Tumour-targetted Boranes. Part 2.[1] Coupling of *closo*-Carboranes to Substituted 2-Nitroimidazoles *via* 1,3-Dipolar Cycloaddition

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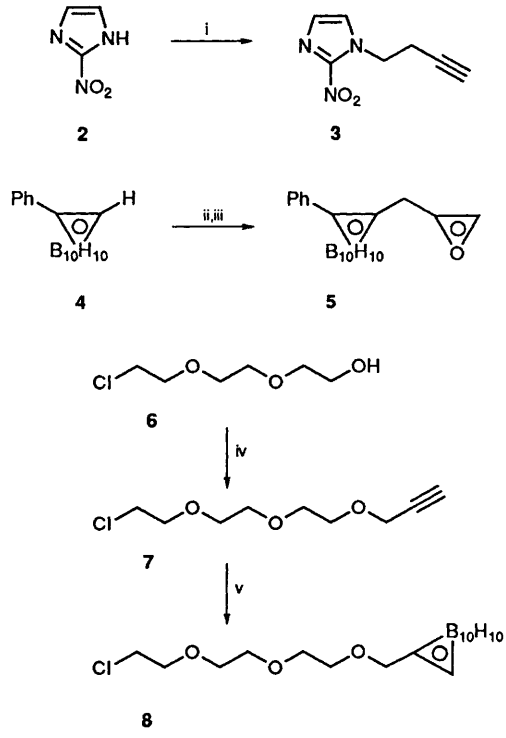
Carboranes targetted to specific tumour tissues are important for boron neutron capture therapy of cancer. Direct syntheses of carboranes linked to 2-nitroimidazole were unsuccessful. A mild procedure for 1,3-dipolar cycloaddition of 4-(carboranylmethoxy)benzonitrile *N*-oxide **32** with a nitroimidazolyl-alkene **27** and with nitroimidazolyl-alkynes **3** and **30** has been developed, using a series of model reactions, yielding a dihydroisoxazole **28** and the isoxazoles **29** and **31**, respectively. The nitrile oxide **32** is unusually stable. Dithioacetals are shown to be suitable protecting groups for aromatic aldehydes under the vigorous reductive and Lewis acidic-basic conditions of carborane formation. 6-Methoxy-4*H*-[1]benzopyrano[4,3-*c*]isoxazole **16** has been synthesised by intramolecular 1,3-dipolar cycloaddition. The structure of the isoxazole derivative **29** has been confirmed by an X-ray crystal structure analysis.

Boron neutron capture therapy (BNCT) is of increasing interest as a strategy for treatment of various cancers, notably gliomas and melanomas.[2] When the ^{10}B isotope is irradiated with slow ('thermal') neutrons, an [n,α] reaction ensues, giving mainly ^{7}Li and ^{4}He nuclei, along with kinetic energy (2.31 MeV). With this energy, the ^{4}He has a range of *ca.* 9 μm in tissue (*ca.* 1 cell diam.). Thus, damage is limited to the cell containing the boron and to adjacent cells. Early studies of BNCT gave mixed results.[3] Failures were attributed to inadequate concentrations of ^{10}B in the tumour tissue or to lack of selectivity of disposition of ^{10}B, leading to damage to normal tissue. Recently, carboranes have been linked to nucleosides,[4] to amino acids[5] and to porphyrins[6] in attempts to target boron to tumours. 1-Substituted 2-nitroimidazoles are known to be selectively retained in poorly vascularised hypoxic tumour tissue by reductive metabolism to electrophiles.[7] As part of a programme of synthesis and evaluation of nitroimidazoles in the treatment of cancer,[1,8-10] we propose that compounds containing 10–12 boron atoms linked to 2-nitroimidazole would form a useful method of concentrating boron in solid tumours. Derivatives of 1,2-dicarba-*closo*-dodecaborane(12)[11] ('carborane', **1**, Fig. 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. Before our preliminary communication,[1] no report of nitroimidazoles bearing boron had been made in the journal literature.

In most cases, carboranes are readily formed[11] by reaction of alkynes and decaborane(14) ($B_{10}H_{14}$) in the presence of boiling Lewis bases for long reaction times. Consequently, the nitroimidazolylalkyne **3** was prepared by alkylation of 2-nitroimidazole **2** with but-3-ynyl tosylate. However, treatment of **3** with decaborane(14) under the standard reaction conditions (acetonitrile, heat) gave only an inseparable mixture of materials probably arising from reduction of the nitroimidazole. Such reduction is unsurprising, since simple and complex boranes are widely used as reducing agents but 1-substituted 2-nitroimidazoles are themselves known to be readily reduced (E^{1}_{7} = −389 mV)[10]. Thus, the carborane must be formed before the nitroimidazole is introduced into the molecule.

2-Nitroimidazole reacts under basic conditions with oxiranes to give substituted nitroimidazolylethanols[8] and the anion of **2** can be alkylated[10] at elevated temperatures (> 130 °C) by a variety of halogenoalkanes and alkyl tosylates. Carboranes bearing both types of electrophile were assembled for investigation of their reaction with **2**. Treatment of phenylethyne with decaborane(14) gave the known[11] monosubstituted carborane **4** and treatment of the corresponding anion with epichlorohydrin gave the carboranylmethyloxirane **5** in good yield. The



Scheme 1 Syntheses of substituted nitroimidazole **3** and substituted carboranes **4**, **5** and **8**, precursors for attempts at 'direct' routes to nitroimidazole-carboranes: i, $HC{\equiv}CCH_2CH_2OTs$–KOBu^t; ii, BuLi; iii, epichlorohydrin; iv, NaH–$HC{\equiv}CCH_2Br$; v, $B_{10}H_{14}$–MeCN

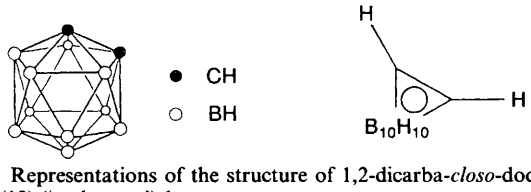
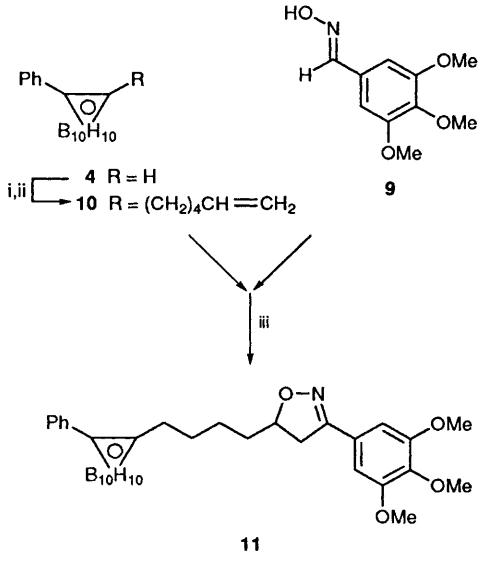


Fig. 1 Representations of the structure of 1,2-dicarba-*closo*-dodecaborane(12) ('carborane') **1**

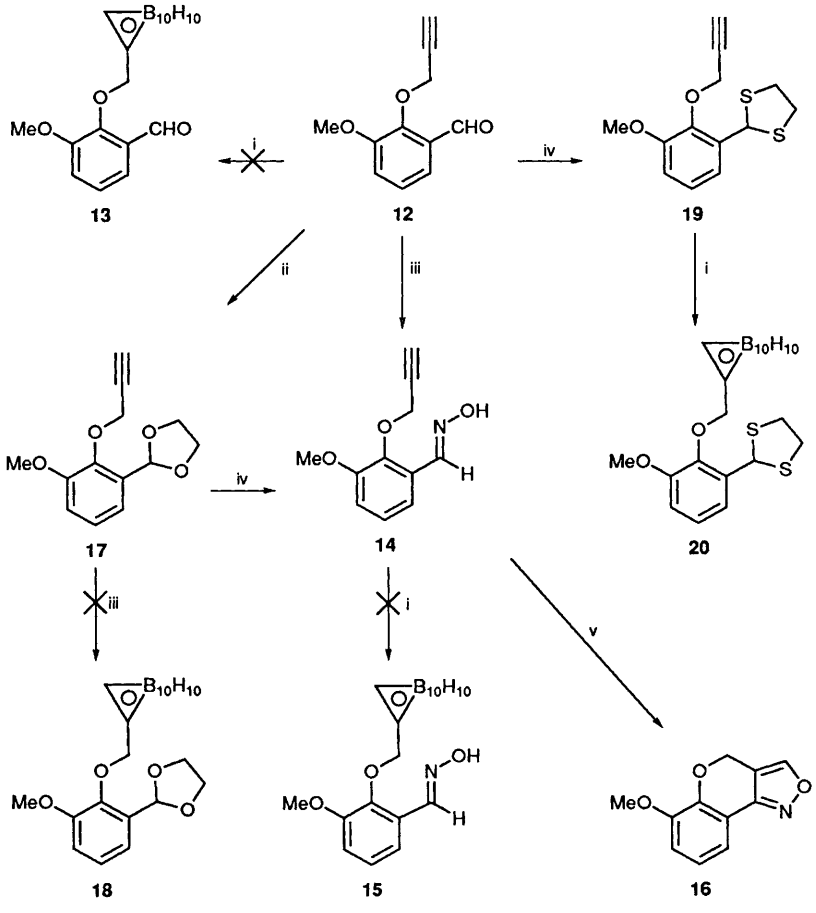
chloro alcohol **6** was alkylated using the reactive electrophile prop-2-ynyl bromide, giving the chloroalkyne **7**. The corresponding carborane **8** was formed in satisfactory yield. Neither **5** nor **8** reacted with 2-nitroimidazole. Similarly, the lithio derivative of **4** did not react with 2-nitro-1-(oxiranylmethyl)imidazole.[8]

Clearly, the conditions required for the formation of nitroimidazolylcarboranes by these 'direct' methods were too harsh to permit the co-existence of the nitroimidazole and the carborane. 1,3-Dipolar cycloadditions of nitrile oxides with alkenes and alkynes proceed[12] under mild conditions; this method of carbon–carbon bond formation was investigated as a route to the target compounds. Nitrile oxides are most conveniently formed by oxidation of the corresponding aldoximes. The series of model reactions shown in Schemes 2 and 3 were studied to check the compatibility of these oxidative conditions (aqueous sodium hypochlorite) with carboranes and the stability of the precursor oximes and synthons thereof to decaborane(14). Treatment of 3,4,5-trimethoxybenzaldehyde oxime **9** with aqueous sodium hypochlorite gave the nitrile oxide which reacted *in situ* with alkenylcarborane **10** (prepared by alkylation of the anion of **4**) to give the dihydroisoxazole **11**. Thus, the stability of carboranes to sodium hypochlorite is demonstrated.

To study the effects of the carborane formation conditions on aldehyde and oxime groups and their synthetic equivalents, 3-methoxy-2-prop-2-ynyloxybenzaldehyde **12** was converted into its oxime **14**, as shown in Scheme 3. However, both aldehyde and oxime functions were found to be degraded by decaborane(14), preventing the synthesis of the model carboranyl aldehyde **13** and the model carboranyl oxime **15** by these direct routes. Interestingly, the intramolecular 1,3-dipolar cycloaddition of the nitrile oxide derived from **14** was successful in giving the 4*H*-[1]benzopyrano[4,3-*c*]isoxazole **16**. The yield was modest, presumably owing to the usually unfavourable regiochemistry of cycloaddition[12] being forced by the geometry



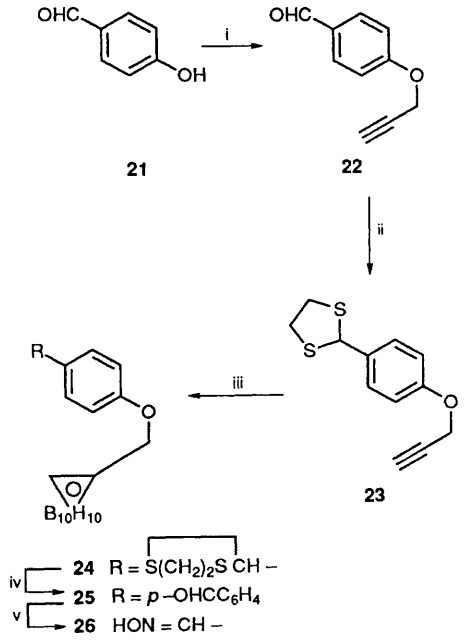
Scheme 2 Model reactions to demonstrate the compatibility of carborane with the conditions required for 1,3-dipolar cycloaddition: i, BuLi; ii, $H_2C{=}CH(CH_2)_4Br$; iii, NaOCl–H_2O–CH_2Cl_2



Scheme 3 Model reactions to investigate the stability of aldehydes and their protected forms to $B_{10}H_{14}$ and synthesis of methoxybenzopyranoisoxazole **16**: i, $B_{10}H_{14}$–MeCN; ii, $HOCH_2CH_2OH$–TsOH; iii, $HONH_2$·HCl–Na_2CO_3; iv, $HSCH_2CH_2SH$–BF_3·Et_2O; v, NaOCl

of the nitrile oxide; this heterocyclic system has hitherto been reported only once.[13] The cyclic acetal **17**, formed from **12** by treatment with ethane-1,2-diol under acidic conditions, was also not stable to decaborane(14). Protection of the aldehyde as the cyclic dithioacetal **19** by Lewis acid-catalysed reaction with ethane-1,2-dithiol was, however, effective in permitting the synthesis of the carborane **20**. Hence, aldehydes can be protected as dithioacetals during formation of carboranes. Assembly of nitroimidazolylcarboranes was, therefore, expected to be feasible by a route involving an appropriate 1,3-dipolar cycloaddition.

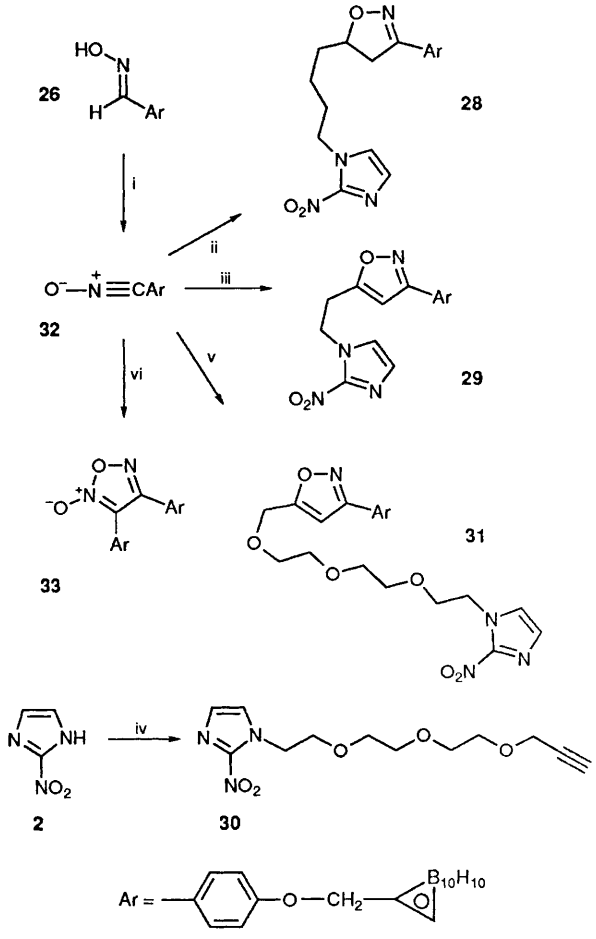
To provide the central framework to support carborane and oxime groups, 4-hydroxybenzaldehyde **21** was prop-2-ynylated by the method of Matolcsy *et al.*,[14] giving the alkynealdehyde **22** (Scheme 4). Protection of the aldehyde as the cyclic dithio-



Scheme 4 Synthesis of the carborane-aldoxime **26**, a precursor of a carborane–nitrile oxide: i, NaH–$HC{\equiv}CCH_2Br$; ii, $HSCH_2CH_2SH$–$BF_3{\cdot}Et_2O$; iii, $B_{10}H_{14}$–MeCN; iv, $Hg(ClO_4)_2$; v, $HONH_2{\cdot}HCl$–Na_2CO_3

acetal **23** was achieved in 80% yield. As predicted by the model experiments, this protecting group resisted prolonged treatment with decarborane(14) in boiling acetonitrile, which furnished the carborane **24**. Deprotection was effected virtually quantitatively within 5 min using mercury(II) perchlorate to give the carboranyl aldehyde **25** which was converted into the carboranyl oxime **26**. This oxime represents the precursor to the nitrile oxide **32** for 1,3-dipolar cycloaddition with the range of nitroimidazolyl-alkenes and -alkynes (Scheme 5). The polyether-linked nitroimidazole **30** was synthesised by reaction of the potassium salt of 2-nitroimidazole with the alkyne **7** under the usual vigorous conditions required for alkylation of this weak nucleophile (dimethylformamide, 130 °C).

Oxidation/elimination of the carboranyl oxime **26** using aqueous sodium hypochlorite to give the intermediate nitrile oxide **32** was very rapid as shown by TLC but prolonged reaction times at ambient temperature were required for cycloaddition *in situ* with nitroimidazolylalkene **27**[10] and nitroimidazolylalkynes **3** and **30**. The dihydroisoxazole-linked compound **28** and the isoxazole-linked compounds **29** and **31**, respectively, in which both 2-nitroimidazole and carborane moieties are present, were formed in excellent yields based on consumption of starting materials (Scheme 5).



Scheme 5 Dipolar cycloaddition reactions of carborane-nitrile oxide **32** and synthesis of nitroimidazole-carboranes **28**, **29** and **31**: i, NaOCl; ii, 1-hex-5-enyl-2-nitroimidazole **27**; iii, nitroimidazole-alkyne **3**; iv, KOBu^t–alkyne **7**; v, nitroimidazole-alkyne **30**; vi, toluene, reflux

In each case, even after reaction for several days, no boron-containing compounds other than **26**, **28**, **29**, **31** and **32** were evident in the reaction mixtures and it was possible to isolate the unchanged nitrile oxide **32** by chromatography. This nitrile oxide is remarkably stable, with little decomposition on storage for several weeks at ambient temperature. In contrast, the half-life of most aromatic nitrile oxides is reported[12] to be only a few hours. It did not react with cyclohexene, a weak dipolarophile,[12] at reflux temperature and was converted into its dimer, the 1,2,5-oxadiazole 2-oxide **33**, only when heated in boiling toluene.

Additional evidence for the structure of target compound **29** was provided by a determination of the crystal structure by X-ray diffraction methods. Recrystallisation of a sample of compound **29** from benzene afforded a crystal which was not of high quality but which diffracted strongly and was, therefore, adequate for this determination. Other solvents gave only microcrystalline material. The crystal had approximate dimensions 0.4 × 0.4 × 0.2 mm.

Crystal Data.—$C_{17}H_{24}B_{10}N_4O_4{\cdot}\frac{1}{2}C_6H_6$, M = 495.5, triclinic, a = 7.320(2), b = 11.275(3), c = 16.359(4) Å, α = 94.86(4), β = 92.83(3), γ = 100.78(4), U = 1318.6 Å^3, space group $P\bar{1}$, Z = 2, D_C = 1.25 g cm^{-3}, μ(Mo-K$_\alpha$) = 0.47 cm^{-1}, F(000) = 514. Data were measured at ambient temperature on a Hilger and Watts Y290 four-circle diffractometer in the range $2 \leqslant \theta \leqslant 22°$. 3444 Reflections were collected, of which 1430 were unique with $I \geqslant 3\sigma(I)$. Data were corrected for Lorentz and polarisation effects but not for absorption. The structure

was solved by direct methods and was refined using the SHELX[15] suite of programmes. In the final least-squares cycles, all the atoms were allowed to vibrate anisotropically. The half portion of benzene solvent molecule which accompanies the structure is proximate to a centre of symmetry. This generates the remaining atoms to complete the benzene ring. Hydrogen atoms were included at calculated positions where appropriate, except in the solvent species. In the later stages of refinement, the molecule and associated solvent of recrystallisation were treated as separate blocks. Final residuals after eight cycles of least squares were $R = R_w = 0.1218$. Maximum final shift/esd was 0.009. The maximum and minimum residual densities were 0.12 and -0.10 eÅ^{-3}, respectively.

Table 1 gives selected bond lengths, Table 2 gives selected bond angles and Table 3 gives selected torsion angles for the structure of the substituted nitroimidazolyl-carborane **29**. Full tables of final fractional coordinates and isothermal parameters, bond distances, bond angles, torsion angles and anisotropic temperature factors have been deposited with the Cambridge Crystallographic Data Centre.* The asymmetric unit is shown in Fig. 2, along with the labelling scheme used. In the crystal, the compound adopts an extended conformation, with torsion angles of the two flexible units linking the nitroimidazole to the isoxazole and the benzene to the carborane [N(1)–C(4)–C(5)–C(6) and C(12)–O(4)–C(15)–C(16), respectively] being close to 180°. The tilt angle between the two adjacent aromatic rings, the benzene and the isoxazole, is 11.4°, *i.e.* the two rings diverge only slightly from coplanarity. The carborane forms a slightly distorted icosahedron, as reported by the bond lengths and bond angles to C(16) and C(17). Hence, this carborane corresponds to the usual icosahedral shape for such C_2B_{10} structures (*e.g.* ref. 16), rather than the 'basket handle' structure proposed by Zakharkin *et al.*[17]

The oxidising character of 2-nitroimidazoles and the potential reductant activity of boron hydrides preclude the formation of linked nitroimidazolyl-carboranes by the vigorous conditions required for 'direct' methods, such as treatment of a nitroimidazolyl-alkyne with decaborane(14) or alkylation of the anion of 2-nitroimidazole with electrophiles linked to carboranes. Model reactions have demonstrated that both 2-nitroimidazole and carborane moieties are stable to the conditions of the generation of nitrile oxides and their 1,3-dipolar cycloaddition to alkenes and alkynes. These model studies have also shown the utility and importance of dithioacetal protection for aromatic aldehydes under the conditions of formation of carboranes. On the basis of these studies, the unusually stable carboranylmethoxyphenyl nitrile

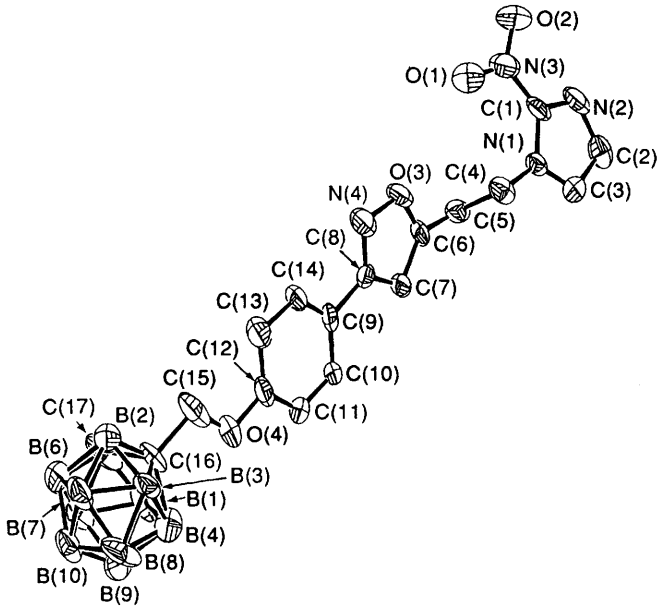


Fig. 2 Asymmetric unit of the crystal structure of the nitroimidazole-carborane **29** with the labelling scheme used for the crystallographic structure determination

Table 1 Selected bond lengths for the crystal structure of the nitroimidazole-carborane **29**

Bond	Bond length (Å)	Bond	Bond length (Å)
O(1)–N(3)	1.20(3)	O(2)–N(3)	1.24(2)
O(3)–N(4)	1.48(2)	O(3)–C(6)	1.29(2)
O(4)–C(12)	1.42(2)	O(4)–C(15)	1.35(3)
N(3)–C(1)	1.42(2)	N(1)–C(1)	1.38(2)
N(2)–C(1)	1.30(3)	N(1)–C(3)	1.28(2)
N(2)–C(2)	1.37(2)	C(2)–C(3)	1.44(3)
C(15)–C(16)	1.63(3)	C(16)–C(17)	1.61(3)
C(16)–B(1)	1.72(3)	C(16)–B(2)	1.51(3)
C(16)–B(3)	1.62(3)	C(16)–B(4)	1.73(3)
C(17)–B(1)	1.67(3)	C(17)–B(2)	1.67(3)
C(17)–B(5)	1.66(3)	C(17)–B(6)	1.66(3)
B(1)–B(4)	1.85(3)	B(1)–B(5)	1.80(3)
B(1)–B(9)	1.85(4)	B(2)–B(3)	1.75(3)
B(2)–B(6)	1.81(3)	B(2)–B(7)	1.79(4)
B(3)–B(4)	1.61(3)	B(3)–B(7)	1.85(3)
B(3)–B(8)	1.78(3)	B(4)–B(8)	1.66(4)
B(4)–B(9)	1.85(3)	B(5)–B(6)	1.59(4)
B(5)–B(9)	1.72(3)	B(5)–B(10)	1.65(4)
B(6)–B(7)	1.91(4)	B(6)–B(10)	1.69(4)
B(7)–B(8)	1.86(3)	B(7)–B(10	1.95(3)
B(8)–B(9)	1.63(4)	B(8)–B(10)	1.66(3)
B(9)–B(10)	1.57(3)		

Table 2 Selected bond angles for the crystal structure of the nitroimidazole-carborane **29**

Atoms	Bond angle (°)	Atoms	Bond angle (°)
N(3)–C(1)–N(1)	123(2)	N(3)–C(1)–N(2)	125(2)
N(1)–C(1)–N(2)	112(1)	C(1)–N(3)–O(1)	121(2)
C(1)–N(3)–O(2)	114(2)	O(1)–N(3)–O(2)	124(2)
C(1)–N(1)–C(4)	129(1)	C(3)–N(1)–C(4)	124(1)
C(5)–C(4)–N(1)	107(1)	C(4)–C(5)–C(6)	105(1)
C(5)–C(6)–O(3)	116(1)	C(5)–C(6)–C(7)	130(1)
C(8)–C(9)–C(10)	117(1)	C(10)–C(9)–C(14)	122(2)
C(11)–C(12)–C(13)	126(2)	O(4)–C(15)–C(16)	111(1)
C(15)–C(16)–C(17)	113(2)	C(15)–C(16)–B(1)	111(1)
C(15)–C(16)–B(2)	117(1)	C(15)–C(16)–B(3)	122(1)
C(15)–C(16)–B(4)	122(1)		

* For details see Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1994, Issue 1.

Table 3 Selected torsion angles for the crystal structure of nitroimidazole-carborane **29**

Atoms	Torsion angle (°)	Atoms	Torsion angle (°)
O(1)–N(3)–C(1)–N(1)	10.5	N(1)–C(4)–C(5)–C(6)	174.9
N(4)–C(8)–C(9)–C(14)	11.4	C(12)–O(4)–C(15)–C(16)	171.4

oxide **32** was synthesised and was shown to react efficiently with nitroimidazolyl-alkenes and -alkynes to give the required linked nitroimidazole-carboranes **28**, **29** and **31**.

1,3-Dipolar cycloaddition of nitrile oxides is, therefore, demonstrated to be a mild process which has great potential in medicinal chemistry for joining chemically sensitive targetting moieties to pharmacophores. A new carbon–carbon bond is formed and the linking (dihydro)isoxazole gives opportunity for further elaboration. Unfortunately, the target compounds **28**, **29** and **31** were found to be insufficiently soluble in water to permit satisfactory biological evaluation. The contruction of alternative, more polar links between nitroimidazole and carborane is under active investigation.

Experimental

JEOL GX270 and EX400 instruments furnished the NMR spectra. $CDCl_3$ was the solvent for NMR spectroscopy unless otherwise noted. The external reference for ^{11}B NMR was boron trifluoride–diethyl ether complex. *J* Values are recorded in Hz. Solutions in organic solvents were dried with anhydrous magnesium sulfate. Solvents were evaporated under reduced pressure. The chromatographic stationary phase was silica gel. Distillation was carried out using a Büchi Kugelrohr apparatus; b.p.s refer to the temperature of the oven. 1-(Hex-5-enyl)-2-nitroimidazole **27** was prepared as described previously by us.[10] DMF refers to dimethylformamide; THF refers to tetrahydrofuran. M.p.s are uncorrected.

1-*But*-3-*ynyl*-2-*nitroimidazole* **3**.—2-Nitroimidazole **2** (340 mg, 3 mmol) in dry DMF (10 cm^3) was treated with potassium *tert*-butoxide (340 mg, 3 mmol) at 130 °C until it dissolved and then for a further 10 min. The mixture was cooled to 80 °C, but-3-ynyl-4-methylbenzenesulfonate[18] (670 mg, 3 mmol) and sodium iodide (10 mg) were added to it and the whole heated at 130 °C for 10 min. Evaporation of the solvent from the mixture left a residue which was dissolved in water (5 cm^3) and the solution was filtered and extracted with chloroform. The extract was evaporated to give a yellow semi-solid which was recrystallised from pentane–benzene (CAUTION) to afford the *title compound* **3** (290 mg, 59%) as pale yellow crystals, m.p. 71–72 °C (Found: C, 50.8; H, 4.2; N, 25.8. $C_7H_7N_3O_2$ requires C, 50.9; H, 4.25; N, 25.45%); δ 2.08 (1 H, t, *J* 2.5, C≡CH), 2.81 (2 H, dt, *J* 2.5 and 6.4, $CH_2C{\equiv}C$), 4.58 (2 H, t, *J* 6.4, imidazole-CH_2) and 7.17 (1 H, br s) and 7.24 (1 H, br s) (imidazole 4,5-H).

[(2-*Phenyl*-1,2-*dicarba*-closo-*dodecaboran*(12)-1-*yl*)*methyl*]-*oxirane* **5**.—Butyllithium (1.6 mol dm^{-3} in hexanes; 3.1 cm^3, 5 mmol) was added to 1-phenyl-1,2-dicarba-*closo*-dodecaborane(12) **4**[11] (880 mg, 4 mmol) in dry THF (20 cm^3) at −78 °C. The mixture was stirred at −78 °C for 30 min after which chloromethyloxirane (460 mg, 5 mmol) was added to it. The mixture was then allowed to warm to 20 °C during 16 h after which it was partitioned between water and dichloromethane. The organic phase was separated and evaporated and the residue was chromatographed (pentane–dichloromethane, 1:1) to give the *title compound* **5** (850 mg, 62%) as a white solid, m.p. 63–65 °C (Found: C, 47.7; H, 7.35. $C_{11}H_{20}B_{10}O$ requires C, 47.8; H, 7.3%); δ_H 1.7–3.1 (10 H, br m, $B_{10}H_{10}$), 1.90 (1 H, dd, *J* 15.4 and 5.9) and 2.08 (1 H, dd, *J* 15.4 and 6.1) (carborane-CH_2), 2.17 (1 H, dd, *J* 4.9 and 2.4) and 2.71 (1 H, dd, *J* 4.6 and 4.1) (oxirane 2-H_2), 2.97 (1 H, m, oxirane 1-H) and 7.45–7.65 (5 H, m, Ph-H_5); δ_B −15.5 to −12.5 (8 B, br) and −7.04 (2 B, d, J_{BH} 150).

3-{2-[2-(2-*Chloroethoxy*)*ethoxy*]*ethoxy*}*prop*-2-*yne* **7**.—2-[2-(2-Chloroethoxy)ethoxy]ethanol **6** (6.74 g, 40 mmol) was added to sodium hydride (oil-free; 960 mg, 40 mmol) in dry THF (50 cm^3) at −20 °C. After 15 min at −78 °C, 3-bromopropyne (4.76 g, 40 mmol) was added to the mixture which was then boiled under reflux for 1 h. The mixture was evaporated and the residue was treated with water (50 cm^3) and extracted with dichloromethane. The extract was dried and evaporated and the residue was distilled to give the *title compound* **7** (5.83 g, 71%) as a colourless oil, b.p. 160 °C at 0.1 mmHg; ν_{max}/cm^{-1} 2120w; δ 2.44 (1 H, t, *J* 2.4, C≡CH), 3.6–3.8 (12 H, m, 5 × OCH_2 + $ClCH_2$) and 4.21 (2 H, d, *J* 2.4, $CH_2C{\equiv}C$); *m/z* (CI) 207.0788 (M + H) ($C_9H_{16}{}^{35}ClO_3$ requires 207.0788).

1-({2-[2-(2-*Chloroethoxy*)*ethoxy*]*ethoxy*}*methyl*)-1,2-*dicarba*-closo-*dodecaborane*(12) **8**.—Decaborane(14) ($B_{10}H_{14}$) (1.22 g, 10 mmol) was stirred with acetonitrile (20 cm^3) for 3 h before addition of the alkyne **7** (2.07 g, 10 mmol). The mixture was boiled under reflux for 3 d and then evaporated. Chromatography (pentane–dichloromethane 1:1) of the residue gave the *title compound* **8** (2.10 g, 65%) as a pale yellow oil; ν_{max}/cm^{-1} 2590; δ 1.3–3.1 (10 H, br m, $B_{10}H_{10}$), 3.6–3.8 (12 H, m, 5 × OCH_2 + $ClCH_2$), 3.96 (2 H, s, carborane-CH_2), and 4.07 (1 H, br s, carborane 2-H); *m/z* (CI) $^{10}B/^{11}B$ $^{35}Cl/^{37}Cl$ cluster centred at 326 (M); *m/z* (FAB, positive ion) 325.2587 (M + H) ($C_9H_{26}{}^{10}B_2{}^{11}B_8{}^{35}ClO_3$ requires 325.2574).

2-*Hex*-5-*enyl*-1-*phenyl*-1,2-*dicarba*-closo-*dodecaborane*(12) **10**.—Butyllithium (1.6 mol dm^{-3} in hexanes; 2.76 cm^3, 4.4 mmol) was added to 1-phenyl-1,2-dicarba-*closo*-dodecaborane(12) **4**[12] (720 mg, 3.3 mmol) in dry THF (10 cm^3) under nitrogen and the mixture was stirred for 30 min. 1-Bromohex-5-ene (720 mg, 4.4 mmol) was added to the mixture which was then stirred for 18 h. It was then washed with water and extracted with diethyl ether. The extract was evaporated and the residue chromatographed (pentane) to give the *title compound* **10** (800 mg, 81%) as a colourless oil; ν_{max}/cm^{-1} 3080, 2580 and 1640; δ 1.08 (2 H, quintet, *J* 7.3, $CH_2CH_2CH_2$), 1.2–3.3 (10 H, br m, $B_{10}H_{10}$), 1.34 (2 H, m, $CH_2CH_2CH_2$), 1.68 (2 H, m, $CH_2CH_2CH_2$), 1.80 (2 H, qt, *J* 7.5 and 1, $CH_2C{=}C$), 4.81 (2 H, m, C=CH_2), 5.55 (1 H, m, C=CH) and 7.25–7.57 (5 H, m, Ph-H_5); *m/z* (EI) 303.3010 (M) ($C_{14}H_{26}{}^{10}B^{11}B_9$ requires 303.3001), 302.3014 (M) ($C_{14}H_{26}{}^{10}B_2{}^{11}B_8$ requires 302.3034); *m/z* (CI) $^{10}B/^{11}B$ cluster centred at 605 (2M + H), $^{10}B/^{11}B$ cluster centred at 302 (M).

4,5-*Dihydro*-4-[4-(2-*phenyl*-1,2-*dicarba*-closo-*dodecaboran*-(12)-1-*yl*)*butyl*]-3-(3,4,5-*trimethoxyphenyl*)*isoxazole* **11**.—3,4,5-Trimethoxybenzaldehyde oxime **9**[19] (210 mg, 1 mmol) and the carborane **10** (300 mg, 1 mmol) in dichloromethane (20 cm^3) were stirred vigorously with aqueous sodium hypochlorite (8% available chlorine; 1.5 cm^3) for 16 h; further aqueous sodium hypochlorite (1.5 cm^3) was then added to the mixture. After 30 min, the mixture was diluted with water and extracted with dichloromethane. The extract was evaporated and the residue was chromatographed (pentane–dichloromethane, 3:1, then dichloromethane–ethyl acetate, 10:1, and then ethyl acetate). The starting carborane **10** (37%) and oxime **9** (29%) were isolated from the first and last portions of eluate, respectively. Evaporation of the solvent from the second portion of eluate gave the *title compound* **11** (300 mg, 59%) as a colourless oil; δ_H 1.0–3.2 (10 H, br m, $B_{10}H_{10}$), 1.26 (2 H, m, CH_2), 1.47 (4 H, m, 2 × CH_2), 1.79 (2 H, m, CH_2), 2.85 (1 H, dd, *J* 16.5 and 7.2) and 3.33 (1 H, dd, *J* 16.5 and 10.3) (isoxazole 4-H_2), 3.87 (9 H, s, 3 × OCH_3), 4.61 (1 H, m, isoxazole 5-H), 6.85 (2 H, s, Ar-H_2) and 7.35–7.64 (5 H, m, Ph-H_5); δ_C 24.7, 29.6, 34.7, 34.8, 40.0, 56.1, 56.1, 60.9, 80.7, 80.8, 82.1, 83.5, 103.8, 125.0, 128.9, 130.6, 131.0, 153.3 and 156.1; *m/z* (FAB, positive ion) $^{10}B/^{11}B$ cluster centred at 512 (M + H); *m/z* (FAB,

negative ion) 510.3657 (M − H) ($C_{24}H_{36}{}^{10}B_2{}^{11}B_8NO_4$ requires 510.3648).

3-*Methoxy*-2-*prop*-2-*ynyloxybenzaldehyde Oxime* **14**.—3-Methoxy-2-prop-2-ynyloxybenzaldehyde **12**[20] (1.16 g, 6.1 mmol) was stirred with sodium carbonate (640 mg, 6 mmol) and hydroxylamine hydrochloride (830 mg, 12 mmol) in ethanol (50 cm^3) for 16 h. The mixture was evaporated and the residue was dissolved in dichloromethane and the solution washed with water, dried and evaporated to give the *title compound* **14** (890 mg, 71%) as a white solid, m.p. 76–78 °C; ν_{max}/cm^{-1} 3270; δ 2.48 (1 H, t, *J* 2.4, C≡CH), 3.88 (3 H, s, OCH_3), 4.77 (2 H, d, *J* 2.4, $CH_2C{\equiv}C$), 6.95 (1 H, dd, *J* 8.2 and 1.5, Ar 4-H), 7.10 (1 H, t, *J* 8.1, Ar 5-H), 7.38 (1 H, dd, *J* 8.0 and 1.5, Ar 6-H), 8.21 (1 H, s, C*H*NOH) and 8.60 (1 H, s, OH). This material was used without further purification.

6-*Methoxy*-4H-[1]*benzopyrano*[4,3-c]*isoxazole* **16**.—The oxime **14** (150 mg, 0.75 mmol) in dichloromethane (10 cm^3) was stirred with aqueous sodium hypochlorite (8% available chlorine; 2 cm^3) for 48 h. The mixture was extracted with dichloromethane and the extract was washed with water and evaporated. Chromatography (dichloromethane–pentane, 1:1) of the residue gave the *title compound* **16** (20 mg, 13%) as a white solid, m.p. 126–128 °C; δ 3.92 (3 H, s, OCH_3), 5.33 (2 H, d, *J* 1.1, pyran-H_2), 6.99 (1 H, dd, *J* 8.1 and 1.8, ArH), 7.04 (1 H, t, *J* 8, ArH), 7.50 (1 H, dd, *J* 7.5 and 1.8, ArH) and 8.23 (1 H, t, *J* 1.1, isoxazole-H); *m*/*z* (EI) 203.1606 (M) ($C_{11}H_9NO_3$ requires 203.1582).

2-(3-*Methoxy*-2-*prop*-2-*ynyloxyphenyl*)-4,5-*dihydro*-1,3-*dioxole* **17**.—The aldehyde **12** (1.90 g, 10 mmol) was stirred at reflux with ethane-1,2-diol (680 mg, 11 mmol) and 4-methylbenzenesulfonic acid hydrate (10 mg) in toluene (25 cm^3) with azeotropic removal of water for 24 h. The mixture was evaporated and the residue chromatographed (dichloromethane–pentane, 1:1) to give the *title compound* **17** (2.11 g, 90%) as a white solid, m.p. 93–94 °C (Found: C, 66.55; H, 5.95. $C_{13}H_{14}O_4$ requires C, 66.65; H, 6.00%); δ 2.49 (1 H, br, C≡CH), 3.87 (3 H, s, OCH_3), 4.00–4.20 (4 H, m, CH_2CH_2), 4.77 (2 H, d, *J* 1.5, $CH_2C{\equiv}C$), 6.23 (1 H, s, dioxole 2-H) and 6.95–7.15 (3 H, m, Ar-H_3); *m*/*z* (EI) 234.0876 (M) ($C_{13}H_{14}O_4$ requires 234.0892).

2-(3-*Methoxy*-2-*prop*-2-*ynyloxyphenyl*)-4,5-*dihydro*-1,3-*dithiole* **19**.—The aldehyde **12** (950 mg, 5 mmol) and ethane-1,2-dithiol (940 mg, 10 mmol) in dry dichloromethane (10 cm^3) were treated dropwise with boron trifluoride–diethyl ether complex (710 mg, 5 mmol). The mixture was stirred for 24 h after which it was diluted with water (10 cm^3) and extracted with chloroform. The extract was evaporated and the residue chromatographed (pentane–dichloromethane, 4:1) to give the *title compound* **19** (700 mg, 53%) as a colourless oil; δ 2.49 (1 H, t, *J* 2.4, C≡CH), 3.30–3.54 (4 H, m, CH_2CH_2), 3.85 (3 H, s, OCH_3), 4.79 (2 H, d, *J* 2.4, $CH_2C{\equiv}C$), 6.21 (1 H, s, dithiole 2-H) and 6.81–7.35 (3 H, m, Ar-H_3).

2-[2-(1,2-*Dicarba*-closo-*dodecaboran*(12)-1-*yl*)*methoxy*-3-*methoxyphenyl*]-4,5-*dihydro*-1,3-*dithiole* **20**.—Decaborane(14) ($B_{10}H_{14}$) (120 mg, 1 mmol) was stirred in dry acetonitrile (10 cm^3) for 2 h after which the dithiole **19** (270 mg, 1 mmol) was added to it and the mixture boiled under reflux for 3 d. Evaporation of the mixture gave a residue which was chromatographed (pentane–dichloromethane, 10:1) and the resulting product recrystallised from hexane–benzene (CAUTION) to furnish the *title compound* **20** (200 mg, 52%) as white crystals, m.p. 132–133 °C (Found: C, 40.6; H, 6.35. $C_{13}H_{24}B_{10}O_2S_2$ requires C, 40.6; H, 6.25%); ν_{max}/cm^{-1} 2540; δ 1.0–3.2 (10 H, br m, $B_{10}H_{10}$), 3.41 (4 H, m, CH_2CH_2), 3.83 (3 H, s, OCH_3), 4.31 (1 H, br s, carborane 2-H), 4.44 (2 H, s, carborane-CH_2), 5.89 (1 H, s, dithiole 2-H) and 6.81–7.33 (3 H, m, Ar-H_3); *m*/*z* (FAB, positive ion) $^{10}B/^{11}B$ cluster centred at 385 (M + H).

4-*Prop*-2-*ynyloxybenzaldehyde* **22**.—4-Hydroxybenzaldehyde **21** (6.1 g, 50 mmol) was added to sodium ethoxide (50 mmol) in dry ethanol (100 cm^3), followed by 3-bromopropyne (6.55 g, 55 mmol). The mixture was boiled under reflux for 3 h and then evaporated. The residue was dissolved in dichloromethane and the solution washed with water, dried and evaporated to afford the *title compound* **22** (5.08 g, 64%) as a buff solid, m.p. 70–72 °C (lit.,[21] m.p. 79–80 °C); δ 2.58 (1 H, t, *J* 2.5, C≡CH), 4.79 (2 H, d, *J* 2.5, $CH_2C{\equiv}C$), 7.10 (2 H, d, *J* 8.8, Ar 3,5-H_2), 7.86 (2 H, d, *J* 8.8, A 2,6-H_2) and 9.91 (1 H, s, CHO).

2-(4-*Prop*-2-*ynyloxyphenyl*)-4,5-*dihydro*-1,3-*dithiole* **23**.—Boron trifluoride–diethyl ether complex (4.26 g, 30 mmol) was added to the aldehyde **22** (4.8 g, 30 mmol) and ethane-1,2-dithiol (5.64 g, 60 mmol) in dichloromethane (150 cm^2) at 0 °C and the mixture was stirred at ambient temperature for 16 h. It was then washed with water and evaporated. Chromatography (pentane–dichloromethane, 4:1) of the residue gave the *title compound* **23** (5.68 g, 80%) as a colourless oil; δ 2.52 (1 H, t, *J* 2.5, C≡CH), 3.33 (2 H, m) and 3.47 (2 H, m) (CH_2CH_2), 4.65 (2 H, d, *J* 2.5, $CH_2C{\equiv}C$), 5.63 (1 H, s, dithiole 2-H), 6.91 (2 H, d, *J* 8.8, Ar 3,5-H_2) and 7.46 (2 H, d, *J* 8.8, Ar 2,6-H_2). This material was used directly without further purification.

1-[4-(4,5-*Dihydro*-1,3-*dithiol*-2-*yl*)*phenoxymethyl*]-1,2-*dicarba*-closo-*dodecaborane*(12) **24**.—Decaborane(14) ($B_{10}H_{14}$) (2.44 g, 20 mmol) was stirred with acetonitrile (200 cm^3) for 3 h after which the dithiole **23** (4.72 g, 20 mmol) was added to the mixture. After being boiled under reflux for 3 d the mixture was evaporated and the residue chromatographed (pentane–dichloromethane, 4:1) to yield the *title compound* **24** (3.62 g, 51%) as a white solid, m.p. 123–125 °C (Found: C, 40.9; H, 6.2. $C_{12}H_{22}B_{10}OS_2$ requires C, 40.7; H, 6.3%); ν_{max}/cm^{-1} 2590; δ_H 1.5-3.0 (10 H, br m, $B_{10}H_{10}$), 3.34 (2 H, m) and 3.49 (2 H, m) (CH_2CH_2), 4.08 (1 H, br s, carborane 2-H), 4.39 (2 H, s, carborane-CH_2), 5.60 (1 H, s, dithiole 2-H), 6.77 (2 H, d, *J* 8.8, Ar 3,5-H_2) and 7.46 (2 H, d, *J* 8.8, Ar 2,6-H_2); δ_B (H-decoupled) −15.0 (4 B), −13.5 (2 B), −10.7 (2 B), −6.5 (1 B) and −4.5 (1 B); *m*/*z* (EI) $^{10}B/^{11}B$ cluster centred at 354 (M), $^{10}B^{11}B$ isotope cluster centred at 326 (M − C_2H_4).

1-(4-*Formylphenoxymethyl*)-1,2-*dicarba*-closo-*dodecaborane*(12) **25**.—The dithiole **24** (356 mg, 1 mmol) was stirred with mercury(II) perchlorate trihydrate (1.00 g, 2.2 mmol) in THF (8 cm^3) for 5 min. The suspension was then filtered and the filtrate evaporated to afford a residue which was dissolved in dichloromethane and the solution washed twice with aqueous sodium carbonate (10%), dried and evaporated to give the *title compound* **25** (250 mg, 90%) as white crystals, m.p. 148–151 °C (Found: C, 42.8; H, 6.5. $C_{10}H_{18}B_{10}O_2$ requires C, 40.7; H, 6.3%); ν_{max}/cm^{-1} 2580 and 1690; δ 1.3–3.4 (10 H, br m, $B_{10}H_{10}$), 4.07 (1 H, br s, carborane 2-H), 4.51 (2 H, s, carborane-CH_2), 6.97 (2 H, d, *J* 8.8, Ar 2,6-H_2), 7.87 (2 H, d, *J* 8.8, Ar 3,5-H_2) and 9.92 (1 H, s, CHO); *m*/*z* (EI) $^{10}B/^{11}B$ cluster centred at 278 (M).

1-[4-(*Hydroxyiminomethyl*)*phenoxymethyl*]1,2-*dicarba*-closo-*dodecaborane*(12) **26**.—The aldehyde **25** (1.39 g, 5 mmol) was stirred with hydroxylamine hydrochloride (1.74 g, 25 mmol) and sodium carbonate (1.33 g, 12.5 mmol) in dry ethanol (50 cm^3) for 2 d after which the mixture was evaporated. The residue was dissolved in ethyl acetate and the solution washed with water and dried. Chromatography (dichloromethane) gave the title compound **26** (830 mg, 71%) as a white solid, m.p. 174–176 °C; ν_{max}/cm^{-1} 3300 and 2600; δ[$(CD_3)_2CO$] 1.3–3.4 (10 H,

br m, $B_{10}H_{10}$), 4.70 (2 H, s, carborane-CH_2), 5.00 (1 H, br s, carborane 2-H), 7.02 (2 H, d, *J* 9.1, Ar 2,6-H_2), 7.57 (2 H, d, *J* 9.1, Ar 3,5-H_2), 8.08 (1 H, s, C*H*NOH) and 10.19 (1 H, s, OH); *m/z* (EI) 295.2388 (M) ($C_{10}H_{19}{}^{11}B_{10}NO_2$ requires 295.2346), 294.2420 (M) ($C_{10}H_{19}{}^{10}B^{11}B_9NO_2$ requires 294.2381), 293.2449 (M) ($C_{10}H_{19}{}^{10}B_2{}^{11}B_8NO_2$ requires 293.2419) and 292.2454 (M) ($C_{10}H_{19}{}^{10}B_3{}^{11}B_7NO_2$ requires 292.2455).

1-(4-{3-[4-(1,2-*Dicarba*-closo-*dodecaboran*(12)-1-*ylmethoxy*)*phenyl*]-4,5-*dihydroisoxazol*-5-*yl*}*butyl*)-2-*nitroimidazole* **28** *and* 4-(1,2-*Dicarba*-closo-*dodecaboran*(12)-1-*ylmethoxy*)-*benzonitrile* N-*Oxide* **32**.—The oxime **26** (290 mg, 1 mmol) and 1-hex-5-enyl-2-nitroimidazole **27**[9] (200 mg, 1 mmol) in dichloromethane (8 cm^3) were stirred vigorously with aqueous sodium hypochlorite (8% available chlorine; 2 cm^3) for 18 h. Further aqueous sodium hypochlorite (6 cm^3) was added to the mixture which was then stirred for a further 1.5 h. It was then washed with water and evaporated and the residue chromatographed (pentane–dichloromethane, 1:1, then dichloromethane, then ethyl acetate) to give the *title compound* **32** (110 mg, 38%) (from the first fraction) as a white solid, m.p. 212–216 °C (decomp.); ν_{max}/cm^{-1} 2600 and 2310 cm^{-1}; δ 1.0–3.2 (10 H, br m, $B_{10}H_{10}$), 3.97 (1 H, br s, carborane 2-H), 4.38 (2 H, s, carborane-CH_2), 6.82 (2 H, d, *J* 9.0, Ar 3,5-H_2) and 7.40 (2 H, d, *J* 9.0, Ar 2,6-H_2); *m/z* (EI) 291.2262 (M) ($C_{10}H_{17}{}^{10}B_2{}^{11}B_8NO_2$ requires 291.2262), $^{10}B/^{11}B$ cluster centred on 291 (M), and $^{10}B/^{11}B$ isotope cluster centred on 275 (100%) (M − O). From the third fraction was obtained the *title compound* **28** (280 mg, 57%) as a gummy solid; ν_{max}/cm^{-1} 2600; δ 1.3–3.3 (10 H, br m, $B_{10}H_{10}$), 1.5–2.0 (6 H, m, imidazole-$CH_2CH_2CH_2CH_2$), 2.93 (1 H, dd, *J* 16.5 and 7.9) and 3.40 (1 H, dd, *J* 16.5 and 10.4) (isoxazole 4-H_2), 4.09 (1 H, br s, carborane 2-H), 4.45 (4 H, m, carborane-CH_2 + imidazole-CH_2), 4.73 (1 H, ddt, *J* 10, 8 and 7, isoxazole 5-H), 6.87 (2 H, d, *J* 9.0, Ar 3,5-H_2), 7.11 (1 H, s) and 7.15 (1 H, s) (imidazole 4,5-H_2) and 7.61 (2 H, s, *J* 9.0, Ar 2,6-H_2); *m/z* (FAB, positive ion) 487.3296 (M + H) ($C_{19}H_{31}{}^{10}B_2{}^{11}B_8N_4O_4$ requires 487.3348).

1-(2-{3-[4-(1,2-*Dicarba*-closo-*dodecaboran*(12)-1-*ylmethoxy*)*phenyl*]*isoxazol*-5-*yl*}*ethyl*)-2-*nitroimidazole* **29**.—The oxime **26** and the nitroimidazolealkyne **3** were treated with sodium hypochlorite, as for the synthesis of compound **28** above. Chromatography (pentane–dichloromethane, 1:1, then dichloromethane, then dichloromethane–diethyl ether, 2:1) gave the *N*-oxide **32** (38%) (from the first fraction) and then the *title compound* **29** (57%) (from the third fraction) as a white solid, m.p. 151–154 °C; ν_{max}/cm^{-1} 2590; δ 1.3–3.3 (10 H, br m, $B_{10}H_{10}$), 3.42 (2 H, t, *J* 6.7, imidazole-CH_2CH_2), 4.09 (1 H, br s, carborane 2-H), 4.46 (2 H, s, carborane-CH_2), 4.82 (2 H, t, *J* 6.7, imidazole-CH_2), 6.26 (1 H, s, isoxazole 4-H), 6.92 (2 H, d, *J* 8.8, Ar 3,5-H_2), 6.96 (1 H, s) and 7.09 (1 H, s) (imidazole 4,5-H_2) and 7.70 (2 H, s, *J* 9.0, Ar 2,6-H_2); *m/z* (EI) 458.2786 (M) ($C_{17}H_{24}{}^{11}B_{10}N_4O_4$ requires 458.2728), 457.2798 (M) ($C_{17}H_{24}{}^{10}B^{11}B_9N_4O_4$ requires 457.2764), 456.2827 (M) ($C_{17}H_{24}{}^{10}B_2{}^{11}B_8N_4O_4$ requires 456.2801), 455.2865 (M) ($C_{17}H_{24}{}^{10}B_3{}^{11}B_7N_4O_4$ requires 455.2837) and 454.2886 (M) ($C_{17}H_{24}{}^{10}B_4{}^{11}B_6N_4O_4$ requires 454.2873).

2-*Nitro*-1-{2-[2-(2-*prop*-2-*ynyloxyethoxy*)*ethoxy*]*ethyl*}*imidazole* **30**.—2-Nitroimidazole **2** (460 mg, 4 mmol) was stirred at 130 °C in DMF (10 cm^3) with potassium *tert*-butoxide (440 mg, 4 mmol) for 30 min. Potassium iodide (20 mg) and the alkyne **7** (840 mg, 4 mmol) were added to the mixture which was then stirred at 130 °C for 13 h. The mixture was evaporated and the residue was dissolved in dichloromethane and the solution washed with water, dried and evaporated. Chromatography (dichloromethane) of the residue gave the *title compound* **30** (490 mg, 43%) as a yellow oil; δ 2.45 (1 H, t, *J* 2.4, C≡CH), 3.60 (4 H, s) and 3.6–3.7 (4 H, m) (2 × OCH_2CH_2O), 3.86 (2 H, t, *J* 4.9, imidazole-CH_2CH_2), 4.20 (2 H, d, *J* 2.4, $CH_2C{\equiv}C$), 4.63 (2 H, t, *J* 4.9, imidazole-CH_2), and 7.14 (1 H, s) and 7.29 (1 H, s) (imidazole 4,5-H_2); *m/z* (CI) 284.1246 (M + H) ($C_{12}H_{18}N_3O_5$ requires 284.1246).

3-[4-(1,2-*Dicarba*-closo-*dodecaboran*(12)-1-*ylmethoxy*)-*phenyl*]-5-(2-{2-[2-(2-*nitroimidazol*-1-*yl*)*ethoxy*]*ethoxy*}*methyl*)*isoxazole* **31**.—The oxime **26** and the alkyne **30** were treated with sodium hypochlorite, as for the synthesis of compound **28** above. Chromatography (pentane–dichloromethane, 1:1, then dichloromethane–diethyl ether, 1:1) gave the *title compound* **31** (79%) as a pale yellow oil; ν_{max}/cm^{-1} 2600; δ [$(CD_3)_2SO$] 1.2–3.1 (10 H, br, $B_{10}H_{10}$), 3.45–3.65 (8 H, m, 2 × OCH_2CH_2O), 3.76 (2 H, t, *J* 5.1, imidazole-CH_2CH_2), 4.57 (2 H, t, *J* 5.1, imidazole-CH_2), 4.65 (2 H, s, carborane-CH_2), 5.37 (1 H, br s, carborane 2-H), 5.76 (1 H, s, isoxazole 4-H), 7.12 (2 H, d, *J* 9.0, Ar 2,6-H_2), 7.14 (1 H, d, *J* 1.1, imidazole 4-H), 7.62 (1 H, d, *J* 1.1, imidazole 5-H) and 7.84 (2 H, d, *J* 9.0, Ar 3,5-H_2); *m/z* (FAB, positive ion) 577.344 (M + H) (100%) ($C_{22}H_{35}{}^{11}B_{10}N_4O_7$ requires 577.344).

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