5-Nitrofuran-2-ylmethyl group as a potential bioreductively activated pro-drug system

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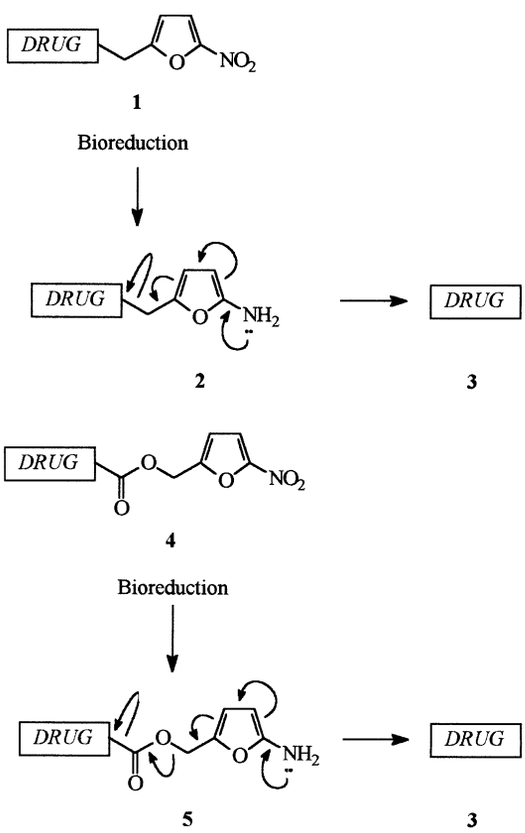
5-Substituted isoquinolin-1-ones have been synthesised by one-pot Curtius rearrangement of the corresponding substituted 3-phenylpropenoyl azides and cyclisation. Arylmethylation of the anions of the isoquinolinones with benzyl halides [4-methoxybenzyl chloride, 2-(chloromethyl)furan and 5-nitro-2-(tosyloxymethyl)furan] takes place exclusively at nitrogen. Nitration of 2-(furan-2-ylmethyl)isoquinolin-1-one in strongly acidic medium gives 2-(5-nitrofuran-2-ylmethyl)isoquinolin-1-one, whereas weaker acidic conditions lead to dinitration. Curtius rearrangement of 3-carboranylbutanoyl azide and trapping with 5-nitrofuran-2-ylmethanol gives 5-nitrofuran-2-ylmethyl *N*-(3-carboranylpropyl)carbamate. Biomimetic reduction of these nitrofuranylmethyl derivatives of anticancer drugs triggers release of the parent drugs. Thus, these nitrofurans have potential applications as pro-drugs for selective release of therapeutic drugs in hypoxic solid tumours.

Regions of chronic and acute hypoxia are present in most solid tumours owing to the primitive state of the tumour vasculature.[1] Viable cells in such tissue are relatively resistant to radiotherapy and to many chemotherapeutic strategies.[1] Much effort has been expended[2] on development of radiosensitisers with electron-affinity and bioreductively activated cytotoxins for selective therapy of this tissue, and of a variety of pro-drugs to deliver cytotoxins selectively to tumours. 1-Substituted 2-nitroimidazoles are known[3,4] to be selectively retained in hypoxic tissue by reductive metabolism. However, relatively little attention has hitherto been focussed on exploiting the physiological difference in concentration of molecular oxygen between normal and hypoxic tumour tissue by design of biologically inactive pro-drug systems which, upon selective bioreduction in hypoxic tissue, would release known therapeutic drugs only in that tissue. This would improve greatly the selectivity of biodistribution of such agents. Sykes *et al*. have reported[5] early studies on a bioreductively triggered release system based on 2-nitroarylamides, whereas 4-nitrobenzyloxycarbonyl pro-drugs have been put forward[6] for use in the Antibody-Directed Enzyme Prodrug Therapy (ADEPT) strategy, using a bacterial nitroreductase attached to a tumour-selective antibody. For the potential pro-drugs described here, 2-nitrofuran was selected as the redox-sensitive moiety. The redox potential of this heterocycle is relatively high [E^1_7 = −325 mV for 2-methyl-5-nitro-*N*-(prop-2-enyl)furan-3-carboxamide],[7] which would favour selective reductive metabolism in hypoxic tumour tissue effected by endogenous enzymes such as cytochrome P450 reductase.[8] The general design of the pro-drugs and the mechanisms of bioreductively triggered release are shown in Scheme 1. For the simpler pro-drugs **1**, the 5-nitrofuran-2-ylmethyl unit is attached to a heteroatom in the drug. Reduction in hypoxic tumour tissue will give the corresponding aminofuran **2** (or the analogous hydroxylamine). The presence of an available electron pair will then promote fragmentation as shown to release the drug **3** in the tumour tissue. This fragmentation is clearly not available to the nitrofuran **1**. Where appropriate, the nitrofuranylmethyl unit could be linked to the drug by an additional readily fissile group, as in the carbamate pro-drugs **4**. Bioreductively triggered fragmentation will again afford **3** according to the mechanism shown. Here



Scheme 1 Proposed mechanisms of bioreductively triggered release of drugs from general nitrofuranylmethyl pro-drugs **1** and **4**

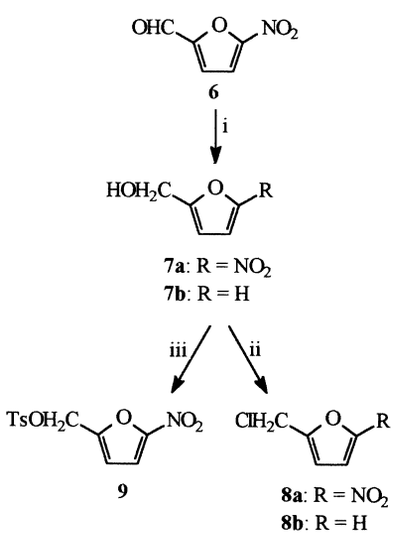
we report syntheses of examples of pro-drugs of each type (**1** and **4**) and biomimetic studies on the release of parent drugs **3**.

Isoquinolin-1-one **18d** and several 5-substituted analogues are potent inhibitors[9] of poly(ADP-ribose)polymerase (PARP), an enzyme with a central role in initiating excision repair of DNA following damage by radiation or electrophilic drugs. Thus inhibitors of PARP are potentiators of these

therapeutic strategies. Prodrugs which selectively release isoquinolinones in hypoxic tumour tissue would therefore act as tumour-selective radiosensitisers. In the design of these pro-drugs, it is necessary to conceal the arylcarboxamide motif, with the N–H held *syn* to the carbonyl oxygen, which is essential for enzyme inhibitory activity.[9,10] Within the context of the nitrofuranylmethyl system, this could be achieved through either 1-(5-nitrofuran-2-ylmethoxy)isoquinolines or 2-(5-nitrofuran-2-ylmethyl)isoquinolin-1-ones, pro-drugs of general type **1**.

To form examples of pro-drugs of type **4**, with the carbamate link, 2-phenylethylamine was selected as a model and a carboranylalkylamine was selected as a drug for delivery. Boron neutron capture therapy (BNCT) is under active investigation for the treatment of various cancers, notably gliomas and melanomas.[11] When the ^{10}B isotope is irradiated with slow ('thermal') neutrons, an [n,α] reaction ensues, giving ^{7}Li and ^{4}He nuclei with kinetic energy (2.31 MeV). With this energy, the α-particle has a range of *ca*. one cell diameter in biological tissue and damage is limited to the cell containing the boron. Early clinical failures of BNCT were attributed[12,13] to inadequate concentrations of ^{10}B in the tumour tissue or to lack of selectivity of disposition of ^{10}B, leading to damage of normal tissue. Carboranes have been linked to nucleosides,[14] to porphyrins[15] and to nitroimidazoles[4,16,17] in attempts to target boron selectively to tumours. Where a 5-nitrofuran-2-ylmethyl *N*-(carboranylalkyl)carbamate forms pro-drug **4**, selective bioreduction in a hypoxic tumour cell would release a carboranylalkylamine, which, at the relatively acidic pH of a tumour cell, would be protonated and hence unable to diffuse out through the cell membrane. Boron would therefore accumulate in the tumour tissue.

To provide nucleophilic and electrophilic reagents to introduce the nitrofuranylmethyl group into the pro-drugs, the alcohol **7a** and the nitrofuranylmethyl electrophiles **8a** and **9** were prepared (Scheme 2). Attempts to reduce 5-nitrofuran-2-



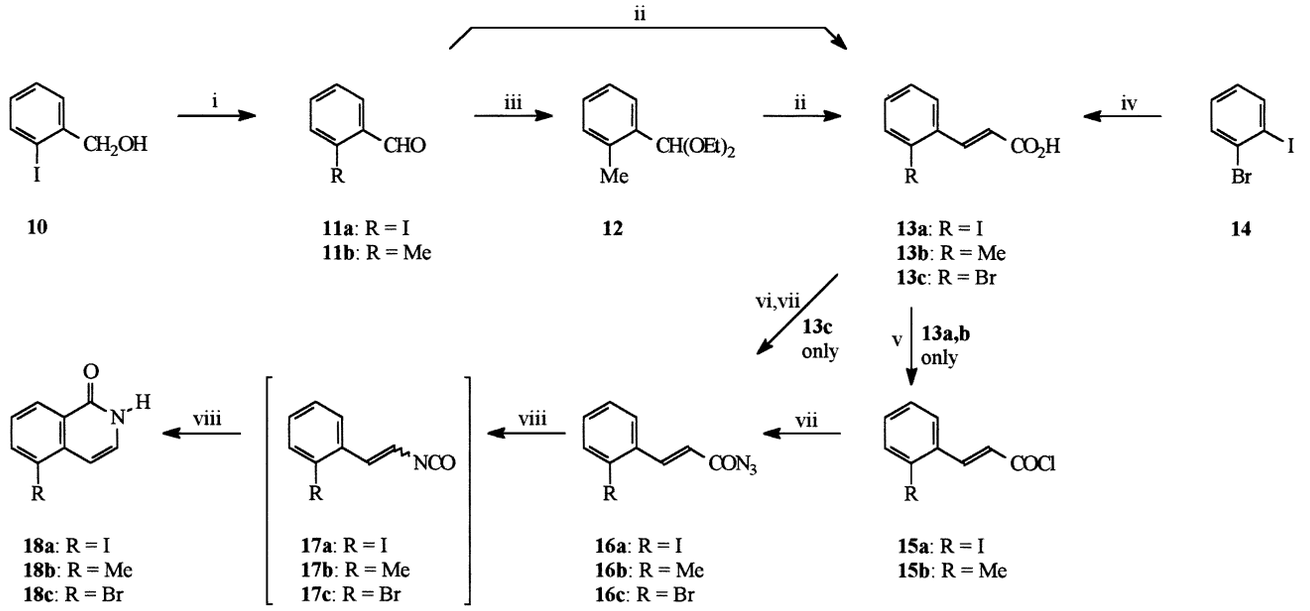
Scheme 2 Synthesis of electrophilic (nitro)furan-2-ylmethyl reagents **8a,b** and **9**. *Reagents:* i, $Al(OPr^i)_3$, Pr^iOH; ii, $SOCl_2$, pyridine, $CHCl_3$; iii, TsCl, KOH, THF.

carbaldehyde **6** selectively at the aldehyde using sodium borohydride were unsuccessful, leading only to products of degradation, in contrast to a previous report.[18] However, Meerwein–Ponndorf–Verley reduction gave the required nitrofuranylmethanol **7a** almost quantitatively. Activation of the methylene as an electrophile was attempted through conversion into the corresponding chloromethylnitrofuran **8a** and the tosylate **9**, respectively. Replacement of OH with Cl to give **8a** was achieved by treatment of **7a** with thionyl chloride and pyridine in a modification of the method of Wang *et al*.[19] Reaction of **7a** with tosyl chloride in the presence of powdered potassium hydroxide afforded the tosylate **9** in modest isolated yield.

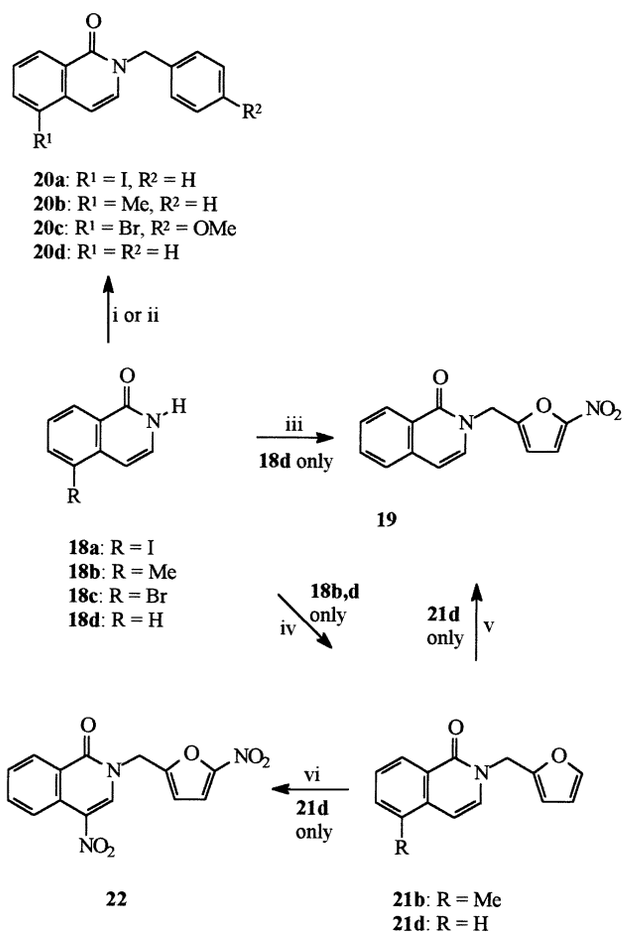
1-Alkoxyisoquinolines have been prepared by substitution in the corresponding 1-chloroisoquinolines using sodium alkoxides under vigorous conditions, although the range of 1-alkoxy substituents reported to have been introduced in this way has been restricted to simple examples,[20] such as methoxy and ethoxy. 1-Benzyloxyisoquinoline has not been reported. Treatment of 1-chloroisoquinoline[21] with 5-nitrofuran-2-ylmethanol **7a** and furan-2-ylmethanol **7b** alkoxides gave only products of furan degradation under a variety of reaction conditions, making the corresponding pro-drugs unavailable by this route.

The usual route for preparation of 2-substituted isoquinolin-1-ones has been oxidation of 2-substituted isoquinolinium salts in the presence of hydroxide ion.[22] However, this is inappropriate for preparation of the proposed pro-drugs, owing to the harsh reaction conditions required. Routes employing *N*-alkylation of isoquinolin-1-ones were therefore investigated. A convenient synthesis of isoquinolin-1-ones by Curtius rearrangement of cinnamyl azides and thermal cyclisation, in a one-pot process, has been described by Eloy and Deryckere,[23] although this is limited to isoquinolinones without electron-withdrawing substituents. 2-Iodobenzyl alcohol **10** was oxidised to the corresponding aldehyde **11a** with pyridinium dichromate and a direct condensation with malonic acid afforded the iodocinnamic acid **13a** (Scheme 3). 2-Methylbenzaldehyde **11b** had to be converted into its diethyl acetal **12** for efficient condensation under the Knoevenagel–Doebner conditions[24] to give the methylcinnamic acid **13b**. The corresponding bromocinnamic acid **13c** was prepared from 2-bromoiodobenzene in a convenient modification of the iodine–selective Heck reaction conditions used by Plevyak *et al*.[25] Use of boiling propionitrile as the reaction solvent obviated the need for the sealed tube required to conduct the reaction at 100 °C in acetonitrile. Various modifications of the original conditions of Eloy and Deryckere[23] were investigated for the Curtius rearrangement and cyclisation sequence. The iodocinnamic acid **13a** was converted into its acid chloride **15a** and treatment with sodium azide furnished the acid azide **16a**. For ease of isolation of the product 5-iodoisoquinolin-1-one **18a** from the reaction mixture by precipitation with water, the Curtius rearrangement and cyclisation were effected in boiling dry tetraglyme. The acid chloride **15b** and acid azide **16b** of the methylcinnamic acid were prepared similarly, but the original boiling diphenyl ether was found to be the optimum solvent for the high-yielding synthesis and isolation of 5-methylisoquinolin-1-one **18b**. The bromoisoquinolinone **18c** was prepared similarly but in poor yield, using the acid azide **16c** formed from a mixed anhydride.

The relatively few reports[26] of alkylation of isoquinolinones indicate that alkylation of isoquinolin-1-ones with simple halogeno alkanes occurs predominantly at the nitrogen of the conjugate anion under a variety of conditions. Two sets of conditions were used in a series of model experiments designed to establish the site of reaction of isoquinolinone anions with halogenomethyl arenes and to optimise the reaction conditions. The anion formed from 5-iodoisoquinolinone **18a** and lithium hexamethyldisilazide was benzylated in high yield by benzyl chloride, giving **20a**. The 5-bromo analogue **18c** was also converted into the *N*-(4-methoxybenzyl) derivative **20c** under these conditions. Benzylation of the sodium anion of isoquinolinone **18d** with benzyl bromide in DMF was also highly efficient in forming **20d**, although the yield in the corresponding benzylation of 5-methylisoquinolinone **18b** to give **20b** was poor. However, treatment of the anion derived from reaction of isoquinolin-1-one **18d** with sodium hydride and with lithium hexamethyldisilazide with the chloromethylnitrofuran **8a** failed to give the required *N*-(nitrofuranylmethyl)isoquinolinone **19**. Compound **19** was formed in poor isolated yield (24%) when the sodium salt of **18d** was treated with the more reactive tosylate **9** in



Scheme 3 Synthesis of isoquinolin-1-ones **18a–c**. *Reagents:* i, pyridinium dichromate, CH_2Cl_2; ii, $CH_2(CO_2H)_2$, piperidine, pyridine; iii, $HC(OEt)_3$, $SOCl_2$, EtOH; iv, $H_2C{=}CHCO_2H$, $Pd(OAc)_2$, Et_3N, EtCN; v, $SOCl_2$, DMF; vi, EtO_2CCl, Et_3N, Me_2CO; vii, NaN_3, water, 1,4-dioxane or acetone; viii, heat, Ph_2O or $(MeOCH_2CH_2OCH_2CH_2)_2O$.



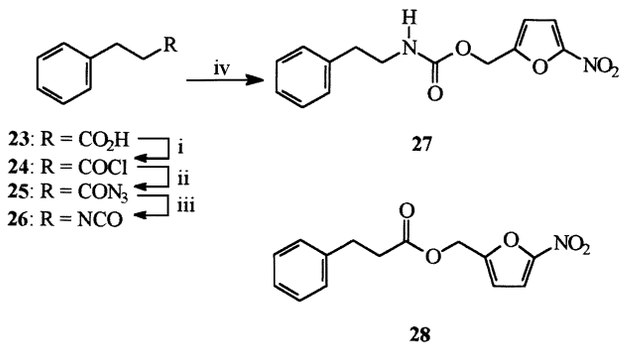
Scheme 4 Synthesis of 1-(arylmethoxy)isoquinolines **20a–d**, 2-(furan-2-ylmethyl)isoquinolin-1-ones **21b,d** and 2-(5-nitrofuran-2-ylmethyl)-isoquinolin-1-one **19**. *Reagents:* i, $LiN(SiMe_3)_2$, BnCl, THF or NaH, BnBr, DMF; ii, $LiN(SiMe_3)_2$, 4-$MeOC_6H_4CH_2Cl$, THF; iii, NaH, **9**, DMF; iv, $LiN(SiMe_3)_2$, **8b**, THF; v, CF_3CO_2H, HNO_3 or $Cu(NO_3)_2$; vi, *e.g.* HNO_3, HOAc.

DMF. Assignment of the structures of **20a,b,d** and **21b,d** as being the *N*-(arylmethyl)isoquinolin-1-ones rather than the 1-(arylmethoxy)isoquinolines was made by ^{13}C NMR spectroscopy and, in the case of **20a**, by IR spectroscopy. The CH_2 groups resonated at δ 51.90, 51.68, 51.59, 44.33 and 44.16, respectively, values which correspond closely to those typical for $ArCH_2N$ but not $ArCH_2O$. The IR spectrum of **20a** contained a band at 1650 cm^{-1}, indicating a carbonyl group. The structure of **20c** was assigned by analogy. Since the target nitrofuran **19** prepared by alkylation of **18d** with **9** was identical with material formed by selective nitration of **21d**, the nitrofuranylmethylation must also have taken place at *N*, rather than at *O*.

As the combined yield over two steps **7a**→**9**→**19** was very low (6%), an alternative longer route was developed. Reaction of the lithium salt of isoquinolin-1-one **18d** with freshly prepared unstable chloromethylfuran **8b**[27] in THF gave a moderate yield of the *N*-furanylmethylisoquinoline **21d**. The 5-methyl analogue **21b** was formed similarly. Selective nitration at the furan 5-position was then required to form **19**. The usual conditions for nitration of furans and related heterocycles are relatively mild, *e.g.* acetyl nitrate or nitric acid in acetic acid. However, all applications of these and other relatively weakly acidic nitrating conditions gave only the dinitrated product **22** where the isoquinolinone 4-position has also reacted. In an extensive study of substitution of isoquinolin-1-ones, Horning *et al.*[28] reported that the principal site of reaction of various electrophiles was the 4-position. However, Kawazoe and Yoshioka[29] noted that, on treatment of **18d** with potassium nitrate in concentrated sulfuric acid, nitration took place at the 5- and 7-positions, presumably owing to deactivation of the heterocyclic ring by protonation. Adopting this approach to selective deactivation of the nitrogen heterocycle, the reaction of a solution of **21d** in trifluoroacetic acid with nitric acid or, preferably, copper(II) nitrate at low temperature effected selective mononitration on the furan, giving the target *N*-(nitrofuranylmethyl)isoquinolinone **19**. Traces of the dinitro compound **22** were also isolated but the major by-product was the parent isoquinolinone **18d** resulting from dealkylation under the acidic conditions. The 5-methyl analogue **21b** gave the parent 5-methylisoquinolinone **18b** as the only isolable product. Thus the sequence **7b**→**8b**→**21d**→**19** proceeded in higher overall yield (16%) than the more direct sequence above.

Since it was planned to form the carbamate link in the target carborane-nitrofuran **38** by addition of 5-nitrofuran-2-ylmethanol **7a** to an appropriate isocyanate, model reactions for the Curtius rearrangement and addition were investigated. The model sequence, in which phenyl replaces carboranyl, also

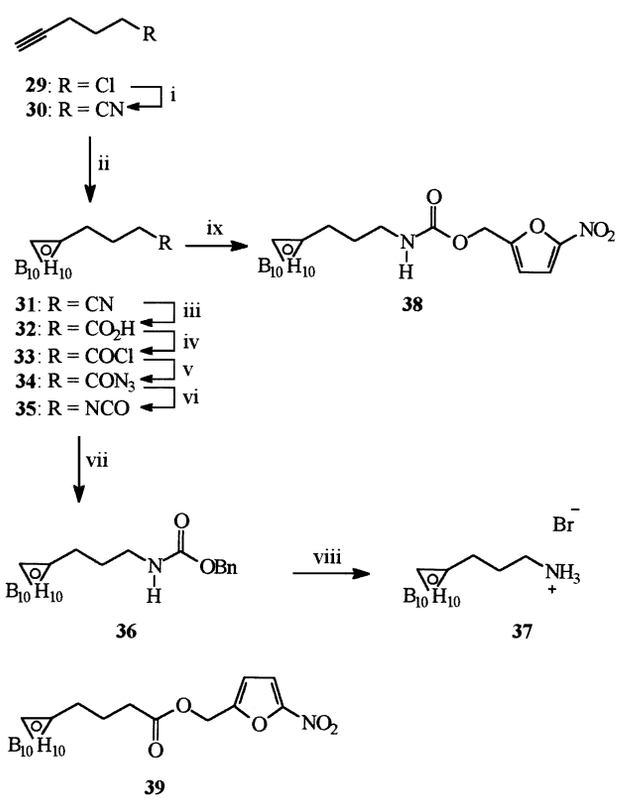
provides another target compound in which the biomimetic reductively triggered release from a pro-drug **4** can be studied. 3-Phenylpropanoic acid **23** was converted into its acid chloride **24** and hence to the acid azide **25** (Scheme 5). Curtius



Scheme 5 Synthesis of nitrofuranylmethyl *N*-(2-phenylethyl)carbamate **27**. *Reagents:* i, $(COCl)_2$; ii, Me_3SiN_3, PhMe; iii, heat, PhMe; iv, **7a**.

rearrangement in boiling toluene gave the isocyanate **26** which was not isolated but was trapped by reaction with **7a** under basic conditions, giving the nitrofuranylmethyl carbamate **27**. From some runs of this reaction, significant yields of the ester **28** were also isolated, indicating incomplete Curtius rearrangement.

Scheme 6 shows the application of this sequence to the synthesis of the nitrofuranylmethyl *N*-(carboranylalkyl)carbamate **38**. Although the carboranebutanoic acid **32** has been reported[30] to be formed by carboxylation of the Grignard reagent derived from 1-(3-bromopropyl)-1,2-dicarba-*closo*-dodecaborane(12), the yield is low, owing to a competing cyclisation to give cyclopentano[1,2]-1,2-dicarba-*closo*-dodecaborane(12). An alternative method, in which all the required carbon atoms were present as the carborane was formed, was therefore developed. Hex-5-ynenitrile **30** was prepared straightforwardly from 5-chloropentyne **29**. Following the standard method for synthesis of carboranes from alkynes and decaborane(14) at elevated temperature in the presence of a Lewis base,[16,17,31] the cyanopropylcarborane **31** was prepared in excellent yield. Acidic hydrolysis afforded the carboranebutanoic acid **32**. Formation of the acid chloride **33**, substitution with sodium azide and Curtius rearrangement of **34** in warm chloroform afforded the isocyanate **35**. This was not isolated but was treated with benzyl alcohol under basic conditions to give the Z-protected carboranylpropylamine **36**. This sequence served both as a model for the reaction of **35** with arylmethanols and as an entry into the synthesis of the hitherto unreported carboranylpropylamine. Interestingly, treatment of **36** with hydrogen in the presence of palladium did not effect deprotection and it was necessary to remove the Z group with hydrogen bromide to give the salt **37**. With the carboranylpropylamine 'drug' **37** now available, the corresponding pro-drug **38** was prepared by addition of nitrofuranylmethanol **7a** to the isocyanate **35**. As with the phenylethyl series above, quantities of the analogous nitrofuranylmethyl ester **39** were obtained from some runs, again indicating incomplete Curtius rearrangement.

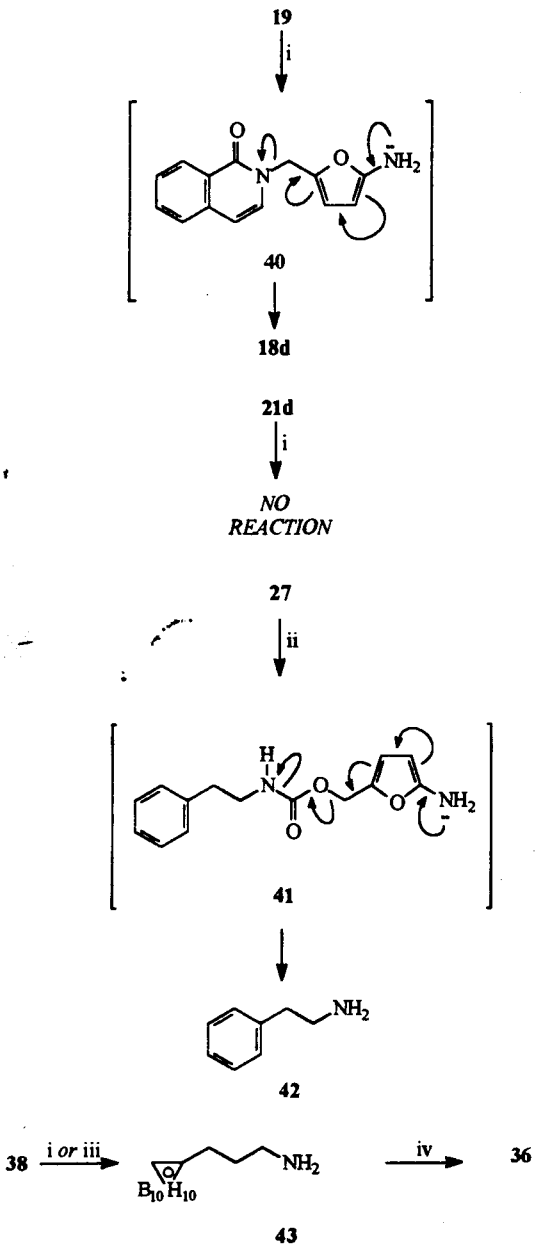


Scheme 6 Synthesis of nitrofuranylmethyl *N*-(3-carboranylpropyl)-carbamate **38**. *Reagents:* i, KCN, EtOH, water; ii, $B_{10}H_{14}$, MeCN; iii, H_2SO_4, water; iv, $SOCl_2$, DMF; v, NaN_3, Me_2CO, water; vi, heat, $CHCl_3$; vii, BnOH, Et_3N, $CHCl_3$; viii, HBr, HOAc; ix, **7a**, Et_3N, $CHCl_3$.

A mild method for selective chemical reduction of the nitro group was needed to test release of 'drugs' from the two types of pro-drug **1** and **4**. In particular, the conditions must not permit hydrogenolysis of the 'benzylic' CH_2–O or CH_2–N bonds, which would not be biomimetic for the nitroreductases and the cytochrome P450 reductase enzymes. Sodium borohydride in the presence of palladium fulfils these criteria,[17,32] although the usual solvent, methanol, was replaced by propan-2-ol in these studies to minimise any alcoholysis. Firstly, isoquinolinone **18d** was released in 67% yield by this method from pro-drug **19**, through the intermediacy of the aminofuran **40** (Scheme 7). The failure of the furanylmethyl analogue **21d** to release **18d** under the same conditions serves to validate the selectivity of the reduction by excluding a benzylic hydrogenolysis mechanism. An analogous selective reduction of the nitro group in the nitrofuranylmethyl carbamate **27** caused release of 2-phenylethylamine **42** in satisfactory yield, *via* the aminofuran **41**. The physical properties of the carboranylpropylamine were not conducive to easy isolation from boron-containing by-products in this reaction mixture. Therefore, after reductively triggered cleavage, the amine **43** was trapped as its Z derivative **36** by treatment with benzyl chloroformate. The Z-trapped drug was obtained in 26% yield, the relatively low yield being probably due to the isolation procedure. As a final positive control experiment, the pro-drug **38** was subjected to selective reduction of the nitro group by tin(II) chloride.[33] After the tin complex had been decomposed with sodium hydroxide, the carboranylpropylamine **43** was isolated in 40% yield.

A preliminary evaluation of the biological activities of the pro-drug **19** and the corresponding delivered drug **18d** was made to check that the pro-drug is indeed a less potent inhibitor of the target enzyme, PARP, than is the 2-unsubstituted isoquinolin-1-one drug. PARP was extracted with aqueous sodium chloride (0.4 M) from nuclei isolated from L929 murine areolar cells. The enzyme activity was measured in the presence and absence of test compounds by the rate of incorporation of radioactivity from NAD^+ labelled with ^3H in the adenosine into acid-insoluble material. At the test concentration, 10 μM, the pro-drug **19** inhibited the enzyme by 60% whereas isoquinolin-1-one **18d** inhibited the activity by >95% at the same concentration.

In conclusion, it can be seen that a potential bioreductively triggered pro-drug system has been developed, based on reduction of 5-nitrofuran-2-ylmethyl derivatives. The nitrofuranylmethyl group has been linked directly to the 2-position of iso-



Scheme 7 Reductively activated release of isoquinolinone **18d** and amines **42** and **43** from nitrofuranylmethyl ether **19** and carbamates **27** and **38**, respectively. *Reagents:* i, $NaBH_4$, Pd–C, Pr^iOH, water; ii, $NaBH_4$, Pd–C, MeOH, water; iii, $SnCl_2$, HCl, water; iv, ZCl, Et_3N, 4-pyrrolidinylopyridine, CH_2Cl_2.

quinolinone and through a carbamate to a carboranylalkylamine. Efficient syntheses of isoquinolinones **18a–c** and arylmethylations of these isoquinolinones have been developed. New selective methods for nitration of a furan in the competing presence of an isoquinolinone have been identified. Biomimetic reduction of the nitro group initiated efficient expulsion of isoquinolinone **18d** from pro-drug **19** and of the carboranylpropylamine **43** and carbon dioxide from the nitrofuranylmethyl carbamate pro-drug **38**. This pro-drug strategy could be extended into use of nitroheterocycles of different redox potentials carrying other functionalities to modify the physical properties and biodistribution of the pro-drugs.

Experimental

NMR Spectra were obtained of solutions in deuteriochloroform, unless otherwise stated; *J* values are given in Hz. Solutions in organic solvents were dried with anhydrous magnesium sulfate, unless otherwise noted. Solvents were evaporated under reduced pressure. The stationary phase for chromatography was silica gel. Brine refers to saturated aqueous sodium chloride. Ether refers to diethyl ether, unless otherwise stated. DMF refers to dry dimethylformamide, THF refers to dry tetrahydrofuran and EtOAc refers to ethyl acetate.

5-Nitrofuran-2-ylmethanol 7a

5-Nitrofuran-2-carbaldehyde **6** (3.8 g, 27 mmol) was boiled under reflux with aluminium isopropoxide (5.5 g, 27 mmol) in propan-2-ol (50 cm^3) for 4 h and the solvent was then evaporated. After the mixture had been treated with hydrochloric acid (1 M; 50 cm^3) and diluted with ether, it was washed (water), dried and evaporated. Chromatography (EtOAc–hexane, 1:1) of the residue gave the alcohol **7a** (3.8 g, 99%) as a pale yellow oil (lit.,[18,34] oil); δ_H 2.72 (1 H, br s, OH), 4.73 (2 H, s, CH_2), 6.57 (1 H, d, *J* 3.7, furan 3-H) and 7.30 (1 H, d, *J* 3.7, furan 4-H).

2-Chloromethyl-5-nitrofuran 8a

Thionyl chloride (383 mg, 2.8 mmol) in chloroform (1.2 cm^3) was added during 5 min to **7a** (220 mg, 1.5 mmol) in chloroform (1.2 cm^3) and pyridine (0.30 cm^3) at −10 °C and the mixture was stirred at −10 °C for 3 h. It was then washed twice with hydrochloric acid (1 M) and once with aqueous sodium hydroxide (3%), dried and evaporated. Chromatography (EtOAc–hexane, 1:1) of the residue gave the chloromethylnitrofuran **8a** (40 mg, 16%) as a yellow oil (lit.,[35,36] oil); δ_H 4.61 (2 H, s, CH_2), 6.64 (1 H, d, *J* 3.7, furan 3-H) and 7.29 (1 H, d, *J* 3.7, furan 4-H); *m/z* (EI) 163/161 (M) and 126 (M − Cl).

2-(4-Methylphenylsulfonyloxymethyl)-5-nitrofuran 9

A mixture of 4-methylbenzenesulfonyl chloride (2.7 g, 14 mmol), **7a** (2.0 g, 14 mmol) and potassium hydroxide powder (2.0 g, 35 mmol) in THF (75 cm^3) was stirred for 4 h after which it was evaporated. The residue was dissolved in EtOAc, and the solution was washed twice with water, dried and evaporated. Chromatography (dichloromethane–hexane, 1:1) of the residue gave the tosylate **9** (1.06 g, 25%) as a yellow wax (compound reported by Adams *et al.*[37]); δ_H 2.45 (3 H, s, Me), 5.10 (2 H, s, CH_2), 6.64 (1 H, d, *J* 3.7, furan 3-H), 7.20 (1 H, d, *J* 3.7, furan 4-H), 7.35 (2 H, d, *J* 8.0, Ar 3,5-H_2) and 7.78 (2 H, d, *J* 8.0, Ar 2,6-H_2); *m/z* (CI) 298 (M + H).

2-Iodobenzaldehyde 11a

2-Iodophenylmethanol **10** (20.0 g, 85.5 mmol) was stirred with pyridinium dichromate (49.2 g, 130 mmol) in dichloromethane (195 cm^3) for 3 h, after which the mixture was diluted with ether (60 cm^3), filtered and distilled to give the aldehyde **11a** (12.33 g, 62%) as a pale yellow wax, bp 109 °C/1.5 mmHg (lit.,[38] bp 129 °C/1.5 mmHg, lit.,[39] mp 37 °C); δ_H 7.29 (1 H, dt, *J* 1.8, 7.7, 5-H), 7.46 (1 H, t, *J* 7.7, 4-H), 7.88 (1 H, dd, *J* 7.7, 1.8, 3-H), 7.96 (1 H, d, *J* 7.7, 6-H) and 10.08 (1 H, s, CHO).

2-(Diethoxymethyl)methylbenzene 12

Thionyl chloride (5 cm^3) was added to dry ethanol (50 cm^3) at 5 °C, followed by **11b** (10.0 g, 83 mmol) and triethyl orthoformate (100 g, 676 mmol). The mixture was boiled under reflux for 5 h, after which it was cooled and treated with sodium carbonate (10 g). After 15 min the mixture was diluted with ether (150 cm^3) and filtered. After evaporation of the filtrate, the residue was dissolved in EtOAc, washed with aqueous potassium metabisulfite (10%) and water, dried and evaporated to give the acetal **12** (12.3 g, 76%) as a colourless oil (lit.,[40] oil); δ_H 1.23 (6 H, t, *J* 7.0, 2 × CH_2CH_3), 3.53 (2 H, dq, *J* 9.3, 7.0, CH_2CH_3), 3.60 (2 H, dq, *J* 9.3, 7.0, CH_2CH_3), 5.56 [1 H, s, $CH(OEt)_2$], 7.15–7.25 (3 H, m, Ar 3,4,5-H_3) and 7.56 (1 H, m, Ar 6-H). This compound was taken forward without further characterisation.

(*E*)-3-(2-Iodophenyl)propenoic acid 13a

2-Iodobenzaldehyde **11a** (5.00 g, 21.5 mmol) was boiled under reflux with propanedioic acid (4.89 g, 47 mmol) and piperidine (0.2 cm^3) in pyridine (10 cm^3) for 1 h. The cooled mixture was

added to hydrochloric acid (2 M; 150 cm^3) to give a precipitate. This was washed with water and dried to give the acid **13a** (4.86 g, 82%) as colourless needles, mp 218–220 °C (lit.,[41] mp 212–214 °C); δ_H 6.48 (1 H, d, *J* 15.8, 2-H), 7.16 (1 H, t, *J* 8.1, Ar 4-H), 7.44 (1 H, t, *J* 8.1, Ar 5-H), 7.63 (1 H, d, *J* 15.8, 3-H), 7.83 (2 H, m, Ar 3,6-H_2) and 12.67 (1 H, br, CO_2H).

(*E*)-3-(2-Methylphenyl)propenoic acid 13b

The acetal **12** was treated with propanedioic acid, pyridine and piperidine as for the synthesis of **13a** from **11a**, except that the reaction time was 3.5 h. Chromatography (EtOAc–hexane, 1 : 1) of the crude product gave the acid **13b** (3.62 g, 86%) as a white solid, mp 178 °C (lit.,[24] 180 °C); δ_H 2.47 (3 H, s, Me), 6.39 (1 H, d, *J* 15.9, 2-H), 7.20–7.35 (3 H, m, Ar 3,4,5-H_3), 7.59 (1 H, *ca.* d, *J ca.* 7.5, Ar 6-H), 8.10 (1 H, d, *J* 15.9, 3-H) and 11.5 (1 H, br, CO_2H).

(*E*)-3-(2-Bromophenyl)propenoic acid 13c

2-Bromoiodobenzene **14** (14.05 g, 50 mmol) was boiled under reflux with propenoic acid (4.73 g, 66 mmol), palladium(II) acetate (111 mg, 490 μmol) and triethylamine (12.55 g, 124 mmol) in propanenitrile (20 cm^3) for 1.5 h. Hydrochloric acid (2 M; 800 cm^3) was added to the cooled mixture. A solution of the resulting precipitate, in hot ethanol, was filtered and cooled to give the acid **13c** (8.53 g, 76%) as white crystals, mp 202–204 °C (decomp.) (lit.,[42] mp 212–212.5 °C); δ_H[$(CD_3)_2SO$] 6.57 (1 H, d, *J* 16.1, 2-H), 7.35 (1 H, dt, *J* 1.5, 7.7, Ar 4-H), 7.44 (1 H, t, *J* 7.7, Ar 5-H), 7.71 (1 H, dd, *J* 7.7, 1.5, Ar 6-H), 7.83 (1 H, d, *J* 16.1, 3-H), 7.90 (1 H, dd, *J* 7.7, 1.5, Ar 3-H) and 12.66 (1 H, br, CO_2H).

5-Iodoisoquinolin-1-one 18a

The acid **13a** (4.00 g, 14.6 mmol) was stirred with thionyl chloride (10 cm^3) and DMF (0.05 cm^3) for 16 h and then evaporated. The residue (crude **15a**), in 1,4-dioxane (5 cm^3), was added to sodium azide (2.85 g, 44 mmol) in water (6 cm^3) and 1,4-dioxane (6 cm^3) during 15 min. After the mixture had been stirred for 45 min, it was diluted with water (11 cm^3) and extracted thrice with dichloromethane. The dried extract was evaporated to give a residue (crude **16a**) which, in dichloromethane (10 cm^3), was added to boiling dry bis[2-(2-methoxyethoxy)ethyl] ether (12 cm^3) in portions. The solution was boiled under reflux for 1 h and then cooled. The resulting solid was recrystallised (acetone) to give *5-iodoisoquinolin-1-one* **18a** (1.65 mg, 42%) as white needles, mp 238–244 °C (decomp.) (Found: C, 39.8; H, 2.32; N, 5.06. C_9H_6INO requires C, 39.9; H, 2.23; N, 5.17%); δ_H[$(CD_3)_2SO$] 6.55 (1 H, d, *J* 7.3, 4-H), 7.23 (1 H, t, *J* 7.7, 7-H), 7.31 (1 H, d, *J* 7.3, 3-H), 8.22 (2 H, m, 6,8-H_2) and 11.52 (1 H, br, NH); *m/z* (EI) 270.9492 (M, 100%. C_9H_6INO requires *M*, 270.9494).

5-Methylisoquinolin-1-one 18b

Compound **13b** (1.4 g, 8.6 mmol) was stirred with thionyl chloride (15 cm^3) and DMF (0.05 cm^3) for 16 h and then evaporated. The residue (crude **15b**) was stirred with sodium azide (2.0 g, 30 mmol) in acetone (14 cm^3), water (4 cm^3) and acetone (4 cm^3) for 50 min at 5 °C after which it was treated with diphenyl ether (10 cm^3). The suspension was washed with water, dried ($CaCl_2$) and evaporated. The residual solution of crude **16b** was added to boiling diphenyl ether (15 cm^3) during 15 min and the mixture was heated at reflux for 2 h. It was then evaporated and the residue was chromatographed (EtOAc) to give the isoquinolinone **18b** (900 mg, 66%) as a white solid, mp 180–181 °C (lit.,[43] mp 182–183 °C); δ_H 2.55 (3 H, s, Me), 6.71 (1 H, d, *J* 7.3, 4-H), 7.25 (1 H, d, *J* 7.3, 3-H), 7.40 (1 H, dd, *J* 7.9, 7.0, 7-H), 7.51 (1 H, d, *J* 7.0, 6-H), 8.31 (1 H, d, *J* 7.9, 8-H) and 12.16 (1 H, br, NH); δ_C 19.17 (CH_3), 103.47 (CH), 125.18 (CH), 125.95 (C_q), 126.10 (C_q), 126.39 (CH), 127.47 (CH), 133.45 (CH), 137.18 (C_q) and 164.90 (C_q); *m/z* (EI) 160.0712 (M. $C_9{}^{13}CH_9NO$ requires *M*, 160.0718) and 159.0682 (100%, M. $C_{10}H_9NO$ requires *M*, 159.0684).

5-Bromoisoquinolin-1-one 18c

Triethylamine (1.6 g, 16 mmol) was added to **13c** (3.00 g, 13 mmol) in dry acetone (35 cm^3) at 0 °C followed by ethyl chloroformate (1.72 g, 16 mmol) in dry acetone (3 cm^3). The mixture was stirred at 0 °C for 30 min, after which it was treated with sodium azide (1.2 g, 18.5 mmol) in water (3 cm^3), added during 15 min. The mixture was poured onto ice and extracted with dichloromethane. The extract was dried ($CaCl_2$) and then added carefully to boiling diphenyl ether (10 cm^3). The solution was boiled under reflux for 1 h after which it was evaporated and the residue was chromatographed (ether). Recrystallisation (acetonitrile) of the crude product gave the *title compound* **18c** (305 mg, 10%) as white needles, mp 242–244 °C (Found: C, 47.9; H, 2.59; N, 6.14. C_9H_6BrNO requires C, 48.2; H, 2.70; N, 6.25%); δ_H[$(CD_3)_2SO$] 6.65 (1 H, d, *J* 7.3, 4-H), 7.36 (1 H, t, *J* 7, 7-H), 7.42 (1 H, d, *J* 7.3, 3-H), 8.02 (1 H, d, *J* 7, 6-H), 8.21 (1 H, d, *J* 7, 8-H) and 11.55 (1 H, br, NH); *m/z* (EI) 224.9628 (M. $C_9H_6{}^{81}BrNO$ requires *M*, 224.9612) and 222.9635 (M. $C_9H_6{}^{79}BrNO$ requires *M*, 222.9633).

2-(5-Nitrofuran-2-ylmethyl)isoquinolin-1-one 19

Method A. Sodium hydride (60% in oil; 6.0 mg, 153 μmol) was stirred with **18d** (22 mg, 153 μmol) in DMF (1.0 cm^3) for 1 h and the mixture was then cooled to 5 °C. Compound **9** (50 mg, 168 μmol) was added to the mixture which was then stirred for 2 d at 20 °C. Evaporation of the mixture and chromatography (EtOAc) of the residue gave the *title compound* **19** (10 mg, 24%), the properties of which are described below.

Method B. Conc. nitric acid (60%; 0.10 cm^3) was stirred with **21d** (118 mg, 520 μmol) in trifluoroacetic acid (1.0 cm^3) at −10 °C for 1 h and at 20 °C for 16 h. The mixture was adjusted to pH 5 with aqueous sodium hydroxide (2 M) and was then extracted with EtOAc. The extract was washed with water, aqueous sodium hydrogen carbonate and brine, dried and evaporated. Chromatography (first column using EtOAc–hexane, 1 : 1; and then a second column using dichloromethane) of the residue afforded the *nitrofuran* **19** (21 mg, 17%) as a yellow solid, mp 77–79 °C; δ_H 5.23 (2 H, s, CH_2), 6.58 (1 H, d, *J* 7.3, isoquinoline 4-H), 6.66 (1 H, d, *J* 3.6, furan 3-H), 7.24 (1 H, d, *J* 7.3, isoquinoline 3-H), 7.25 (1 H, d, *J* 3.6, furan 4-H), 7.5 (2 H, m, isoquinoline 5,7-H_2), 7.57 (1 H, br t, *J* 7.5, isoquinoline 6-H) and 8.39 (1 H, br d, *J* 7.9, isoquinoline 8-H); *m/z* (EI) 270.0637 (M. $C_{14}H_{10}N_2O_4$ requires *M*, 270.0641) and 224 (M − NO_2).

Method C. Copper(II) nitrate (118 mg, 480 μmol) was added to **21d** (55 mg, 240 μmol) in trifluoroacetic acid (2.0 cm^3) at −20 °C and the mixture was stirred at 20 °C for 2 d. Work-up as for Method B afforded the *nitrofuran* **19** (28 mg, 42%) with properties as described above.

5-Iodo-2-phenylmethylisoquinolin-1-one 20a

Lithium hexamethyldisilazide (1.0 M in THF; 0.6 cm^3, 600 μmol) was stirred with **18a** (100 mg, 370 μmol) in THF (10 cm^3) for 2 h, after which chloromethylbenzene (60 mg, 480 μmol) in THF (10 cm^3) was added to the mixture, followed by sodium iodide (5 mg). After the mixture had been stirred for 5 d, it was evaporated and the residue, in EtOAc, was washed with water and brine, dried and evaporated. Chromatography (EtOAc–hexane, 3 : 7) of the residue gave the N-*benzylisoquinolinone* **20a** (123 mg, 92%) as a white solid, mp 118–120 °C (Found: H, 3.46; N, 3.82. $C_{16}H_{12}INO$ requires H, 3.35; N, 3.88%); ν_{max}(KBr disc)/cm^{-1} 1650, 1620 and 1585; δ_H 5.22 (2 H, s, CH_2), 6.72 (1 H, d, *J* 7.3, isoquinoline 4-H), 7.19 (2 H, m, isoquinoline 3,7-H_2), 7.33 (5 H, m, Ph-H_5), 8.15 (1 H, dd, *J* 7.7, 1.3, isoquinoline 6-H) and 8.47 (1 H, dd, *J* 8.1, 1.3, isoquinoline 8-H); δ_C 51.90 (CH_2), 96.29 (C_q), 109.91 (CH), 127.21 (C_q), 127.96 (CH), 128.14 (CH + C_q), 128.69 (CH), 128.86 (CH), 132.55 (CH), 136.41

(C_q), 139.02 (C_q), 143.01 (CH) and 161.45 (C_q); *m/z* (EI) 360.9960 (M. $C_{16}H_{12}INO$ requires *M*, 360.9964) and 91 (100%, Bn).

5-Methyl-2-phenylmethylisoquinolin-1-one 20b

Sodium hydride (60% in oil; 13 mg, 320 μmol) was stirred with **18b** (50 mg, 314 μmol) in DMF (3.0 cm^3) for 1 h after which bromomethylbenzene (59 mg, 350 μmol) was added to the mixture; stirring was then continued for 20 h. Evaporation of the mixture gave a residue, which, as a solution in EtOAc, was washed with water, dried and evaporated. Chromatography (dichloromethane→dichloromethane–methanol 49:1) of the residue furnished the N-*benzylisoquinolinone* **20b** (15 mg, 19%) as a white solid, mp 84–86 °C; δ_H 2.51 (3 H, s, Me), 5.23 (2 H, s, CH_2), 6.61 (1 H, d, *J* 7.6, isoquinoline 4-H), 7.12 (1 H, d, *J* 7.6, isoquinoline 3-H), 7.30–7.35 (5 H, m, Ph-H_5), 7.38 (1 H, t, *J* 7.6, isoquinoline 7-H), 7.47 (1 H, br d, *J* 7.5, isoquinoline 6-H) and 8.34 (1 H, br d, *J* 7.5, isoquinoline 8-H); δ_C 18.93 (CH_3), 51.68 (CH_2), 103.13 (CH), 126.07 (CH), 126.58 (C_q), 127.80 (CH), 127.93 (CH), 128.39 (C_q), 128.79 (CH), 130.90 (CH), 133.03 (CH), 133.16 (CH), 135.91 (C_q), 136.91 (C_q) and 162.50 (C_q); *m/z* (EI) 249.1153 (M. $C_{17}H_{15}NO$ requires *M*, 249.1154) and 91 (100%, Bn).

5-Bromo-2-(4-methoxyphenylmethyl)isoquinolin-1-one 20c

Compound **18c** was treated with lithium hexamethyldisilazide, sodium iodide and 1-chloromethyl-4-methoxybenzene in THF as for the synthesis of **20a** to give the *title compound* **20c** (156 mg, 100%) as a white solid, mp 98–100 °C (Found: C, 59.4; H, 4.18; N, 3.88. $C_{17}H_{14}BrNO$ requires C, 59.3; H, 4.10; N, 4.07%); δ_H 3.78 (3 H, s, Me), 5.15 (2 H, s, CH_2), 6.84 (3 H, m, isoquinoline 4-H + Ar 3,5-H_2), 7.18 (1 H, d, *J* 7.7, isoquinoline 3-H), 7.3 (3 H, m, isoquinoline 7-H + Ar 2,6-H_2), 7.87 (1 H, d, *J* 7.7, isoquinoline 6-H) and 8.43 (1 H, d, *J* 8, isoquinoline 8-H); *m/z* (CI) 345/343 (M + H) and 121 (100%, MeOBn).

2-Phenylmethylisoquinolin-1-one 20d

Sodium hydride (60% in oil; 15 mg, 340 μmol) was stirred with **18d** (50 mg, 340 μmol) in DMF (3.0 cm^3) for 1 h after which bromomethylbenzene (65 mg, 380 μmol) was added to the mixture; stirring was continued for 2 h. Evaporation of the mixture gave a residue which, as a solution in EtOAc, was washed with water, dried and evaporated. Chromatography (dichloromethane–methanol, 19:1) of the residue gave the *title compound* **20d** (77 mg, 96%) as a colourless oil (lit.,[44] mp 67–69 °C); δ_H 5.20 (2 H, s, CH_2), 6.46 (1 H, d, *J* 7.5, isoquinoline 4-H), 7.06 (1 H, d, *J* 7.4, isoquinoline 3-H), 7.30 (5 H, m, Ph-H_5), 7.49 (2 H, m, isoquinoline 5,7-H_2), 7.61 (1 H, dt, *J* 1.5, 7.5, isoquinoline 6-H) and 8.42 (1 H, br d, *J* 7.5, isoquinoline 8-H); δ_C 51.59 (CH_2), 106.37 (CH), 125.85 (CH), 126.20 (C_q), 126.80 (CH), 127.73 (CH), 127.86 (CH), 127.96 (CH), 128.70 (CH), 131.20 (CH), 132.14 (CH), 136.81 (C_q), 136.91 (C_q) and 162.16 (C_q); *m/z* (EI) 236.1031 (M. $C_{15}{}^{13}CH_{13}NO$ requires *M*, 236.1031) and 235.0995 (M. $C_{16}H_{13}NO$ requires *M*, 235.0997); *m/z* (FAB positive ion) 236 (100%, M + H) and 91 (Bn).

2-(Furan-2-ylmethyl)-5-methylisoquinolin-1-one 21b

Lithium hexamethyldisilazide (1.0 M in THF; 6.0 cm^3, 6.0 mmol) was stirred with **18b** (450 mg, 2.8 mmol) in THF (40 cm^3) for 2 h. Crude **8b** (as in the synthesis of **21d**) (3.3 g, 28 mmol) in THF (30 cm^3) was added to this solution at 0 °C and the mixture was boiled under reflux for 3 d. Evaporation of the mixture gave a residue which, dissolved in EtOAc, was washed with water and brine, dried and evaporated. Chromatography (EtOAc–hexane, 1:1) and further chromatography (EtOAc–hexane, 1:5) of the residue gave the *title compound* **21b** (84 mg, 12%) as a pale yellow solid, mp 85–87 °C (lit.,[45] mp 84–86 °C for 2-([^{18}O]furan-2-ylmethyl)-5-methylisoquinolin-1-one (8% isotopic enrichment); δ_H 2.51 (3 H, s, Me), 5.20 (2 H, s, CH_2), 6.34 (1 H, dd, *J* 3.1, 1.8, furan 4-H), 6.42 (1 H, d, *J* 3.1, furan 3-H), 6.62 (1 H, d, *J* 7.5, isoquinoline 4-H), 7.21 (1 H, d, *J* 7.5, isoquinoline 3-H), 7.37 (2 H, m, furan 5-H + isoquinoline 7-H), 7.46 (1 H, br d, *J* 7.2, isoquinoline 6-H) and 8.32 (1 H, br d, *J* 8.0, isoquinoline 8-H); δ_C 18.91 (CH_3), 44.33 (CH_2), 103.04 (CH), 109.42 (CH), 110.64 (CH), 125.95 (CH), 126.37 (C_q), 126.54 (CH), 130.54 (CH), 133.06 (CH), 133.17 (CH), 135.90 (C_q), 142.76 (CH), 149.78 (C_q) and 162.14 (C_q); *m/z* (EI) 240.0980 (M. $C_{14}{}^{13}CH_{13}NO_2$ requires *M*, 240.0980), 239.0945 (M. $C_{15}H_{13}NO_2$ requires *M*, 239.0946) and 81 (furanCH_2).

2-(Furan-2-ylmethyl)isoquinolin-1-one 21d

Thionyl chloride (4.05 g, 35 mmol) in chloroform (5 cm^3) was added during 10 min to **7b** (2.0 g, 2 mmol) in chloroform (5 cm^3) and pyridine (3 cm^3) at −10 °C. The mixture was stirred at this temperature for 3 h and then poured into hydrochloric acid (1 M) at 0 °C. The organic phase was separated, washed rapidly with cold hydrochloric acid (1 M) and cold aqueous sodium hydroxide (3%), dried (K_2CO_3) and was evaporated to give crude 2-chloromethylfuran **8b** (1.08 g, 45%) as an unstable pale yellow oil; δ_H 4.63 (2 H, s, CH_2), 6.4 (2 H, m, furan 3,4-H_2) and 7.46 (1 H, dd, *J* 1.8, 0.9, furan 5-H). Lithium hexamethyldisilazide (1.0 M in THF; 7.0 cm^3, 7.0 mmol) was stirred with **18d** (500 mg, 3.4 mmol) in THF (50 cm^3) for 1.5 h after which crude **8b** (1.08 g, 9.3 mmol) in THF (50 cm^3) was added to it at −10 °C, followed by sodium iodide (50 mg). The mixture was stirred at 20 °C for 24 h after which it was evaporated to give a residue, which, dissolved in EtOAc, was washed with water and brine, dried and evaporated. Chromatography (EtOAc–hexane, 1:2) gave the *title compound* **21d** (646 mg, 83%) as a pale yellow oil; δ_H 5.17 (2 H, s, CH_2), 6.31 (1 H, dd, *J* 3.0, 2.0, furan 4-H), 6.40 (1 H, br d, *J* 3.0, furan 3-H), 6.45 (1 H, d, *J* 7.3, isoquinoline 4-H), 7.14 (1 H, d, *J* 7.3, isoquinoline 3-H), 7.35 (1 H, dd, *J* 2.0, 1.0, furan 5-H), 7.44 (1 H, dt, *J* 1.0, 6.8, isoquinoline 7-H), 7.45 (1 H, d, *J* 7.8, isoquinoline 5-H), 7.57 (1 H, dt, *J* 1.0, 7, isoquinoline 6-H) and 8.42 (1 H, br d, *J* 7.8, isoquinoline 8-H); δ_C 44.16 (CH_2), 106.19 (CH), 109.28 (CH), 110.49 (CH), 125.77 (CH), 125.99 (C_q), 126.71 (CH), 127.77 (CH), 130.79 (CH), 132.10 (CH), 136.86 (C_q), 142.62 (CH), 149.62 (C_q) and 161.75 (C_q); *m/z* (EI) 226.0819 (M. $C_{13}{}^{13}CH_{11}NO_2$ requires *M*, 226.0823), 225.0788 (M. $C_{14}H_{11}NO_2$ requires *M*, 225.0790) and 81 (furanCH_2).

4-Nitro-2-(5-nitrofuran-2-ylmethyl)isoquinolin-1-one 22

Fuming nitric acid (90%; 0.09 cm^3, 2.0 mmol) was added to acetic anhydride (0.2 cm^3) at −30 °C. The mixture was stirred with **21d** (92 mg, 410 μmol) in acetic anhydride (1.0 cm^3) at −10 °C for 1 h and then poured onto ice. After adjustment to pH 5 with aqueous sodium hydroxide (2 M), the mixture was extracted with EtOAc. The extract was washed with aqueous sodium hydrogen carbonate and brine, dried and evaporated. Chromatography (EtOAc–hexane, 1:1) of the residue gave the *dinitro compound* **22** (26 mg, 20%) as a yellow oil; δ_H 5.34 (2 H, s, CH_2), 6.78 (1 H, d, *J* 3.8, furan 3-H), 7.29 (1 H, d, *J* 3.7, furan 4-H), 7.66 (1 H, *ca.* t, *J ca.* 8, isoquinoline 6-H or 7-H), 7.88 (1 H, *ca.* t, *J ca.* 8, isoquinoline 7-H or 6-H), 8.46 (1 H, dd, *J* 8.1, 1.2, isoquinoline 5-H or 8-H), 8.68 (1 H, br d, *J* 8.5, isoquinoline 8-H or 5-H) and 8.77 (1 H, s, isoquinoline 3-H); δ_C 45.94 (CH_2), 112.12 (CH), 113.62 (CH), 123.99 (CH), 124.30 (C_q), 128.93 (CH), 129.02 (CH), 129.15 (C_q), 134.75 (CH), 135.00 (C_q), 135.95 (CH), 150.88 (2 × C_q) and 161.08 (C_q); *m/z* (EI) 315.0487 (M. $C_{14}H_9N_3O_6$ requires *M*, 315.0491), 270 (M − NO_2) and 190 (4-nitroisoquinolin-1-one).

5-Nitrofuran-2-ylmethyl *N*-(2-phenylethyl)carbamate 27 and 5-nitrofuran-2-ylmethyl 3-phenylpropanoate 28

3-Phenylpropanoic acid **23** (100 mg, 670 μmol) was stirred with oxalyl chloride (1.0 cm^3) for 2 h after which it was evaporated. The resulting residue (crude **24**) was boiled under reflux with toluene (1 cm^3) and azidotrimethylsilane (87 mg, 730 μmol) for 24 h after which compound **7a** (95 mg, 670 mmol), in toluene (1

cm^3), was added to it; boiling was continued for 4 h. After evaporation of the mixture, the residue, dissolved in EtOAc, was washed with water and brine and evaporated. Chromatography (dichloromethane–hexane, 1:1) gave the *ester* **28** (66 mg, 34%) as a yellow oil; δ_H 2.70 (2 H, t, *J* 7.1, CH_2CO), 2.96 (2 H, t, *J* 7.1, $PhCH_2$), 5.09 (2 H, s, OCH_2), 6.54 (1 H, d, *J* 3.7, furan 3-H) and 7.1–7.3 (6 H, m, Ph-H_5 + furan 4-H); *m/z* (CI) 276.0872 (M + H. $C_{14}H_{14}NO_5$ requires *M*H, 276.0872) and 133 (100%, $PhCH_2CH_2CO$). Further elution gave the *carbamate* **27** (62 mg, 32%) as a colourless gum; δ_H 2.82 (2 H, t, *J* 7.0, $PhCH_2$), 3.46 (2 H, q, *J* 7.1, NCH_2), 4.90 (1 H, br, NH), 5.08 (2 H, s, OCH_2), 6.60 (1 H, d, *J* 3.7, furan 3-H) and 7.1–7.3 (6 H, m, Ph-H_5 + furan 4-H); *m/z* (CI) 291 (M + H) and 122 ($PhCH_2CH_2NH_2$); *m/z* (FAB positive ion) 291.1002 (M + H. $C_{14}H_{15}N_2O_5$ requires *M*H, 291.0981).

Hex-5-ynenitrile 30

A mixture of 5-chloropent-1-yne **29** (10.0 g, 97 mmol), potassium cyanide (**CAUTION**) (9.8 g, 150 mmol), ethanol (100 cm^3) and water (30 cm^3) was boiled under reflux for 2 d after which it was diluted with water (50 cm^3) and extracted with ether. The extract was dried and evaporated and the residue was chromatographed (EtOAc–hexane, 1:1→EtQAc) to give the nitrile **30** (3.2 g, 36%) as a colourless oil (lit.,[46] oil, lit.,[47] liquid); ν_{max}/cm^{-1} 3300, 2260 and 2040; δ_H 1.88 (2 H, quintet, *J* 7.0, 3-H_2), 2.09 (1 H, t, *J* 2.6, 6-H), 2.38 (2 H, dt, *J* 2.6, 7.0, 4-H_2) and 2.52 (2 H, t, *J* 7.0, 2-H_2).

1-(3-Cyanopropyl)-1,2-dicarba-*closo*-dodecaborane(12) 31

Decaborane(14) ($B_{10}H_{14}$; 328 mg, 2.7 mmol) was stirred with dry acetonitrile (5.0 cm^3) for 3 h, after which compound **30** (250 mg, 2.7 mmol) was added to the mixture. After being boiled under reflux for 5 d, the mixture was evaporated and the residue was chromatographed (pentane–dichloromethane, 2:1) to give the cyanopropylcarborane **31** (420 mg, 74%) as a colourless gum (lit.,[13] mp 81–82 °C); ν_{max}/cm^{-1} 2560 and 2260; $\delta_H(CDCl_3)$ 1.86 (2 H, m, $CH_2CH_2CH_2$), 2.2 (10 H, br q, J_{BH} *ca.* 150, 10 × BH), 2.35 (2 H, m, carborane-CH_2), 2.39 (2 H, t, *J* 6.7, CH_2CN) and 3.67 (1 H, br, carborane 2-H); $\delta_H[(CD_3)_2CO]$ 1.87 (2 H, m, $CH_2CH_2CH_2$), 2.2 (10 H, br q, J_{BH} *ca.* 150, 10 × BH), 2.50 (2 H, m, carborane-CH_2), 2.49 (2 H, t, *J* 7.0, CH_2CN) and 4.69 (1 H, br, carborane 2-H); $\delta_B[(CD_3)_2CO]$ −14.09 (2 B, J_{BH} 135), −12.80 (4 B, J_{BH} 145), −10.71 (2 B, J_{BH} 149), −7.04 (1 B, J_{BH} 146) and −3.95 (1 B, J_{BH} 146); *m/z* (EI) cluster centred at 211 (M).

1,2-Dicarba-*closo*-dodecaboran(12)-1-ylbutanoic acid 32

Compound **31** (1.54 g, 7.3 mmol) was boiled under reflux with conc. sulfuric acid (35 cm^3) and water (7 cm^3) for 30 h, after which it was diluted with water (200 cm^3). The resulting precipitate, dissolved in dichloromethane, was washed with water and brine, dried and evaporated to give the acid **32** (1.45 g, 87%) as a white solid, mp 155–157 °C (lit.,[48] mp 158–159 °C); δ_H 1.81 (2 H, m, $CH_2CH_2CH_2$), 2.2 (10 H, br q, J_{BH} *ca.* 150, 10 × BH), 2.27 (2 H, m, carborane-CH_2), 2.37 (2 H, t, *J* 7.0, CH_2CO), 3.58 (1 H, br, carborane 2-H) and 10.5 (1 H, br, CO_2H); *m/z* (EI) cluster centred at 230 (M), cluster centred at 213 (M − OH).

Phenylmethyl *N*-[3-(1,2-dicarba-*closo*-dodecaboran-1-yl)propyl]-carbamate 36

The isocyanate **35** (90 mg, 0.4 mmol) (as in the synthesis of **38**) was boiled under reflux with phenylmethanol (42 mg, 0.4 mmol) and triethylamine (5 mg) in chloroform (5 cm^3) for 24 h. The mixture was evaporated and the residue, dissolved in EtOAc, was washed with water and brine, dried and evaporated. Chromatography (dichloromethane–hexane, 1:1) of the residue gave the *carbamate* **36** (62 mg, 48%) as a pale yellow oil; δ_H 1.69 (2 H, m, $CH_2CH_2CH_2$), 2.2 (10 H, br q, J_{BH} *ca.* 150, 10 × BH), 2.22 (2 H, m, carborane-CH_2), 3.17 (2 H, q, *J* 6.6, NCH_2), 3.58 (1 H, br, carborane 2-H), 4.78 (1 H, br, NH), 5.09 (2 H. s, $PhCH_2$) and 7.35 (5 H, s, Ph-H_5); δ_C 29.97 (CH_2), 35.19 (CH_2), 39.96 (CH_2), 61.27 (CH), 66.91 (CH_2), 74.52 (C_q), 128.15 (CH), 128.30 (CH), 128.59 (CH), 136.26 (C_q) and 156.42 (C_q); δ_B(^{1}H-decoupled) −11.77 (6 B, m), −9.30 (2 B, s), −5.69 (1 B, s) and −2.25 (1 B, s); *m/z* (EI) 337.2822 (M. $C_{13}H_{25}{}^{11}B_{10}NO_2$ requires 337.2816), 336.2844 (M. $C_{13}H_{25}{}^{11}B_9{}^{10}BNO_2$ requires *M*, 336.2852), 335.2874 (M. $C_{13}H_{25}{}^{11}B_8{}^{10}B_2NO_2$ requires *M*, 335.2888), 334.2898 (M. $C_{13}H_{25}{}^{11}B_7{}^{10}B_3NO_2$ requires *M*, 334.2925), 333.2923 (M. $C_{13}H_{25}{}^{11}B_6{}^{10}B_4NO_2$ requires *M*, 333.2961) and 332.2946 (M. $C_{13}H_{25}{}^{11}B_5{}^{10}B_5NO_2$ requires *M*, 332.2997).

1-(3-Aminopropyl)-1,2-dicarba-*closo*-dodecaborane(12) hydrobromide 37

The carbamate **36** (60 mg, 180 μmol) was stirred with hydrogen bromide in acetic acid (5%; 6 cm^3) for 30 min, after which the mixture was evaporated. The residue was triturated with dry ether (5 × 10 cm^3) and dried to afford the *aminopropylcarborane salt* **37** (39 mg, 98%) as a white solid, mp 295–297 °C; $\delta_H(D_2O)$ 1.86 (2 H, *ca.* quintet, *J ca.* 7, $CH_2CH_2CH_2$), 2.2 (10 H, br q, J_{BH} *ca.* 150, 10 × BH), 2.38 (2 H, *ca.* t, *J ca.* 7, carborane-CH_2), 2.95 (2 H, t, *J* 7.5, NCH_2) and 4.38 (1 H, br, carborane 2-H); *m/z* (EI) 203.2436 (M. $C_5H_{19}{}^{11}B_{10}N$ requires *M*, 203.2448).

5-Nitrofuran-2-ylmethyl *N*-[3-(1,2-dicarba-*closo*-dodecaboran-(12)-1-yl)propyl]carbamate 38 and 5-nitrofuran-2-ylmethyl 4-[1,2-dicarba-*closo*-dodecaboran(12)-1-yl]butanoate 39

Compound **32** (500 mg, 2.2 mmol) was boiled under reflux with thionyl chloride (25 cm^3) and DMF (0.05 cm^3) for 16 h. After the evaporation of the solvent, the residue (crude **33**) was stirred with sodium azide (**CAUTION**) (495 mg, 7.6 mmol) in acetone (25 cm^3) and water (5 cm^3) at 0 °C for 45 min, after which it was diluted with chloroform (100 cm^3). The suspension was washed with water and brine, dried and evaporated to give crude 1,2-dicarba-*closo*-dodecaboran-1-ylbutanoyl azide **34**; ν_{max}/cm^{-1} 2600, 2150 and 1725. This material was stirred in chloroform (10 cm^3) at 40 °C for 27 h to give a solution of crude 1-(3-isocyanatopropyl)-1,2-dicarba-*closo*-carborane(12) **35**; ν_{max}/cm^{-1} 2600 and 2280. This solution was boiled under reflux with **7a** (310 mg, 2.2 mmol) and triethylamine (10 mg) for 2 d after which it was evaporated. The residue, dissolved in EtOAc, was washed with water and brine, dried and evaporated. Chromatography (dichloromethane–methanol, 40:1) of the residue gave the *ester* **39** (90 mg, 14%) as a pale yellow wax; δ_H 1.82 (2 H, m, $CH_2CH_2CH_2$), 2.2 (10 H, br q, J_{BH} *ca.* 150, 10 × BH), 2.25 (2 H, m, carborane-CH_2), 2.38 (2 H, t, *J* 7.0, CH_2CO), 3.60 (1 H, br, carborane 2-H), 5.12 (2 H, s, furan-CH_2), 5.25 (1 H, br, NH), 6.63 (1 H, d, *J* 3.7, furan 3-H) and 7.29 (1 H, d, *J* 3.7, furan 4-H); *m/z* (CI) cluster centred at 355 (M + H), cluster centred at 213 [carborane$(CH_2)_3CO$] and 143 (nitrofuranmethanol); *m/z* (FAB positive ion) 357.2477 (M. $C_{11}H_{22}{}^{11}B_9{}^{10}BNO_5$ requires *M*, 357.2465). Further elution gave the *carbamate* **38** (289 mg, 36%) as a pale yellow oil; δ_H 1.40 (2 H, m, $CH_2CH_2CH_2$), 2.2 (10 H, br q, J_{BH} *ca.* 150, 10 × BH), 2.48 (2 H, m, carborane-CH_2), 3.37 (2 H, *ca.* q, *J ca.* 7, NCH_2), 3.68 (1 H, br, carborane 2-H), 4.73 (2 H, s, furan-CH_2), 5.25 (1 H, br, NH), 6.56 (1 H, d, *J* 3.6, furan 3-H) and 7.29 (1 H, d, *J* 3.6, furan 4-H); δ_C 29.74 (CH_2), 35.13 (CH_2), 40.12 (CH_2), 57.96 (CH_2), 61.35 (CH), 74.39 (C_q), 112.11 (CH), 113.05 (CH), 153.00 (C_q) and 155.43 (C_q) (one C_q was not observed); δ_B(^{1}H-decoupled) −11.83 (6 B, m), −9.30 (2 B, s), −5.69 (1 B, s) and −2.31 (1 B, s); *m/z* (CI) cluster centred at 371 (M + H); *m/z* (FAB positive ion) 372.2599 (M + H. $C_{11}H_{23}{}^{11}B_9{}^{10}BN_2O_5$ requires MH^+, 372.2574) and 369.2704 (M + H. $C_{11}H_{23}{}^{11}B_6{}^{10}B_4N_2O_5$ requires MH^+, 369.2683).

Reductively activated release of isoquinolin-1-one 18d from 2-(5-nitrofuran-2-ylmethyl)isoquinolin-1-one 19 (sodium borohydride–palladium method)

Sodium borohydride (16 mg, 410 μmol) in water (0.3 cm^3) was

stirred with **19** (37 mg, 140 μmol) and palladium-on-charcoal (10%; 4 mg) in propan-2-ol (2.0 cm^3) for 16 h after which the suspension was filtered through Celite®. Evaporation of the mixture gave a residue, which, dissolved in dichloromethane, was washed with water and brine, dried and evaporated to give isoquinolin-1-one **18d** (13 mg, 67%) with properties as described above.

Control experiment for sodium borohydride–palladium method of reductively activated release

Sodium borohydride (15 mg, 400 μmol) in water (0.3 cm^3) was stirred with **21d** (30 mg, 133 μmol) and palladium-on-charcoal (10%; 3 mg) in propan-2-ol (1.0 cm^3) for 2 d. After the suspension had been filtered through Celite®, it was evaporated and the residue, dissolved in dichloromethane, was washed with water and brine, dried and evaporated to give recovered **21d** (28 mg, 94%).

Reductively activated release of 2-phenylethylamine 42 from 5-nitrofuran-2-ylmethyl *N*-(2-phenylethyl)carbamate 27 (sodium borohydride–palladium method)

Sodium borohydride (18 mg, 470 μmol) in water (0.15 cm^3) was stirred with **27** (30 mg, 100 μmol) and palladium-on-charcoal (10%; 3 mg) in methanol (2.0 cm^3) for 2 d. After the suspension had been filtered through Celite®, it was evaporated and the residue, dissolved in dichloromethane, was washed with water and brine, dried and evaporated to give 2-phenylethylamine **42** (5.0 mg, 41%), the properties of which were identical with those of a commercial sample.

Reductively activated release of 1-(3-aminopropyl)-1,2-dicarba-*closo*-dodecaborane(12) 43 from 5-nitrofuran-2-ylmethyl *N*-{3-[1,2-dicarba-*closo*-dodecaboran(12)-1-yl]propyl}carbamate 38

Sodium borohydride–palladium method. Sodium borohydride (33 mg, 870 μmol) in water (1.0 cm^3) was stirred with **38** (100 mg, 270 μmol) and palladium-on-charcoal (10%; 10 mg) in propan-2-ol (5.0 cm^3) for 16 h. Filtration (Celite®) and evaporation of the mixture gave crude 1-(3-aminopropyl)-1,2-dicarba-*closo*-dodecaborane(12) **43**. This material, dissolved in dichloromethane (10 cm^3), was stirred with phenylmethyl chloroformate (76 mg, 450 μmol), triethylamine (75 mg, 750 μmol) and 4-pyrrolidinylpyridine (2 mg) for 16 h. The solution was washed with water, aqueous citric acid (5%) and brine, dried and evaporated. Chromatography of the residue gave the Z-protected carboranylpropylamine **36** (14 mg, 26%), the properties of which were identical with those reported above.

Tin(II) chloride method. Tin(II) chloride (74 mg, 390 μmol) and **38** (19 mg, 65 μmol) were boiled under reflux in hydrochloric acid (1.5 cm^3) for 90 min. The cooled mixture was basified to pH 9 by the addition of aqueous sodium hydroxide (10 M) and extracted with dichloromethane. The extract was washed with water, dried and evaporated to give the amine **43** (3 mg, 40%) as a pale yellow gum, chromatographically identical with the free base of **37**.

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