the *closo*-1,12-carborane cage in the precursor at −12 and −14 ppm appear as overlapping broad singlets at −13.41 ppm. In the ^{13}C{^{1}H} NMR spectrum of **7**, the signals arising from the carbon atoms which are directly coupled to ^{31}P were confirmed by ^{13}C{^{1}H,^{31}P} decoupling and 2D-HSQC experiments. For example, the one-bond coupling constant associated with the P–CH_2 group ($^1J_{PC}$ = 52 Hz) is similar in magnitude to that of the C_{cage}P ($^1J_{PC}$ = 54 Hz) and C_{ipso} of the phenyl groups ($^1J_{PC}$ = 87 Hz).

Although the preparation of **8** also led to the formation of a small amount of the dicationic salt **10**, the preparation of **7** only resulted in a trace amount of the dication **9** (Scheme 2). Since iodide is generally a better leaving group than bromide, this result was not unexpected. The dicationic species **10** was easily separated from the monocationic species **8** by precipitation from CH_3CN solution. In the preparation of **7**, the presence of **9** was confirmed by the existence of small envelopes of peaks corresponding to the species [**9**−2Br]$^{2+}$ and [**9**−Br]$^+$ in the ESI-MS of the crude material. However, none of the dicationic species could be isolated. The optimized synthesis of the dicationic salt **10** was achieved by using a 2:1 ratio of phosphine **6** and tetraethyleneglycol diiodide (48% yield). The product was fully characterized by means of ESI-MS, microanalysis, and multinuclear (^{1}H, ^{11}B, ^{13}C, and ^{31}P) NMR spectroscopy. Due to the greater symmetry of the molecule, there are only four resonances assigned to the glycol chain as opposed to the eight resonances in the ^{1}H NMR spectrum of **8**. Two of the signals were ^{31}P-coupled and thus were assigned to the PCH_2CH_2O component (3.70 ppm, $^3J_{PH}$ = 12.7 Hz and 3.25 ppm, $^2J_{PH}$ = 20.1 Hz). The ^{11}B{^{1}H}, ^{13}C{^{1}H}, and ^{31}P{^{1}H} NMR spectra of **10** were similar to those of **7** and **8**. However, the ^{13}C{^{1}H} NMR spectrum of **10** differs in that there are only four resonances corresponding to the glycol chain, again due to the increased symmetry. There is also the absence of any resonance at 5.55 ppm corresponding to a CH_2I component. The ESI mass spectrum contains envelopes of peaks at *m/z* 409 and 945 corresponding to species [**10**−2I]$^{2+}$ and [**10**−I]$^+$, respectively.



Scheme 2. Preparation of phosphonium salts containing tetraethyleneglycol chains.

The aqueous solubilities of **5**, **7**, **8**, **10**, TPMP iodide, and selected parent *closo*-carborane phosphonium salts **1** and **3**[13] were also determined and are presented in Table 1. Compound **7** was found to be the most water-soluble *closo*-carborane phosphonium salt at ambient temperature. Its aqueous solubility was approximately one order of magnitude greater than that of **1** presumably due to the presence of the hydrophilic tetraethyleneglycol group. Although **8** is structurally similar to **7**, it possesses a different halide counter-ion which could also account for its comparatively lower solubility.[35] The dication **5** is more water soluble than **1** due to the additional positive charge, however the *closo*-carborane cage in **5** was found to degrade in aqueous solution over a period of one hour at room temperature (vide supra). Despite possessing two cationic charges, the dication **10** is just as soluble as the monocation **8** presumably because the additional hydrophobic *closo*-carborane cage largely negates any solubility enhancement attributed to the increased positive charge. In summary, it appears that TPMP *closo*-carborane derivatives containing an additional cationic charge or tetraethyleneglycol chain have about a 10-fold greater solubility than **1**. This effect may be negated if an additional *closo*-carborane cage is also present. However, it is clear from these preliminary solubility data that both strategies used in this work have proved to be quite effective at increasing the water solubility of the *closo*-carborane phosphonium salts.

In conclusion, the preparation of two distinct types of hydrophilic, *closo*-carborane phosphonium salts as boronated DLCs for potential use in BNCT has been described. The use of

Table 1
Aqueous solubilities of TPMP iodide and compounds **1**, **3**, **5**, **7**, **8**, and **10** at 23 °C

Compound	Solubility (g L^{-1})
TPMP iodide	19.3
1	0.4
3	0.4
5	3.0
7	7.0
8	0.7
10	0.7

closo-1,12-carborane in place of the 1,2- or 1,7-isomers has proved useful in avoiding the known deboronation reactions and also ensures that the agents retain an overall positive charge, which appears to be critical for mitochondrial targeting in tumors. The incorporation of either a glycol chain or additional cationic charges is an effective strategy for increasing water solubility, particularly as the *closo*-carborane cage is very lipophilic. We are currently evaluating the tumor uptake and biodistribution of these phosphonium salts, including PET imaging studies of ^{18}F-derivatives of **7**, in tumor-bearing mice and the results of these studies will be published in due course.

Experimental

Compound **4**,[24] **6**,[13] and TPMP iodide[36] were prepared according to the previously reported methods. Tetraethyleneglycol diiodide and dibromide were prepared according to a literature methods.[37,38] All reactions were performed under an inert nitrogen atmosphere using standard Schlenk techniques.

Aqueous solubilities were determined by first preparing a saturated solution of the compound in deionized water. The solution was placed in an ultrasonic bath for 5 min and any remaining solid was separated by centrifugation. The clear supernatant solution was collected at 23 °C. Portions of the solution were transferred to three dry glass vials (100 μL per vial) which were placed in a desiccator over P_2O_5 under vacuum for 24 h. The differences in mass of the vials before addition and after drying were then calculated. A mean solubility (g L^{-1}) value for the three vials was determined and is presented in Table 1.

1,12-Dicarba-closo-dodecaboranyl-1,12-bis(diphenylmethylphosphonium) iodide 5

To a solution of **4** (0.723 g, 1.41 mmol) in THF (5 mL) was added iodomethane (2.00 mL, 32.1 mmol). The solution was stirred and heated under reflux overnight. The precipitate that formed was collected by filtration and washed with THF to yield **5** as a colorless powder (1.12 g, 99%). ^{1}H NMR (400.1 MHz, DMF-d_7) δ 8.29 (m, 8H, Ph), 8.05 (m, 4H, Ph), 7.90 (m, 8H, Ph), 3.31 (d, $^2J_{PH}$ = 13.3 Hz, 6H, CH_3). ^{11}B{^{1}H} NMR (128.4 MHz, DMF-d_7) δ −11.27 (br s, 10B). ^{13}C{^{1}H} NMR (100.6 MHz, DMSO-d_6) δ 136.2 (br s, Ph), 134.0 (br s, Ph), 130.1 (br s, Ph), 115.3 (br d, $^1J_{PC}$ = 88 Hz, Ph), 76.3 (br d, $^1J_{PC}$ = 54 Hz, C_{cage}P), 6.9 (d, $^1J_{PC}$ = 56 Hz, CH_3). ^{31}P{^{1}H} NMR (162.0 MHz, DMF-d_7) δ 27.8 (s, 2P). *m/z* (ESI-MS, +ve) 271.6 $[M-2I]^{2+}$. Calcd for $C_{28}H_{36}B_{10}I_2P_2{\cdot}H_2O$: C, 41.29; H, 4.70. Found: C, 41.28; H, 4.36.

Tetraethylene glycol bis(1,12-dicarba-closo-dodecaboranyldiphenylphosphonium) iodide 10

To a stirred solution of **6** (0.718 g, 2.19 mmol) in DMF (3 mL) was added tetraethyleneglycol diiodide (0.451 g, 1.09 mmol). The solution was heated at 120 °C for 40 h and allowed to cool to room temperature at which point the crude material solidified. The solid was redissolved in DMF (50 mL) and washed with *n*-hexane (3 × 50 mL) and the *n*-hexane layers were discarded. The DMF was removed in vacuo and to the residue was added acetone (2 mL). The solution was triturated with diethyl ether (5 mL) at which point the product immediately precipitated from the solution. The solid was collected by filtration, washed with acetone (2 mL) and diethyl ether (2 mL), and air-dried. The solid was further dried under vacuum over P_2O_5 to afford **10** as a dull-gray powder (0.558 g, 48%). ^{1}H (400.1 MHz, DMSO-d_6) δ 8.01 (dd, $^3J_{HH}$ = 7.8 Hz, $^3J_{PH}$ = 12.7 Hz, 8H, Ph), 7.92 (t, $^3J_{HH}$ = 8.1 Hz, 4H, Ph), 7.74 (dt, $^3J_{HH}$ = 7.6 Hz, $^4J_{PH}$ = 3.9 Hz, 8H, Ph), 4.32 (br s, 2H, C_{cage}H), 3.70 (dt, $^3J_{HH}$ = 5.6 Hz, $^3J_{PH}$ = 12.7 Hz, 4H, PCH_2CH_2), 3.25 (dt, $^3J_{HH}$ = 5.4 Hz, $^2J_{PH}$ = 20.1 Hz, 4H, PCH_2), 2.63 (t, $^3J_{HH}$ = 3.4 Hz, 4H, CH_2O), 2.43 (t, $^3J_{HH}$ = 3.7 Hz, 4H, CH_2O). ^{11}B{^{1}H} (128.4 MHz, DMSO-d_6) δ −13.55 (overl. br s, 20B). ^{13}C{^{1}H} (100.6 MHz, DMSO-d_6) δ 135.8 (s, Ph), 134.7 (d, $^3J_{PC}$ = 10 Hz, Ph), 129.6 (d, $^2J_{PC}$ = 13 Hz, Ph), 113.9 (d, $^1J_{PC}$ = 86 Hz, Ph), 71.0 (s, C_{cage}H), 70.9 (d, $^1J_{PC}$ = 53 Hz, C_{cage}P), 69.7 (s, CH_2O), 68.7 (s, CH_2O), 63.6 (d, $^2J_{PC}$ = 5 Hz, PCH_2CH_2), 22.2 (d, $^1J_{PC}$ = 52 Hz, PCH_2). ^{31}P{^{1}H} (162.0 MHz, DMSO-d_6) δ 30.5 (s, 2P). *m/z* (ESI-MS, +ve) Calcd for $C_{36}H_{58}B_{20}O_3P_2$: 408.29283. Found: 408.29326 $[M-2I]^{2+}$. Calcd for $C_{36}H_{58}B_{20}I_2O_3P_2$: C, 40.38; H, 5.46. Found: C, 40.09; H, 5.75.

1,12-Dicarba-closo-dodecaboranyldiphenyl{1-bromo-2-[2-(2-ethoxyethoxy)ethoxy]ethyl}phosphonium bromide 7

To a stirred solution of **6** (0.975 g, 2.97 mmol) in DMF (10 mL) was added tetraethyleneglycol dibromide (4.74 g, 14.8 mmol). The solution was heated at 120 °C for 24 h and allowed to cool to room temperature. The solution was washed with *n*-hexane (3 × 50 mL) and the *n*-hexane layers were discarded. The DMF was removed in vacuo and to the residue was added water (50 mL). The solution was washed with diethyl ether (3 × 50 mL) and the organic layers were discarded. The water was removed in vacuo and the product was recrystallized from an acetone–water (1:1) mixture. The solid was collected by filtration, washed with a small amount of acetone, air-dried, and dried in a desiccator over P_2O_5 to afford **6** as a colorless powder (0.45 g, 23%). ^{1}H NMR (300.1 MHz, $CDCl_3$) δ 8.03 (m, 4H, Ph), 7.83 (m, 2H, Ph), 7.73 (m, 4H, Ph), 3.92 (dt, $^3J_{HH}$ = 5.7 Hz, $^3J_{PH}$ = 12.1 Hz, 2H, PCH_2CH_2), 3.76 (t, $^3J_{HH}$ = 6.0 Hz, 2H, CH_2O), 3.64 (dt, $^3J_{HH}$ = 5.5 Hz, $^2J_{PH}$ = 22.4 Hz, 2H, PCH_2), 3.46 (m, 4H, 2 × CH_2O), 3.24 (m, 2H, CH_2O), 3.14 (br s, 1H, C_{cage}H), 3.06 (m, 2H, CH_2O), 3.00 (m, 2H, CH_2O). ^{11}B{^{1}H} NMR (128.4 MHz, DMSO-d_6) δ −13.41 (overl. br s, 10B). ^{13}C{^{1}H} NMR (100.6 MHz, DMSO-d_6) δ 135.8 (d, $^4J_{PC}$ = 2 Hz, Ph), 134.9 (d, $^3J_{PC}$ = 10 Hz, Ph), 129.6 (d, $^2J_{PC}$ = 13 Hz, Ph), 114.0 (d, $^1J_{PC}$ = 87 Hz, Ph), 71.0 (s, C_{cage}H), 71.0 (d, $^1J_{PC}$ = 54 Hz, C_{cage}P), 70.3 (s, CH_2O), 70.1 (s, CH_2O), 69.5 (s, CH_2O), 69.4 (s, CH_2O), 69.1 (s, CH_2O), 63.7 (d, $^2J_{PC}$ = 5 Hz, PCH_2CH_2), 32.4 (s, CH_2Br), 22.3 (d, $^1J_{PC}$ = 52 Hz, PCH_2). ^{31}P{^{1}H} NMR (162.0 MHz, DMSO-d_6) δ 31.7 (s, 1P). *m/z* (ESI-MS, +ve) Calcd for $C_{22}H_{37}O_3B_{10}BrP$: 568.26251. Found: 568.26481 $[M-Br]^+$. Calcd for $C_{22}H_{37}O_3B_{10}Br_2P$: C, 40.75; H, 5.75. Found: C, 40.49; H, 5.65.

1,12-Dicarba-closo-dodecaboranyldiphenyl{1-iodo-2-[2-(2-ethoxyethoxy)ethoxy]ethyl}phosphonium iodide 8

To a stirred solution of **6** (0.560 g, 1.70 mmol) in DMF (3 mL) was added tetraethyleneglycol diiodide (1.06 g, 2.56 mmol). The solution was heated at 90 °C for 40 h and allowed to cool to room temperature. The solution was diluted to 25 mL with DMF, washed with *n*-hexane (3 × 25 mL) and the *n*-hexane layers were discarded. The DMF was removed in vacuo and to the residue was added CH_2Cl_2 (25 mL). The solution was washed with water (3 × 25 mL) and the aqueous layers were discarded. The CH_2Cl_2 was removed in vacuo to give a yellow-red solid. The product was suspended in a small amount of acetone (1 mL) and collected by filtration. The solid was then re-suspended in CH_3CN (30 mL) and the remaining solid impurities were separated by centrifugation. The supernatant was reserved and the CH_3CN was removed in vacuo. The resulting solid was re-suspended in acetone (1 mL) and was collected by filtration. The product was dried under vacuum over P_2O_5 to afford **8** as a pale-yellow powder (0.406 g, 33%). ^{1}H NMR (400.1 MHz, DMSO-d_6) δ 8.08 (m, 4H, Ph), 7.96 (m, 2H, Ph), 7.80 (m, 4H, Ph), 4.32 (br s, 1H, C_{cage}H), 3.74 (dt, $^3J_{HH}$ = 5.6 Hz, $^3J_{PH}$ = 12.5 Hz, 2H, PCH_2CH_2), 3.58 (t, $^3J_{HH}$ = 6.2 Hz,

2H, CH_2O), 3.32 (m, 4H, $CH_2O + PCH_2$), 3.28 (t, $^3J_{HH}$ = 6.6 Hz, 2H, CH_2O), 3.05 (t, $^3J_{HH}$ = 4.4 Hz, 2H, CH_2O), 2.93 (m, 2H, CH_2O), 2.87 (m, 2H, CH_2O). $^{11}B\{^1H\}$ (128.4 MHz, DMSO-d_6) δ −13.55 (overl. br s, 10B). $^{13}C\{^1H\}$ NMR (100.6 MHz, DMSO-d_6) δ 135.8 (s, Ph), 134.8 (d, $^3J_{PC}$ = 10 Hz, Ph), 129.6 (d, $^2J_{PC}$ = 13 Hz, Ph), 113.9 (d, $^1J_{PC}$ = 86 Hz, Ph), 71.0 (s, $C_{cage}H$), 70.9 (d, $^1J_{PC}$ = 53 Hz, $C_{cage}P$), 70.9 (s, CH_2O), 70.0 (s, CH_2O), 69.4 (s, CH_2O), 69.1 (overl. s, 2 × CH_2O), 63.7 (d, $^2J_{PC}$ = 5 Hz, PCH_2CH_2), 22.3 (d, $^1J_{PC}$ = 52 Hz, PCH_2), 5.6 (s, CH_2I). $^{31}P\{^1H\}$ (162.0 MHz, DMSO-d_6) δ 30.8 (s, 1P). *m/z* (ESI-MS, +ve) Calcd for $C_{22}H_{37}O_3B_{10}IP$: 615.25227. Found: 615.25347 $[M-I]^+$. Calcd for $C_{22}H_{37}B_{10}I_2O_3P\cdot(CH_3)_2CO$: C, 37.51; H, 5.41. Found: C, 37.19; H, 5.50.

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References and notes

1. Fantin, V. R.; Leder, P. *Oncogene* **2006**, *25*, 4787.
2. Galeano, E.; Nieto, E.; Garcia-Perez, A. I.; Delgado, M. D.; Pinilla, M.; Sancho, P. *Leuk. Res.* **2005**, *29*, 1201.
3. McKeage, M. J.; Maharaj, L.; Berners-Price, S. J. *Coord. Chem. Rev.* **2002**, *232*, 127.
4. Modica-Napolitano, J. S.; Aprille, J. R. *Adv. Drug Delivery Rev.* **2001**, *49*, 63.
5. Modica-Napolitano, J. S.; Nalbandian, R.; Kidd, M. E.; Nalbandian, A.; Nguyen, C. C. *Cancer Lett.* **2003**, *198*, 59.
6. Rowe, T. C.; Weissig, V.; Lawrence, J. W. *Adv. Drug Delivery Rev.* **2001**, *49*, 175.
7. Takasu, K.; Shimogama, T.; Saiin, C.; Kim, H.-S.; Wataya, Y.; Brun, R.; Ihara, M. *Chem. Pharm. Bull.* **2005**, *53*, 653.
8. Modica-Napolitano, J. S.; Aprille, J. R. *Cancer Res.* **1987**, *47*, 4361.
9. Madar, I.; Anderson, J. H.; Szabo, Z.; Scheffel, U.; Kao, P.-F.; Ravert, H. T.; Dannals, R. F. *J. Nucl. Med.* **1999**, *40*, 1180.
10. Yokoyama, K.; Miyatake, S.-I.; Kajimoto, Y.; Kawabata, S.; Doi, A.; Yoshida, T.; Asano, T.; Kirihata, M.; Ono, K.; Kuroiwa, T. *J. Neuro-Oncol.* **2006**, *78*, 227.
11. Barth, R. F.; Coderre, J. A.; Vicente, M. G. H.; Blue, T. E. *Clin. Cancer Res.* **2005**, *11*, 3987.
12. Soloway, A. H.; Tjarks, W.; Barnum, B. A.; Rong, F.-G.; Barth, R. F.; Codogni, I. M.; Wilson, J. G. *Chem. Rev.* **1998**, *98*, 1515.
13. Ioppolo, J. A.; Clegg, J. K.; Rendina, L. M. *Dalton Trans.* **2007**, 1982.
14. Adams, D. M.; Ji, W.; Barth, R. F.; Tjarks, W. *Anticancer Res.* **2000**, *20*, 3395.
15. Calabrese, G.; Gomes, A. C. N. M.; Barbu, E.; Nevell, T. G.; Tsibouklis, J. *J. Mater. Chem.* **2008**, *18*, 4864.
16. Fauchere, J. L.; Kim Quang, D.; Jow, P. Y. C.; Hansch, C. *Experientia* **1980**, *36*, 1203.
17. Valliant, J. F.; Guenther, K. J.; King, A. S.; Morel, P.; Schaffer, P.; Sogbein, O. O.; Stephenson, K. A. *Coord. Chem. Rev.* **2002**, *232*, 173.
18. Crossley, E. L.; Caiazza, D.; Rendina, L. M. *Dalton Trans.* **2005**, 2825.
19. Chen, W.; Diaz, M.; Rockwell, J. J.; Knobler, C. B.; Hawthorne, M. F. C. R. *Acad. Sci., Ser. IIc: Chim.* **2000**, *3*, 223.
20. Kalinin, V. N.; Rys, E. G.; Tyutyunov, A. A.; Starikova, Z. A.; Korlyukov, A. A.; Ol'shevskaya, V. A.; Sung, D. D.; Ponomaryov, A. B.; Petrovskii, P. V.; Hey-Hawkins, E. *Dalton Trans.* **2005**, 903.
21. Fox, M. A.; Goeta, A. E.; Hughes, A. K.; Johnson, A. L. *J. Chem. Soc., Dalton Trans.* **2002**, 2132.
22. Drechsel, K.; Lee, C. S.; Leung, E. W.; Kane, R. R.; Hawthorne, M. F. *Tetrahedron Lett.* **1994**, *35*, 6217.
23. Busby, D. C.; Hawthorne, M. F. *Inorg. Chem.* **1982**, *21*, 4101.
24. Ioppolo, J. A.; Kepert, C. J.; Price, D. J.; Rendina, L. M. *Aust. J. Chem.* **2007**, *60*, 816.
25. Fox, M. A.; MacBride, J. A. H.; Wade, K. *Polyhedron* **1997**, *16*, 2499.
26. Teixidor, F.; Angles, P.; Vinas, C. *Inorg. Chem.* **1999**, *38*, 3605.
27. Yoo, J.; Hwang, J.-W.; Do, Y. *Inorg. Chem.* **2001**, *40*, 568.
28. Powell, C. L.; Schulze, M.; Black, S. J.; Thompson, A. S.; Threadgill, M. D. *Tetrahedron Lett.* **2007**, *48*, 1251.
29. Schaeck, J. J.; Kahl, S. B. *Inorg. Chem.* **1999**, *38*, 204.
30. Plesek, J.; Hermanek, S. *Chem. Ind.* **1973**, 381.
31. Ametamey, S. M.; Honer, M.; Schubiger, P. A. *Chem. Rev.* **2008**, *108*, 1501.
32. Nunez, R.; Vinas, C.; Teixidor, F.; Sillanpaa, R.; Kivekas, R. *J. Organomet. Chem.* **2002**, *657*, 224.
33. Teixidor, F.; Nunez, R.; Vinas, C.; Sillanpaeae, R.; Kivekaes, R. *Inorg. Chem.* **2001**, *40*, 2587.
34. King, A. S.; Ferguson, G.; Britten, J. F.; Valliant, J. F. *Inorg. Chem.* **2004**, *43*, 3507.
35. Pedersen, O., Ed. *Pharmaceutical Chemical Analysis: Methods for Limit Tests and Identifications*; CRC Press, Taylor and Francis Group: Boca Raton, Florida, USA, 2006.
36. van Alem, K.; Belder, G.; Lodder, G.; Zuilhof, H. *J. Org. Chem.* **2005**, *70*, 179.
37. Tsiakopoulos, N.; Damianakos, C.; Karigiannis, G.; Vahliotis, D.; Papaioannou, D.; Sindona, G. *ARKIVOC* **2002**, *13*, 79.
38. Mills, O. S.; Mooney, N. J.; Robinson, P. M.; Watt, C. I. F.; Box, B. G. *J. Chem. Soc., Perkin Trans. 2* **1995**, 697.