Tumor-Targeted Boranes. 4.[1] Synthesis of Nitroimidazole–Carboranes with Polyether–Isoxazole Links

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Carboranes targeted to specific tumor tissues are important for boron neutron capture therapy (BNCT) of cancer. Previous attempts to use isoxazolylphenyl-linked nitroimidazole–carboranes for targeting to hypoxic tumors were hampered by the low polarity and very low aqueous solubility of the compounds. Syntheses of polyether-linked nitroimidazole–isoxazole–carborane **17**, **25**, and **26** *via* 1,3-dipolar cycloaddition of appropriate nitroimidazole–alkynes with nitrile oxides derived from aliphatic aldehyde oximes linked by a varying number of water-solubilizing ether units to carborane have been developed. The stabilities of the nitrile oxides were much less than that of the corresponding 4-(carboranylmethoxy)phenyl nitrile oxide and depended on their structure. The yields of isoxazoles varied accordingly and cycloaddition failed when eight ether units were included in the chain. Compounds **17**, **25**, and **26**, with four, five, and six ether units, respectively, had increasingly convenient physical properties to permit biological evaluation.

Introduction

Boron neutron capture therapy (BNCT) is of increasing interest for the treatment of cancer.[2–5] Naturally occurring boron comprises two stable isotopes. ^{11}B, present at 80% abundance, is a convenient nucleus for NMR studies in vitro (sensitivity $0.17 \times {}^1H$, $I = 3/2$). However, when ^{10}B is irradiated with low-energy ("thermal") neutrons, the ^{10}B nucleus captures a neutron and an [n,α] reaction ensues, giving ^7Li and ^4He nuclei, with kinetic energy (2.31 MeV). With this kinetic energy, the α-particles have ranges comparable with one cell diameter in biological tissue. Thus damage should be limited to cells containing the boron. Major endogenous nuclei (^1H, ^{12}C, ^{14}N, ^{16}O) have relatively very small nuclear cross-sections for neutron capture. Failures in early clinical studies of BNCT have been attributed[6–8] to inadequate concentrations of ^{10}B in the tumor tissue at the time of irradiation with neutrons or to lack of selectivity of biodistribution of ^{10}B, leading to damage to normal tissues.

1-Substituted 2-nitroimidazoles are known to be selectively retained in poorly vascularized hypoxic tumor tissue by reductive metabolism to electrophiles.[9–14] As part of a program of synthesis and evaluation of nitroimidazoles in the treatment of cancer,[15–20] we have proposed that compounds containing 10–12 boron atoms linked to 2-nitroimidazole would form a useful method of concentrating boron in solid tumors. Derivatives of 1,2-dicarba-*closo*-dodecaborane(12) ("carborane", Figure 1) were selected for linkage to 2-nitroimidazole in view of their good chemical stability relative to other boron clusters and their predicted metabolic inertness. Prior to our first preliminary communication,[21] no synthesis of a nitroimidazole–carborane had been published in the journal literature, although reports of a short-chain nitroimidazole–*nido*-carborane[22] and a short-chain nitroimidazole–*meta*-carborane[23] have been made in proceedings of conferences.

In a previous paper,[20] we reported the 1,3-dipolar cycloaddition of a variety of nitroimidazole-alkene and -alkyne dipolarophiles with the highly stable 1,3-dipole, 4-(carboranylmethoxy)benzonitrile oxide. Although this strategy was successful in linking the potentially oxidizing 2-nitroimidazole with the carborane to produce the required nitroimidazole–carboranes, these latter materi-

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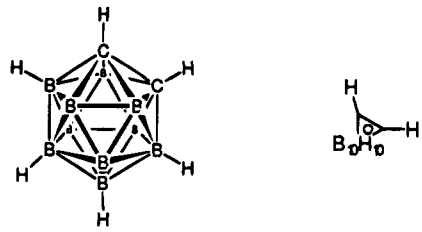
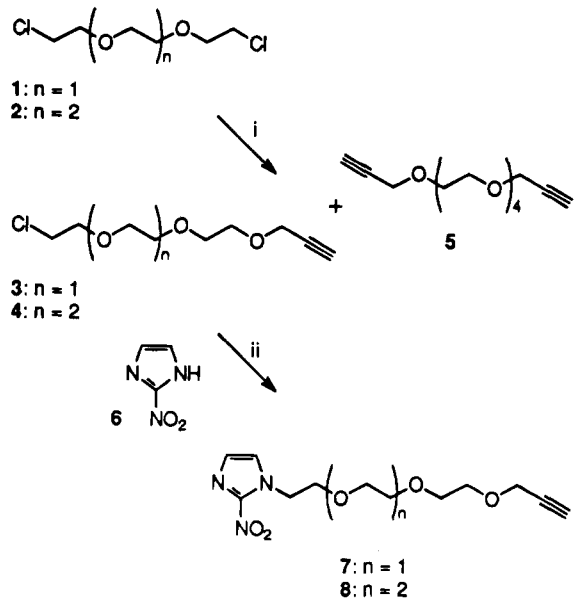


Figure 1. Representations of the structure of 1,2-dicarba-*closo*-dodecaborane(12) ("carborane"). All boron atoms have one hydrogen atom attached but some have been omitted from the diagram for clarity.

Scheme 1. Synthesis of the Polyether-Linked Nitroimidazole-Alkynes 7 and 8[a]



[a] Reagents and conditions: (i) HC≡CCH$_2$OH/NaH/DMF/130 °C; (ii) KOBu^t/DMF/120 °C.

als were insufficiently soluble in aqueous media to permit satisfactory evaluation of their tumor-localizing ability. Cycloadditions of alternative aliphatic carborane-nitrile oxides without the lipophilic aromatic ring have therefore been investigated and are reported here.

Synthesis of NitroimidazoleCarboranes

To provide nitroimidazole-alkynes with water-solubilizing oxyethylene units, the reaction sequences shown in Scheme 1 were adopted. As we reported previously,[20] treatment of 1,2-bis(2-chloroethoxy)ethane (**1**) with 1 equiv of the alkoxide of propargyl alcohol in hot DMF gave a good yield of the monoalkyne **3**. Similar treatment of the higher oligomer **2** afforded the longer-chain monoalkyne **4** in moderate yield, along with a small quantity of the bis-alkyne **5**. The yield of this bis-alkyne was increased in experiments in which an excess of alkoxide was employed. Modification of our previous conditions[20] for the alkylation of the potassium salt of 2-nitroimidazole (**6**) with **3** facilitated an improvement in the yield of the nitroimidazole-alkyne **7** from 43 to 66%. The analogous alkylation of **6** with **4** gave the longer-chain nitroimidazole-alkyne **8** with three ethylenedioxy units.

Construction of the oximes, precursors of the corresponding aliphatic carborane-nitrile oxides, was more challenging. Scheme 2 shows a sequence of model experiments to test the feasibility of use of the aliphatic carborane-nitrile oxides. 1,3-Dithiane (**9**) was lithiated and the anion was alkylated with bromochlorobutane (**10**), giving exclusively the known[24] (chlorobutyl)dithiane (**11**) in high yield. Substitution of chloride by propargyl alkoxide at elevated temperature in dimethylformamide gave the required dithiane-alkyne **13**. This was accompanied by an apparently unavoidable elimination reaction of some of the substrate chlorobutyldithiane to furnish significant amounts of the butenyldithiane **12**. This side reaction is probably due to direct E2 elimination caused by the strongly basic alkoxide. The dithiane-carborane **14** was formed in respectable yield in the usual way[20] by prolonged treatment of alkyne **13** with decaborane(14) ($B_{10}H_{14}$) in boiling acetonitrile, a Lewis base. Thus our use[20] of dithioacetal as a protecting group for aromatic aldehydes against the ravages of this potent reductant can be extended to analogous synthons for aliphatic aldehydes. However, mercury(II)-catalyzed deprotection, which was so successful for the aromatic case,[20] failed completely for the aliphatic dithioacetal, giving only unidentifiable products of degradation. Deprotection was, however, effected by the *N*-bromosuccinimide/silver ion method, although rapid quench with thiosulfate was needed to prevent degradation of the aldehyde **15** under these oxidizing conditions. The oxime **16** was formed as an equimolar mixture of geometrical isomers, as revealed by ^{1}H NMR. Unlike its aromatic counterpart,[20] the corresponding nitrile oxide was not isolable but formation by oxidation of **16** with sodium hypochlorite and reaction *in situ* in a two-phase aqueous dichloromethane system with the nitroimidazole-alkyne **7** gave the model nitroimidazole-isoxazole-carborane **17** in good yield.

On the basis of this successful demonstration of the 1,3-dipolar cycloaddition of a nitroimidazole-alkyne with an aliphatic carborane-nitrile oxide, attention was turned to the incorporation of potentially water-solubilizing multiple OCH_2CH_2O units in the carborane arm of the target structures (Scheme 3). With the aim of introducing two ether oxygens into this chain, 1,3-dithiane (**9**) was lithiated and alkylated with bis(2-chloroethyl) ether (**18**) in tetrahydrofuran, giving the ether-linked (haloalkyl)dithiane **19** in good yield, despite the usually lower reactivity of 3-oxaalkyl halides. Substitution then afforded the desired bis-ether-linked dithiane-alkyne **21**. As predicted by the model tetramethylene system, elimination was a serious problem, giving the enol ether **20** in 36% yield. Clearly, the alkoxide is sufficiently basic even to remove the proton adjacent to ether oxygen to initiate E2 elimination. Conversion of the alkyne **21** to the dithiane-carborane **22** with decaborane(14) was followed by deprotection with *N*-bromosuccinimide/silver nitrate to furnish the carborane aldehyde **23**. This aldehyde was found to be unstable to prolonged storage and was treated immediately with hydroxylamine in anhydrous ethanol, giving an equimolar mixture of *Z* and *E* stereoisomers of the carborane-oxime **24** virtually quantitatively.

With this bis-ether-linked carborane-oxime **24** now available, dipolar cycloaddition with the nitroimidazole alkynes **7** and **8** with three and four ether groups, respectively, was investigated. Oxidative elimination of the mixture of stereoisomers of **24** with sodium hypochlorite gave the corresponding nitrile oxide which was allowed to react in situ with alkynes **7** and **8**. The yield of the shorter-chain nitroimidazole-isoxazole-carborane

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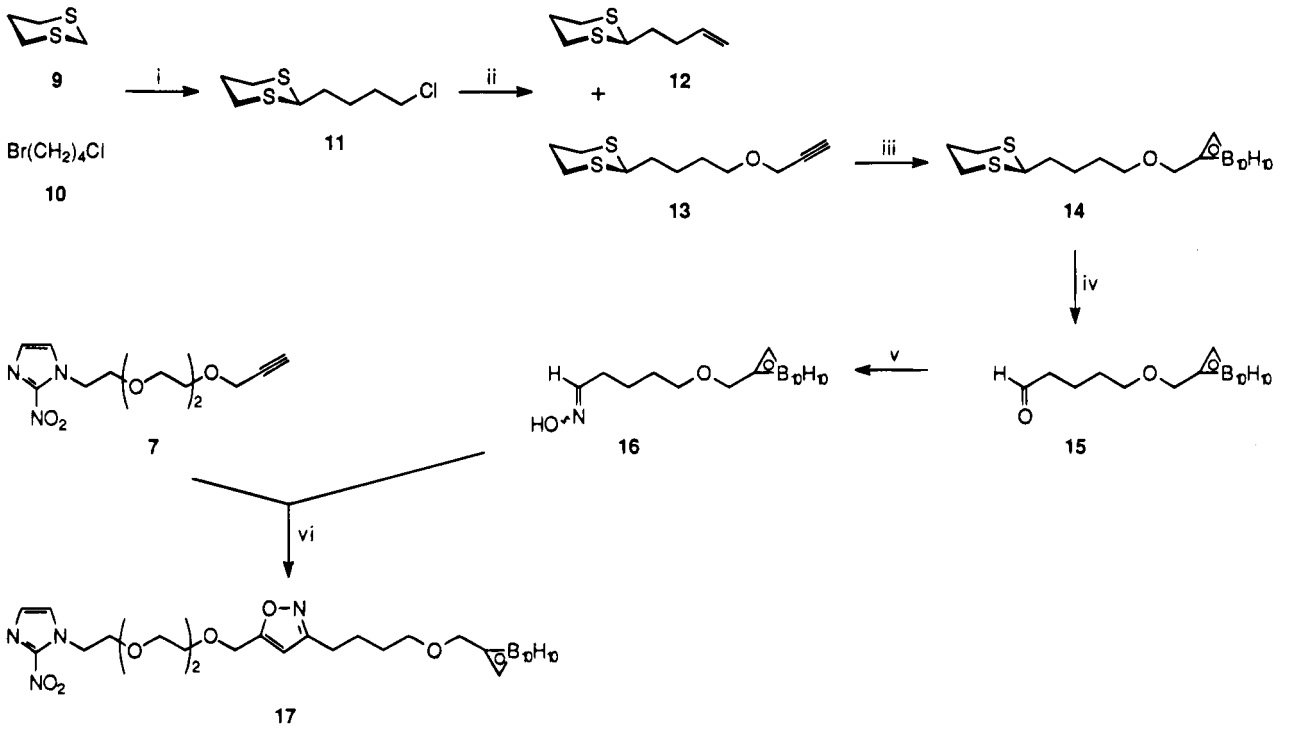
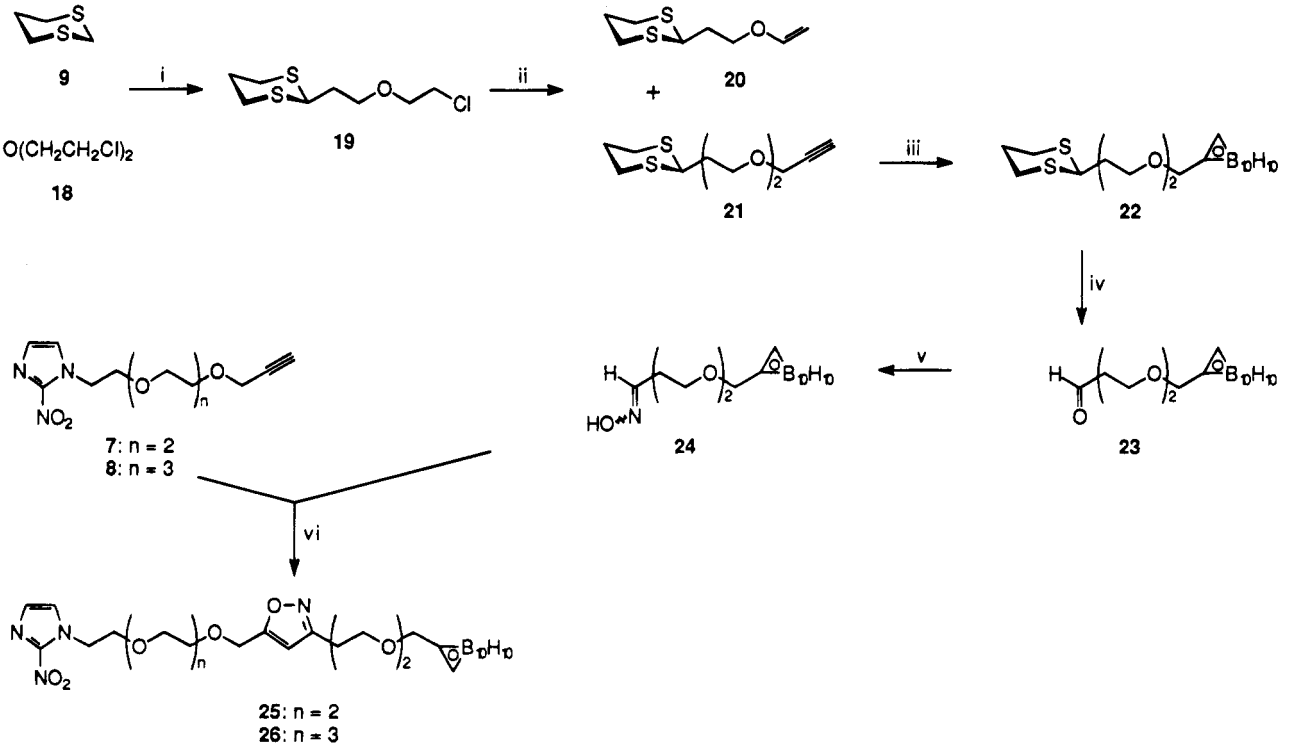
Scheme 2. Model Experimental Sequence for the Synthesis of the Nitroimidazole–Isoxazole–Carborane 17[a]



[a] Reagents and conditions: (i) NaH/THF/−78 °C → −20 °C; (ii) HC≡CCH$_2$OH/NaH/DMF/100 °C; (iii) $B_{10}H_{14}$/MeCN/reflux; (iv) *N*-bromosuccinimide/$AgNO_3$/water/MeCN; (v) NH_2OH·HCl/Na_2CO_3/EtOH; (vi) NaOCl/water/CH_2Cl_2.

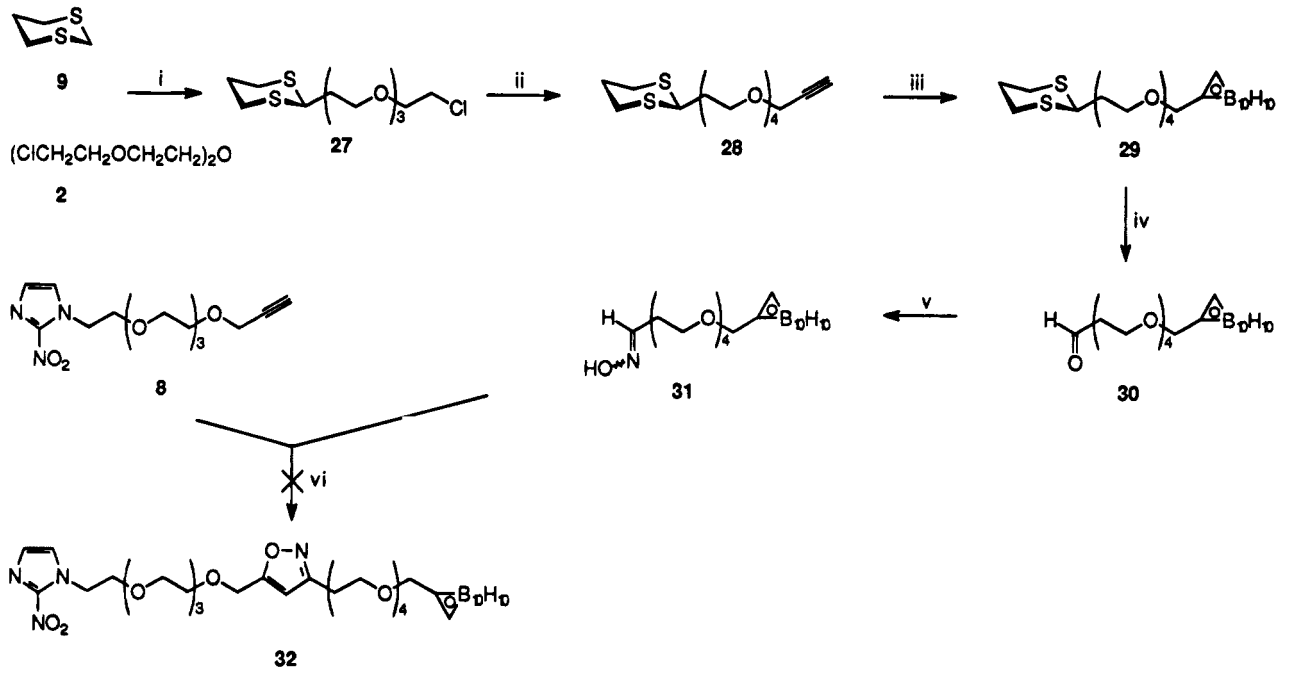
Scheme 3. Synthesis of Target Polyether-Linked Nitroimidazole–Isoxazole–Carboranes 25 and 26[a]



[a] Reagents and conditions: (i) NaH/THF/−78 °C → −20 °C; (ii) NaH/HC≡CCH$_2$OH/DMF/120 °C; (iii) $B_{10}H_{14}$/MeCN/reflux; (iv) *N*-bromosuccinimide/$AgNO_3$/water/MeCN; (v) NH_2OH·HCl/Na_2CO_3/EtOH; (vi) NaOCl/water/CH_2Cl_2.

25 was not able to be raised above a disappointing 13% in experiments where reaction times and concentrations were varied. On the other hand, the longer-chain analogue **26** was formed in 36% yield, based on the oxime **24**, which corresponds to 90% when compared with the amount of nitroimidazole–alkyne **8** not recovered from the reaction mixture. Alternative oxidants, such as chloramine-T, were less effective. The oxime was completely consumed in all experiments and no material containing the nitrile oxide group could be detected amongst the products of the reaction. These observations, coupled with the high recovery of the alkyne, point

Scheme 4. Attempted Synthesis of Extended Polyether–Linked Nitroimidazole–Isoxazole–Carborane 32[a]



[a] Reagents and conditions: (i) NaH/THF/−78 °C → −20 °C; (ii) NaH/HC≡CCH$_2$OH/DMF/120 °C; (iii) $B_{10}H_{14}$/MeCN/reflux; (iv) *N*-bromosuccinimide/$AgNO_3$/water/MeCN; (v) NH_2OH·HCl/Na_2CO_3/EtOH.

to the instability of the intermediate nitrile oxide being the cause of the relatively modest yields of isoxazoles.

Since the physical properties (polarity, solubility, etc.) of nitroimidazole–carboranes **25** and **26**, with five and six ether oxygens, respectively, were considerably improved with respect to the aryl analogues previously reported,[20] synthesis of the extended analogue **32**, with eight ether oxygens, was attempted (Scheme 4). Alkylation of the anion of 1,3-dithiane (**9**) with dichloro compound **2** at ambient temperature gave the (trioxachloroalkyl)dithiane **27**. The decreased reactivity of the polyether chain, as compared with polymethylene analogues, was reflected in the low (25%) yield of the dithiane–alkyne **28** through substitution with propynoxide ion in hot dimethylformamide. The formation of the carborane **29** under the usual conditions (decaborane(14), refluxing acetonitrile) was, however, unaffected and proceeded relatively efficiently. Deprotection was again effected by bromination, giving carborane–aldehyde **30** which was converted immediately to its oxime **31**. However, the sensitivity of the cycloaddition reaction to the structure of the oxime (and hence the nitrile oxide) was revealed in the failure to produce isolable quantities of the desired nitroimidazole–isoxazole–carborane **32** upon treatment of **31** with the nitroimidazole–alkyne **8** and sodium hypochlorite in aqueous dichloromethane. Much unreacted alkyne **8** was detected by TLC, although the oxime **31** was consumed, suggesting that the nitrile oxide derived from **31** was particularly unstable.

Conclusions

The present work has demonstrated the feasibility of extending the known[20] 1,3-dipolar cycloaddition of carborane-substituted aryl nitrile oxides with nitroimidazole–alkynes to the use of the considerably less stable aliphatic carborane–nitrile oxides. The synthesis of the nitroimidazole–carborane **26** in adequate yield based on the relatively expensive starting materials 2-nitroimidazole (overall yield 36%) and decaborane(14) (overall yield 18%) has enabled sufficient quantities of this relatively polar carborane to be available for biological evaluation.

Experimental Section

The solvent for NMR spectra was $CDCl_3$. The external standard for ^{11}B NMR was BF_3·Et_2O. Purity for all novel compounds was assessed by elemental microanalysis or by ^1H NMR; the ^1H NMR spectra for compounds **4**, **5**, **7**, **8**, **12-17**, **19-31** are available as supplementary material. Brine refers to saturated aqueous NaCl. DMF refers to dimethylformamide; THF refers to tetrahydrofuran. Dry EtOH was dried by distillation from $Mg(OEt)_2$ immediately before use. Solutions in organic solvents were dried with anhydrous $MgSO_4$. Distillations were effected using a Kugelrohr apparatus and bps refer to the temperature of the oven. The stationary phase for chromatography was silica gel. Solvents were evaporated under reduced pressure. 3-(2-(2-(2-Chloroethoxy)ethoxy)-ethoxy)propyne (**3**) was prepared as previously described by us.[16]

3-(2-(2-(2-(2-Chloroethoxy)ethoxy)ethoxy)ethoxy)-propyne (4) and Bis(2-(2-(prop-2-ynyloxy)ethoxy)ethyl) Ether (5). Sodium hydride (1.20 g, 50 mmol) was stirred with propyn-3-ol (2.80 g, 50 mmol) in dry DMF for 30 min. Bis(2-(2-chloroethoxy)ethyl) ether **2** (11.55 g, 50 mmol) was added dropwise and the mixture was stirred at 130 °C for 2 h. The solvent was evaporated and the residue, in CH_2Cl_2, was washed with water and dried. The evaporation residue was subjected to chromatography (pentane/Et_2O 3:1, 2:1, and then 1:1). From the first fraction was recovered **2** (3.25 g, 23%). From the second fraction was obtained the monoalkyne **4** (3.67 g, 29%) as a colorless oil: IR ν 2120 cm^{-1}; NMR δ_H 2.43 (1 H, t, J = 2.4 Hz), 3.6–3.8 (16 H, m), 4.21 (2 H, d, J = 2.4 Hz); mass spectrum (CI) m/z 251.1050 (M + H) ($C_{11}H_{20}{}^{35}ClO_4$ requires 251.1050). From the third fraction was isolated the bis-alkyne **5** (950 mg, 7%) as a colorless oil: IR ν 2130 cm^{-1}; NMR δ_H 2.44 (2 H, t, J = 2.4 Hz), 3.67 (8 H, s), 3.69 (8 H, m), 4.21 (4 H, d, J = 2.4 Hz); mass spectrum (CI) m/z 271.1545 (M + H) ($C_{11}H_{20}{}^{35}ClO_4$ requires 271.1545).

2-Nitro-1-(2-(2-(2-(propyn-3-yloxy)ethoxy)ethoxy)ethyl)imidazole (7). 2-Nitroimidazole (**6**) (570 mg, 5 mmol) was stirred at 130 °C with KOBu^t (560 mg, 5 mmol) in DMF (10 mL) for 1 h then cooled to 80 °C. KI (50 mg) and the alkyne **3** (1.03 g, 5 mmol) were added and the mixture was stirred at 120 °C for 16 h. The solvent was evaporated and the residue

was treated with water (10 mL) and then extracted with ether. Chromatography (CH_2Cl_2) of the evaporation residue gave the nitroimidazole–alkyne **7** (930 mg, 66%) as a pale yellow oil: IR ν 2120 cm^{-1}; NMR δ_H 2.45 (1 H, t, J = 2.4 Hz), 3.60 (4 H, s), 3.6–3.7 (4 H, m), 3.86 (2 H, t, J = 4.9 Hz), 4.20 (2 H, d, J = 2.4 Hz), 4.63 (2 H, t, J = 4.9 Hz), 7.14 (1 H, s), 7.29 (1 H, s); mass spectrum (CI) m/z 284.1246 (M + H) ($C_{12}H_{18}N_3O_5$ requires 284.1246).

2-Nitro-1-(2-(2-(2-(2-(propyn-3-yloxy)ethoxy)ethoxy)-ethoxy)ethyl)imidazole (8). 2-Nitroimidazole (**6**) (450 mg, 4 mmol) was stirred at 120 °C with $KOBu^t$ (450 mg, 4 mmol) in DMF (5 mL) for 15 min then cooled to 80 °C. NaI (40 mg) and the alkyne **4** (1.00 g, 4 mmol) were added and the mixture was stirred at 120 °C for 16 h. The evaporation residue was treated with water (20 mL) and was extracted with CH_2Cl_2. Chromatography (CH_2Cl_2/Et_2O 5:1) of the evaporation residue gave the nitroimidazole–alkyne **8** (520 mg, 40%) as a pale yellow oil: NMR δ_H 2.44 (1 H, t, J = 2.4 Hz), 3.6–3.7 (12 H, m), 3.86 (2 H, t, J = 5.0 Hz), 4.19 (2 H, d, J = 2.4 Hz), 4.63 (2 H, t, J = 5.0 Hz), 7.13 (1 H, s), 7.36 (1 H, s); mass spectrum (CI) m/z 328.1509 (M + H) ($C_{14}H_{22}N_3O_6$ requires 328.1509).

2-(4-Chlorobutyl)-1,3-dithiane (11). Butyllithium (2 M in hexanes, 20 mL, 40 mmol) was added to 1,3-dithiane (**9**) (4.80 g, 40 mmol) in THF (100 mL) and the mixture was stirred for 1 h, before being cooled to −78 °C. 1-Bromo-4-chlorobutane (**10**) (8.58 g, 60 mmol) was added and the mixture was stirred at −20 °C for 18 h. The evaporation residue, in CH_2Cl_2, was washed with water and dried. Distillation gave 2-(4-chlorobutyl)-1,3-dithiane (**11**) (6.88 g, 82%) as a colorless liquid: $bp_{0.5}$ 170 °C (lit.[24] $bp_{0.17}$ 110 °C); NMR δ_H 1.6–1.9 (7 H, m), 2.11 (1 H, m), 2.85 (4 H, m), 3.54 (2 H, t, J = 6.5 Hz), 4.06 (1 H, t, J = 6.5 Hz).

2-(But-1-en-4-yl)-1,3-dithiane (12) and 2-(4-(Propyn-3-yloxy)butyl)-1,3-dithiane (13). Propyn-3-ol (220 mg, 4 mmol) was added to sodium hydride (96 mg, 4 mmol) in dry DMF (10 mL) and the mixture was stirred for 30 min. The (chloroalkyl)dithiane **11** (840 mg, 4 mmol) was added and the mixture was heated at 100 °C for 2 h. The evaporation residue, in CH_2Cl_2, was washed with water and dried. The solvent was evaporated and the residue was subjected to chromatography (pentane/CH_2Cl_2 4:1 and then 3:1). From the earlier fraction was obtained 2-(but-1-en-4-yl)-1,3-dithiane (**12**) (240 mg, 34%) as a colorless oil: NMR δ_H 1.85 (2 H, br q, J = 7 Hz), 1.87 (1 H, m), 2.15 (1 H, m), 2.27 (2 H, br q, J = 7 Hz), 2.85 (4 H, m), 4.04 (1 H, t, J = 7.0 Hz), 5.02 (1 H, br d, J = 10 Hz), 5.07 (1 H, br d, J = 17 Hz), 5.80 (1 H, ddt, J = 17.0, 10.3, 6.6 Hz); mass spectrum (EI) m/z 174.0537 (M) ($C_8H_{14}S_2$ requires 174.0537). From the later fraction was isolated 2-(4-(propyn-3-yloxy)butyl)-1,3-dithiane (**13**) (480 mg, 52%) as a colorless oil: NMR δ_H 1.6–2.0 (7 H, m), 2.12 (1 H, m), 2.42 (1 H, t, J = 2.4 Hz), 2.85 (4 H, m), 3.52 (2 H, t, J = 6.2 Hz), 4.05 (1 H, t, J = 6.9 Hz), 4.13 (2 H, d, J = 2.4 Hz); mass spectrum (EI) m/z 230.0799 (M) ($C_{11}H_{18}OS_2$ requires 230.1799).

2-(4-(1,2-Dicarba-*closo*-dodecaboran(12)-1-ylmethoxy)-butyl)-1,3-dithiane (14). Decaborane(14) ($B_{10}H_{14}$) (210 mg, 1.7 mmol) was stirred with dry MeCN (10 mL) for 3 h. The dithiane–alkyne **13** (400 mg, 1.7 mmol) was added and the mixture was boiled under reflux for 3 d. The solvent was evaporated. Chromatography (pentane/CH_2Cl_2 10:1) gave the carborane-dithiane **14** (290 mg, 49%) as a white solid: mp 72–74 °C; NMR δ_H 2.3 (10 H, br q, J_{B-H} = 150 Hz), 1.6–2.2 (8 H, m), 2.85 (4 H, m), 3.46 (2 H, t, J = 5.3 Hz), 3.83 (2 H, s), 3.98 (1 H, br s), 4.05 (1 H, t, J = 6.8 Hz). Anal. ($C_{11}H_{28}B_{10}OS_2$) C, H.

4-(1,2-Dicarba-*closo*-dodecaboran(12)-1-ylmethoxy)-pentanal (15). *N*-Bromosuccinimide (1.25 g, 7 mmol) and $AgNO_3$ (1.36 g, 8 mmol) in MeCN (16 mL) and water (4 mL) were added to the carborane–dithiane **14** (480 mg, 1.4 mmol) in MeCN (16 mL) and water (4 mL), and the mixture was stirred for 10 min. Saturated aqueous Na_2SO_3 (2.0 mL) was added, followed after 1 min by saturated aqueous Na_2CO_3 (2.0 mL), followed after 1 min by brine (2.0 mL). The suspension was filtered through Celite. The filtrate was treated with brine (20 mL) and extracted with CH_2Cl_2. Chromatography (CH_2Cl_2) of the evaporation residue gave the carborane–aldehyde **15** (260 mg, 71%) as a colorless oil: IR ν 1725, 2590 cm^{-1}; NMR δ_H 2.2 (10 H, br q, J_{B-H} = 150 Hz), 1.63 (4 H, m), 2.48 (2 H, dt, J = 1.4, 6.8 Hz), 3.47 (2 H, t, J = 5.9 Hz), 3.84 (2 H, s), 3.94 (1 H, br s), 9.78 (1 H, t, J = 1.4 Hz); mass spectrum (CI) m/z 259.2701 (M + H) ($C_8H_{23}{}^{10}B_2{}^{11}B_8O_2$ requires 259.2701)

5-(1,2-Dicarba-*closo*-dodecaboran(12)-1-ylmethoxy)-pentanal Oxime (16). The carborane–aldehyde **15** (260 mg, 1 mmol) was stirred with hydroxylamine hydrochloride (350 mg, 5 mmol) and anhydrous Na_2CO_3 (270 mg, 2.5 mmol) in dry EtOH (10 mL) for 24 h. Further portions of hydroxylamine hydrochloride (350 mg, 5 mmol) and Na_2CO_3 (270 mg, 2.5 mmol) were added, and stirring was continued for a further 18 h. The solvent was evaporated and the residue, in CH_2Cl_2, was washed with water and dried. Chromatography (CH_2Cl_2) of the evaporation residue gave a mixture of *E* and *Z* isomers of the carborane–oxime **16** (221 mg, 81%) as a colorless oil: IR ν 2590, 3300 (br) cm^{-1}; NMR δ_H 1.21 (4 H, m), 2.2 (10 H, br q, J_{B-H} = 150 Hz), 2.26 (1 H, m), 2.41 (1 H, m), 3.47 (2 H, m), 3.84 (2 H, s), 3.97 (1 H, br s), 6.72 (0.5 H, t, J = 5.5 Hz), 7.42 (0.5 H, t, J = 5.8 Hz), 8.9 (0.5 H, br), 10.5 (0.5 H, br); NMR δ_C 22.51, 22.90, 28.54, 28.80, 28.93, 29.03, 57.57, 71.49, 71.68, 72.59, 151.50, 152.06; mass spectrum (FAB negative ion) m/z 273.2635 (M − H) ($C_8H_{22}{}^{10}B^{11}B_9NO_2$ requires 273.2617), 272.2654 (M − H) ($C_8H_{22}{}^{10}B_2{}^{11}B_8NO_2$ requires 272.2653).

1-(2-(2-(2-((3-(4-(1,2-Dicarba-*closo*-dodecaboran(12)-1-ylmethoxy)butyl)isoxazol-5-yl)methoxy)ethoxy)ethoxy)-ethyl)-2-nitroimidazole (17). The carborane–oxime **16** (140 mg, 0.5 mmol) and the nitroimidazole–alkyne **7** (170 mg, 0.6 mmol) in CH_2Cl_2 (5 mL) were stirred with aqueous NaOCl (8% available chlorine, 2 mL) for 2 d. Water (5 mL) was added and the mixture was extracted with CH_2Cl_2. The evaporation residue was subjected to chromatography (Et_2O and then EtOAc). From the Et_2O fraction was recovered the nitroimidazole–alkyne **7** (90 mg, 53%). From the EtOAc fraction was obtained the nitroimidazole–carborane **17** (130 mg, 47%) as a colorless gum: NMR δ_H 1.65 (4 H, m), 2.2 (10 H, br q, J_{B-H} = 150 Hz), 2.67 (2 H, t, J = 7.2 Hz), 3.48 (2 H, t, J = 6.0 Hz), 3.6–3.7 (8 H, m), 3.84 (2 H, s), 3.85 (2 H, t, J = 5.0 Hz), 3.96 (1 H, br s), 4.61 (2 H, s), 4.61 (2 H, t, J = 5.0 Hz), 6.11 (1 H, s), 7.10 (1 H, d, J = 1.0 Hz), 7.25 (1 H, d, J = 1.0 Hz); mass spectrum (FAB positive ion) m/z 557.3760 (M + H) ($C_{20}H_{39}{}^{11}B_{10}N_4O_7$ requires 557.3749).

2-(2-(2-Chloroethoxy)ethyl)-1,3-dithiane (19). Butyllithium (2 M in hexanes, 50 mL, 100 mmol) was added to 1,3-dithiane (**9**) (12.0 g, 100 mmol) in THF (250 mL) at −78 °C and the mixture was stirred at this temperature for 1 h. Bis-(2-chloroethyl) ether (**18**) (14.3 g, 100 mmol) was added and the mixture was stirred at −20 °C for 16 h. The solvent was evaporated and the residue, in CH_2Cl_2, was washed with water and dried. Distillation gave the (chloroalkyl)dithiane **19** (13.77 g, 61%) as a colorless liquid: $bp_{0.1}$ 160 °C; NMR δ_H 1.89 (1 H, m), 2.03 (2 H, dt, J = 7.0, 6.1 Hz), 2.12 (1 H, m), 2.80–2.95 (4 H, m), 3.60–3.75 (6 H, m), 4.23 (1 H, t, J = 7.0 Hz); mass spectrum m/z (CI) 227.0331 (M + H) ($C_8H_{16}{}^{35}ClOS_2$ requires 227.0331).

2-(2-(Ethenyloxy)ethyl)-1,3-dithiane (20) and 2-(2-(2-(Propyn-3-yloxy)ethoxy)ethyl)-1,3-dithiane (21). A stirred suspension of sodium hydride (1.51 g, 63 mmol) in dry DMF (60 mL) was treated with propyn-3-ol (3.47 g, 62 mmol) in dry DMF (40 mL) and the mixture was stirred for 30 min. NaI (100 mg) and the dithiane **19** (14.04 g, 62 mmol) were added and the mixture was stirred at 120 °C for 3 h. The evaporation residue, in CH_2Cl_2, was washed with water and dried. The evaporation residue was subjected to chromatography (pentane/CH_2Cl_2 1:1, and then CH_2Cl_2). From the earlier fraction was obtained 2-(2-(ethenyloxy)ethyl)-1,3-dithiane (**20**) (4.21 g, 36%) as a colorless oil: IR ν 1625 cm^{-1}; NMR δ_H 1.91 (1 H, m), 2.11 (3 H, m), 2.86 (4 H, m), 3.86 (2 H, t, J = 6.1 Hz), 4.02 (1 H, dd, J = 6.9, 2.1 Hz), 4.21 (1 H, t, J = 7 Hz), 4.21 (1 H, dd, J = 14.3, 2.1 Hz), 6.46 (1 H, dd, J = 14.3, 6.9 Hz); mass spectrum (EI) m/z 190.0486 (M) ($C_8H_{14}OS_2$ requires 190.0486). From the CH_2Cl_2 fraction was obtained the dithiane–alkyne **21** (6.20 g, 47%) as a colorless oil: NMR δ_H 1.88 (1 H, m), 2.04 (2 H, q, J = 7.0 Hz), 2.10 (1 H, m), 2.44 (1 H, t, J = 2.4 Hz), 2.85 (4 H, m), 3.65 (6 H, m), 4.21 (1 H, t, J = 7.0 Hz), 4.22 (2 H, d, J = 2.4 Hz); mass spectrum (EI) m/z 246.0748 (M) ($C_{11}H_{18}O_2S_2$ requires 246.0748).

2-(2-(2-(1,2-Dicarba-*closo*-dodecaboran(12)-1-yl)ethoxy)-ethyl)-1,3-dithiane (22). Decaborane(14) (305 mg, 2.5 mmol) was stirred with MeCN (10 mL) for 3 h. The dithiane–alkyne **21** (620 mg, 2.5 mmol) was added and the mixture was boiled under reflux for 3 d. The solvent was evaporated. Chromatography (pentane/CH_2Cl_2 1:1) gave the carborane-dithiane **22** (550 mg, 60%) as a colorless oil: IR ν 2600 cm^{-1}; NMR δ_H 1.2–3.2 (10 H, br q, J_{B-H} = 150 Hz), 1.86 (1 H, m), 1.98 (2 H, dt, J = 7.1, 5.9 Hz), 2.14 (1 H, m), 2.52 (2 H, t, J = 5.6 Hz), 2.87 (4 H, m), 3.51 (2 H, t, J = 5 Hz), 3.53 (2 H, t, J = 5.9 Hz), 4.08 (1 H, br s), 4.15 (1 H, t, J = 7.1 Hz); NMR δ_C 25.83, 30.12, 36.39, 43.88, 57.60, 67.33, 69.99, 71.28, 72.14, 72.80; mass spectrum m/z (FAB positive ion) 367.2493 (M + H) ($C_{11}H_{29}{}^{11}B_{10}O_2S_2$ requires 367.2540).

3-(2-(1,2-Dicarba-*closo*-dodecaboran(12)-1-ylmethoxy)-ethoxy)propanal (23). The carborane-dithiane **22** was treated with *N*-bromosuccinimide and $AgNO_3$ in aqueous MeCN, as for the synthesis of **16**, to give the carborane–aldehyde **23** (610 mg, 86%) as a yellow oil: IR ν 1725, 2590 cm^{-1}; NMR δ_H 2.2 (10 H, br q, J_{B-H} = 150 Hz), 2.68 (2 H, dt, J = 2.2, 6.7 Hz), 3.6 (4 H, m), 3.79 (2 H, t, J = 6.7 Hz), 3.96 (2 H, s), 4.02 (1 H, br s), 9.89 (1 H, d, J = 2.2 Hz). This material was used immediately without further purification.

3-(2-(1,2-Dicarba-*closo*-dodecaboran(12)-1-ylmethoxy)-ethoxy)propanal Oxime (24). The carborane–aldehyde **23** (450 mg, 1.6 mmol) in dry EtOH (100 mL) was treated with anhydrous Na_2CO_3 (850 mg, 8 mmol) and $HONH_2$·HCl (1.11 g, 16 mmol) for 40 h. The evaporation residue, in CH_2Cl_2, was washed with water and dried. The solvent was evaporated to give the carborane–oxime **24** (460 mg, 97%) as a pale yellow gum: IR ν 2590, 3340 (br) cm^{-1}; NMR δ_H 1.4–2.7 (10 H, br q, J_{B-H} = 150 Hz), 2.48 (1 H, q, J = 6 Hz), 2.66 (1 H, q, J = 5.5 Hz), 3.55–3.67 (6 H, m), 3.94 (1 H, s), 3.95 (1 H, s), 4.13 (1 H, br s), 5.1 (0.5 H, br), 6.81 (0.5 H, t), 7.46 (0.5 H, t, J = 5.8 Hz), 8.0 (0.5 H, br); mass spectrum (CI) m/z 290.2759 (M + H) ($C_8H_{23}{}^{10}B_2{}^{11}B_8NO_3$ requires 290.2759).

1-(2-(2-(2-((3-(2-(2-(1,2-Dicarba-*closo*-dodecaboran(12)-1-ylmethoxy)ethoxy)ethyl)isoxazol-5-yl)methoxy)ethoxy)-ethoxy)ethyl)-2-nitroimidazole (25). The carborane–oxime **24** (40 mg, 0.14 mmol) and the nitroimidazole–alkyne **7** (40 mg, 0.14 mmol) in CH_2Cl_2 (2 mL) were stirred with aqueous NaOCl (8% available chlorine, 2.5 mL) for 3 d. The mixture was extracted with CH_2Cl_2. The evaporation residue was subjected to chromatography (Et_2O and then EtOAc). From the EtOAc fraction was obtained the nitroimidazole–carborane **25** (10 mg, 13%) as a colorless gum: IR ν 2590 cm^{-1}; NMR δ_H 2.2 (10 H, br q, J_{B-H} = 150 Hz), 2.93 (2 H, t, J = 6.6 Hz), 3.60–3.75 (14 H, m), 3.86 (2 H, t, J = 5.2 Hz), 3.92 (2 H, s), 4.13 (1 H, br s), 4.60 (4 H, m), 6.15 (1 H, s), 7.10 (1 H, br s), 7.25 (1 H, br s); mass spectrum (FAB positive ion) m/z 571.3788 (M + H) ($C_{20}H_{39}{}^{10}B_2{}^{11}B_8N_4O_8$ requires 571.3771).

1-(2-(2-(2-(2-((3-(2-(2-(1,2-Dicarba-*closo*-dodecaboran-(12)-1-ylmethoxy)ethoxy)ethyl)isoxazol-5-ylmethoxy)-ethoxy)ethoxy)ethoxy)ethyl)-2-nitroimidazole (26). The carborane–oxime **24** (130 mg, 0.45 mmol) and the nitroimidazole–alkyne **8** (150 mg, 0.45 mmol) in CH_2Cl_2 (5 mL) were stirred with aqueous NaOCl (8% available chlorine, 2 mL) for 2 d. Brine was then added and the mixture was extracted with CH_2Cl_2. The evaporation residue was subjected to chromatography (Et_2O and then EtOAc). From the Et_2O fraction was recovered the nitroimidazole–alkyne **8** (90 mg, 60%). From the EtOAc fraction was obtained the nitroimidazole–carborane **26** (100 mg, 36%) as a pale yellow gum: IR ν 2590cm^{-1}; NMR δ_H 2.2 (10 H, br q, J_{B-H} = 150 Hz), 2.91 (2 H, t, J = 6.4 Hz), 3.60–3.75 (18 H, m), 3.86 (2 H, t, J = 5.0 Hz), 3.92 (2 H, s), 4.15 (1 H, br s), 4.62 (4 H, m), 6.18 (1 H, s), 7.11 (1 H, d, J = 0.8 Hz), 7.28 (1 H, d, J = 0.8 Hz); NMR δ_B −15.18 (4 B, m), −13.66 (2 B, d, J_{B-H} = 150 Hz), −11.14 (2 B, d, J_{B-H} = 147 Hz), −6.90 (1 B, d, J_{B-H} = 150 Hz), −5.04 (1 B, d, J_{B-H} = 150 Hz); mass spectrum (FAB negative ion) m/z 613.3872 (M − H) ($C_{22}H_{41}{}^{10}B_2{}^{11}B_8N_4O_9$ requires 613.3877).

2-(2-(2-(2-(2-Chloroethoxy)ethoxy)ethoxy)ethyl)-1,3-dithiane (27). Butyl lithium (2 M in hexanes, 20.5 mL, 41 mmol) was added to 1,3-dithiane (**9**) (4.80 g, 40 mmol) in dry THF (80 mL) at −78 °C under N_2 and the mixture was stirred at this temperature for 1 h. Bis(2-(2-chloroethoxy)ethyl) ether (**2**) (9.24 g, 40 mmol) was added and the mixture was stirred at −20 °C for 20 h. The solvent was evaorated and the residue, in CH_2Cl_2, was washed with water and dried. Chromatography (pentane/CH_2Cl_2 1:1, and then CH_2Cl_2) gave the (chloroalkyl)dithiane **27** (5.16 g, 49%) as a pale yellow oil: NMR δ_H 1.89 (1 H, m), 2.0–2.2 (3 H, m), 2.85 (4 H, m), 3.6–3.8 (14 H, m), 4.20 (1 H, t, J = 7.0 Hz); mass spectrum (FAB positive ion) m/z 314.0772 (M) ($C_{12}H_{23}{}^{35}ClO_3S_2$ requires 314.0777).

2-(2-(2-(2-(2-(Propyn-3-yloxy)ethoxy)ethoxy)ethoxy)-ethyl)-1,3-dithiane (28). Propyn-3-ol (560 mg, 10 mmol) was added to sodium hydride (240 mg, 10 mmol) in dry DMF (10 mL) and the mixture was stirred for 30 min. The chloroalkyl–dithiane **27** (3.14 g, 10 mmol) was added and the mixture was stirred at 120 °C for 3 h. The solvent was evaporated. The residue, in CH_2Cl_2, was washed with water and dried. Chromatography (CH_2Cl_2/Et_2O 20:1, and then 10:1) gave the dithiane–alkyne **28** (830 mg, 25%) as a pale yellow oil: IR ν 2120 cm^{-1}; NMR δ_H 1.8–2.2 (4 H, m), 2.44 (1 H, t, J = 2.4 Hz), 2.85 (4 H, m), 3.63 (14 H, m), 4.20 (1 H, t, J = 7.1 Hz), 4.21 (2 H, d, J = 2.4 Hz); mass spectrum (FAB positive ion) m/z 335.1317 (M + H) ($C_{15}H_{27}O_4S_2$ requires 335.1351), 334.1272 (M) ($C_{15}H_{26}O_4S_2$ requires 334.1273).

2-(2-(2-(2-(2-(1,2-Dicarba-*closo*-dodecaboran(12)-1-yl-methoxy)ethoxy)ethoxy)ethoxy)ethyl)-1,3-dithiane (29). Decaborane(14) (120 mg, 1 mmol) was stirred in dry MeCN (10 mL) for 3 h. The dithiane–alkyne **28** (330 mg, 1 mmol) was added and the mixture was boiled under reflux for 3 d. Chromatography (CH_2Cl_2/Et_2O 20:1) of the evaporation residue gave the carborane-dithiane **29** (260 mg, 58%) as a pale yellow gum: IR ν 2590 cm^{-1}; NMR δ 1.85 (1 H, m), 2.04 (2 H, q, J = 7.0 Hz), 2.08 (1 H, m), 2.2 (10 H, br q, J_{B-H} = 150 Hz), 2.85 (4 H, m), 3.64 (14 H, m), 3.96 (2 H, s), 4.10 (1 H, br s), 4.19 (1 H, t, J = 7.0 Hz); mass spectrum (FAB positive ion) m/z 452.3060 (M + H) ($C_{15}H_{36}{}^{10}B_2{}^{11}B_8O_4S_2$ requires 452.3058).

3-(2-(2-(2-(1,2-Dicarba-*closo*-dodecaboran(12)-1-yl-methoxy)ethoxy)ethoxy)ethoxy)propanal (30). The carborane–dithiane **29** was treated with *N*-bromosuccinimide and $AgNO_3$ in aqueous MeCN, as for the synthesis of **15**, except that the eluant for chromatography was CH_2Cl_2/Et_2O, to give the carborane–aldehyde **30** (74%) as a pale yellow gum: IR ν 1725, 2590 cm^{-1}; NMR δ_H 2.2 (10 H, br q, J_{B-H} = 150 Hz), 2.70 (2 H, dt, J = 6.2, 1.8 Hz), 3.62 (12 H, m), 3.83 (2 H, t, J = 6.2 Hz (becomes s on decoupling at δ 2.70)), 3.96 (2 H, s), 4.10 (1 H, br s), 9.80 (1 H, t, J = 1.8 Hz); mass spectrum (FAB positive ion) m/z 345.3070 (M + H − H_2O) ($C_{12}H_{29}{}^{10}B_2{}^{11}B_8O_4$ requires 345.3069); mass spectrum (CI) m/z 307.2913 (100%) (M + H − H_2C=CHCHO) ($C_9H_{27}{}^{10}B_2{}^{11}B_8O_4$ requires 307.2913).

3-(2-(2-(2-(1,2-Dicarba-*closo*-dodecaboran(12)-1-yl-methoxy)ethoxy)ethoxy)ethoxy)propanal Oxime (31). The carborane–aldehyde **30** was treated with $HONH_2$·HCl and Na_2CO_3, as for the synthesis of **16**, except that chromatography was omitted, to give an equimolar mixture of geometrical isomers of the carborane–oxime **31** (80%) as a colorless gum: IR ν 2590, 3350 (br) cm^{-1}; NMR δ_H 2.2 (10 H, br q, J_{B-H} = 150 Hz), 2.49 (1 H, q, J = 6.2 Hz), 2.66 (1 H, q, J = 6.2 Hz), 3.64 (14 H, m), 3.96 (2 H, s), 4.12 (1 H, br s), 6.85 (0.5 H, t, J = 6.2 Hz), 7.48 (0.5 H, t, J = 6.2 Hz), 8.0 (1 H, br); mass spectrum (FAB positive ion) $^{10}B/^{11}B$ isotope cluster centered at m/z 378 (M + H).

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Supplementary Material Available: Copies of ^1H NMR spectra of **4**, **5**, **7**, **8**, **12-17**, and **19-31** (23 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.