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THE CHEMISTRY OF BORON ANALOGUES OF BIOMOLECULES

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Boron not only appears to be an essential trace element in living systems [1,2] but has also been found as a constituent of some antibiotics such as boromycin [3] and asplamomycin [4]. However over the past 50 years, there have been other incentives to incorporate boron into biologically active molecules, particularly for applications such as the boroneutrotherapy treatments of certain cancers. Considering the increasing interest in the biological applications of such boron containing biomolecules, and hence in their syntheses, the time seems appropriate to review their chemistry [5-7].

1 Introduction

Boron naturally exists as two isotopes ^{11}B and ^{10}B occuring in an 81.17 to 18.83 ratio. The latter, having a cross-section of 3850 barns, efficiently captures low energy neutrons to give the following nuclear reaction:

$$^{10}B + {}^{1}n \longrightarrow {}^{7}Li + {}^{4}He + \gamma$$

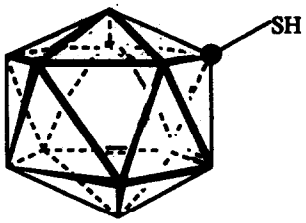
The high kinetic energy released in this transmutation (over 2.50 Mev) enables the resulting fragments to be quite destructive; the path-lengths of the emitted particles are equivalent to cell diameters (*ca.* 10 μm) so if boron could somehow be introduced into malignant cells, selective destruction of unhealthy tissues could result. This is the basic principle of Boron Neutron Capture Therapy (BNCT) [7-16]. Two features of this technique are noteworthy. Due to the fact that boron should be delivered to malignant cells in concentrations estimated at *ca.* 50 μg ^{10}B / g tissue, the toxicity to healthy tissues of the boron compounds employed should be kept low, and, on the other hand, since hydrogen and nitrogen atoms in healthy tissues can also capture neutrons, although to a much lower extent, it is obviously desirable to adjust the neutron flux used.

Interest in this bimodal therapy arose very shortly after the discovery of neutrons. Indeed the first rationale for using boron analogues for this purpose was put forward as soon as 1936 [17] and was rapidly followed by practical experiments [18-21].

These were first performed with inorganic borates [22-24], the so-called "first generation" compounds. These water soluble salts were mainly delivered through aqueous distribution in the body and hence could not sufficiently discriminate sick cells.

Phenylboronic acid derivatives [25-27] and dyes into which boron was incorporated [28,29] were then prepared but efforts to adjust the lipophilicity of these compounds and so enable them to cross the blood/brain barrier to cure cerebral tumors proved unsuccesfull [30-32]. However, the most important compounds from this "second generation" are boron clusters; for example **1** (BSH, Mercaptoborate, Borocaptate) [33-38] was the first clinically useful compound and is currently under evaluation for BNCT. A convenient preparation of ^{10}B-enriched BSH has been published [39] and the development of BSH derivatives along with other subtituted boron cages [40-49] is still a line of research being explored.

"Third generation" compounds exploit biochemical pathways to accumulate boronated biomolecular analogues inside cells and is exemplified by the clinical application of L-4-borono-phenylalanine (BPA), **2**, as a tyrosine analogue [50]. These molecules are the subject of intense research and their syntheses — one of the aspects of this Report — are reviewed in the pages that follow.



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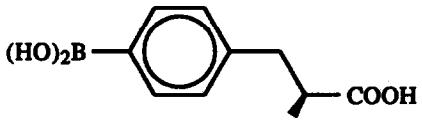


2

It is of interest to note that while BNCT depends on ^{10}B, the other boron isotope, ^{11}B, shows adequate NMR properties [51] and holds some promise for MRI (Magnetic Resonance Imaging), various NMR techniques having been proposed for *in vivo* localisation of boron analogues [52-55,342-345].

Another interesting application for biomolecular boron derivatives, stems from the observation [56] that substituted boronic acids bind chymotrypsine [57-62]. In fact, borates, being tetrahedral, may act as enzyme transition state inhibitors. Physical evidence [63-68,311] including X ray crystallography of a boronic acid adduct [69-74] support this theory. These studies have also been applied to other proteases such as lipase, peptidyl transferase, beta-lactamase and others [75-105]. The synthetic approaches to these boronated amino acid/peptide analogues are detailed later on.

Furthermore, the intermolecular interactions of boronates (in particular with hydroxyl groups such as those contained in carbohydrates or nucleic acids) enable chromatographic separation, chiral discrimination or temporary protection [106-112]; examples of synthetic applications can be found in macrolide transformations [113] and peptide synthesis [114]. Research into the catalytic [115-117] and transport [118-125] properties of organoboron compounds, and in particular the transport of water insoluble reagents through membranes (coined "boradeption"), also reflects the broad interest of the chemical and biochemical communities in these types of compounds.

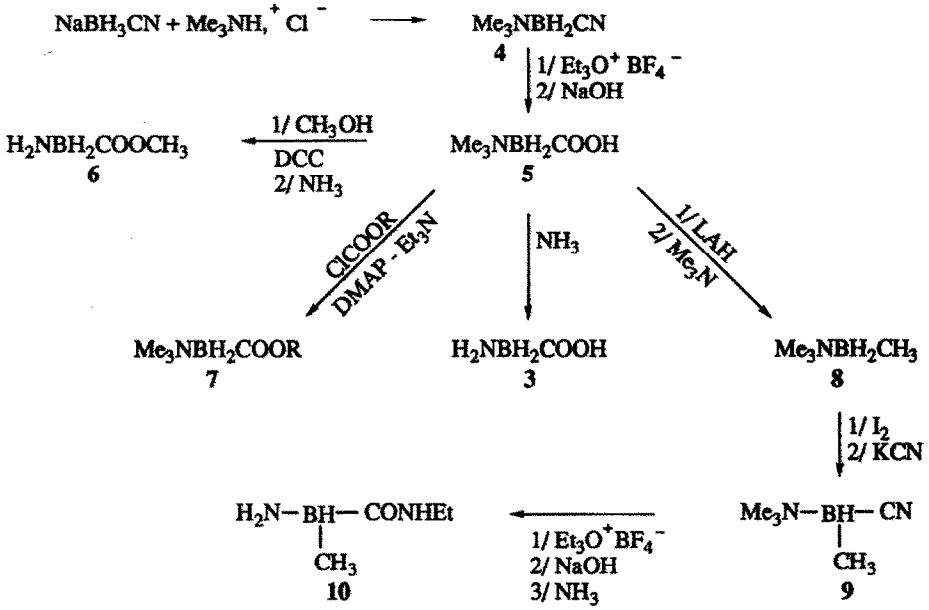
2 Amino acids

Boron analogues of amino acids (AA) constitute a topic of major importance. They present a large array of structural diversity and are of course the logical building blocks for boronated analogues of peptides. These analogues have found uses in biological and biomedical applications such as transition state inhibitors or

agents for BNCT; it also turns out that some of these analogues possess biological activity in their own right. In developing amino acid analogues, boron has been introduced either as a constituent of the backbone or as a side-chain substituent.

In the simplest amino acid, glycine, replacement of the central methylene by boron, as depicted in **3** would give an isoelectronic and isostructural analogue. Thus the reaction of sodium cyanoborohydride with trimethylammonium hydrochloride gave **4**. Since direct hydrolysis of the nitrile group could not be achieved, its conversion to a carboxylic acid was performed in two steps: action of Meerwein's reagent, followed by alkaline hydrolysis of the intermediate nitrilium salt [126-128] .The metal complexing capabilities and basicity of this betaine **5** have been discussed previously [129]. Upon displacement of the trimethylamine with a large excess of liquid ammonia, the desired glycine analogue **3** was isolated and unambiguously characterized by X-ray crystallography [130]. Although readily hydrolysed under acidic conditions, **3** was reasonably stable to neutral or basic hydrolysis, and to thermal conditions. This molecule has also been the subject of a theoretical investigation [131] .

In connection with boroneutrotherapy, the above scheme has been carried out with ^{10}B enriched sodium cyanoborohydride [132] and, in this context, amine exchange reactions with other aliphatic amines have also been described [133].

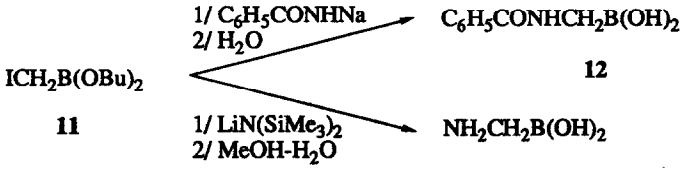


Some derivatives of **5** have been obtained; for example the methyl ester was formed in the presence of dicyclohexylcarbodiimide (DCC) which then was submitted to an amine exchange to give the glycine analogue **6** [134]. Reaction of the carboxylic group to give esters **7** can be accomplished in varying yields upon reaction of chloroformates in the presence of triethylamine and 4-dimethylaminopyridine (DMAP); these conditions were

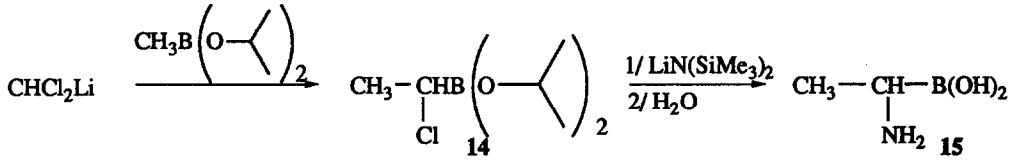
found to be more advantageous than using DCC [135]. However it should be noted that DCC is recognised to be efficient in the formation of amide bonds in similar cases [136] and this process can be viewed as a first step towards peptide bond formation. Other derivatives have also been obtained from intermediate nitrilium salts [137-139]. Conversion of **5** into an alanine derivative has also been reported. Thus, lithium aluminum hydride reduction of **5** followed by quenching with trimethylamine hydrochloride afforded **8** which was subsequently iodinated and cyanated to give **9**. Action of Meerwein's reagent followed by basic hydrolysis and amine exchange gave the desired amide **10** [140].

When the carboxylic acid group of an amino acid is replaced by boron, a boronic acid derivative is created. These acids may act as transition-state inhibitors of various hydrolytic enzymes (*vide supra*) by resembling the postulated tetrahedral enzyme-substrate intermediate [75-105].

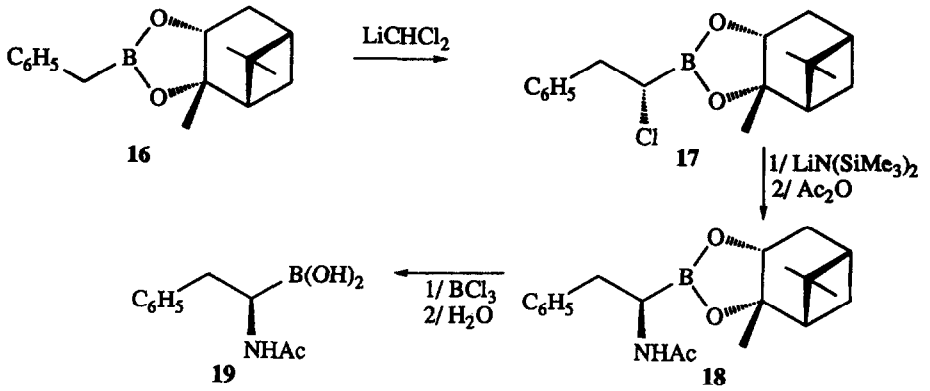
The initial synthetic efforts to obtain such amino acid-based inhibitors used N-acylated analogues of glycine. Thus dibutyl iodomethaneboronate **11** was alkylated with the sodium salt of benzamide to afford **12** (obtained after hydrolysis of the boronate esters) [141] and was shown to be a potent inhibitor of α-chymotrypsin. However the actual structure of this molecule has been subsequently questioned [142]. Modification of the reaction to prepare the parent compound was made possible by the use of a seemingly improbable nucleophile — namely the lithio derivative of hexamethyldisilazane ! Although the condensation was successful, the glycine analogue obtained after hydrolytic work-up was found to be unstable [143,144].



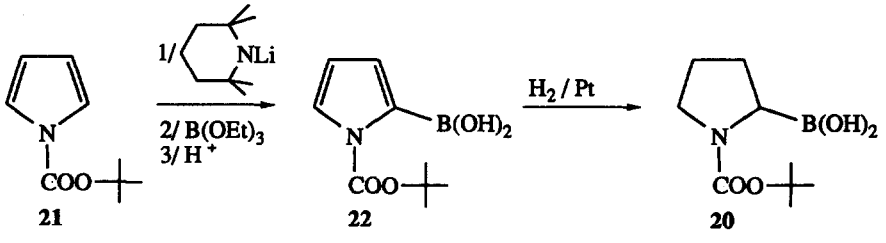
The corresponding alanine analogue however, was found to be more stable. To obtain it, dichloromethyl lithium was first boronated with diisopropyl methylboronate to give **14** and this intermediate submitted to nucleophilic displacement of lithium hexamethyldisilazide. Upon hydrolytic deprotection, the alanine analogue **15**, obtained in racemic form, was stable enough to be used for alanine racemase and D-alanine-D-alanine ligase inhibition studies [145].



An optically active boron analogue of phenylalanine has been obtained using the α-haloboronic ester methodology [146]. The use of (+)-pinanediol for boronic acid protection allowed the preparation of an optically pure material after the homologation reaction of **16**. **17** was then reacted as above with lithium hexamethyldisilazide but the pure desilylated material could not be obtained and so direct acetylation to **18** was required. The acetamido derivative of phenylalanine **19** thus obtained after deprotection of the boronate could be obtained as either epimer [142]. Extension of this methodology to other boronated amino acid derivatives based on alanine, valine, leucine, isoleucine or methionine has also been reported [147-150].

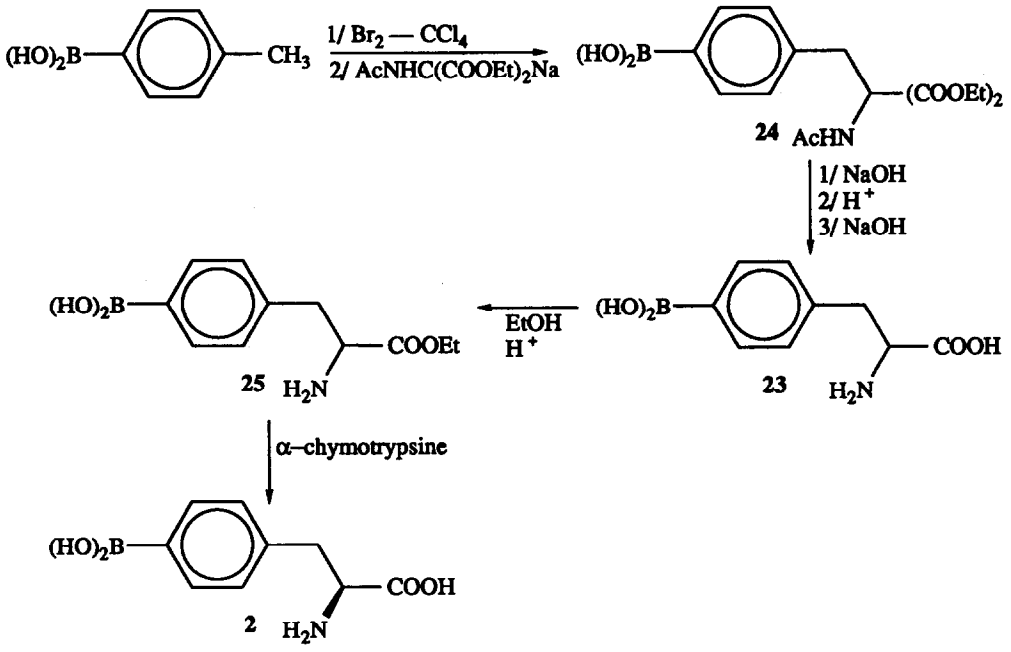


The proline derivative **20** is another example of a simple amino acid analogue which can be prepared in optically pure form – in this case after a resolution step. The protected pyrrole **21** could be lithiated then boronated to **22**. Hydrogenation of the ring gave the pyrrolidine **20** in excellent overall yield. Resolution of this racemic boronic acid could be accomplished by formation of diastereoisomeric esters with optically active pinanediol. X-ray crystallography analysis of one diastereoisomer allowed determination of the absolute configuration of the parent boronated proline analogue [151].



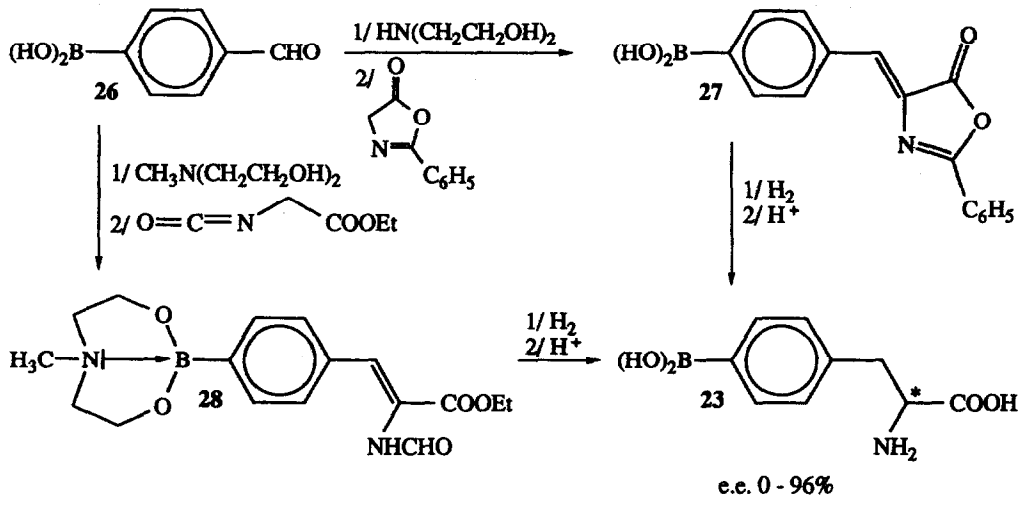
A fundamentally different approach to boronated amino acid analogues incorporates a boron moiety with an amino acid side-group and has the great advantage of retaining the chiral core intact.

The most important compound prepared using this approach is currently L-BPA **2**, which has been clinically tested for BNCT [50]. It appears that **2** mimicks L-tyrosine in the early stage of melanin biosynthesis and, not being further metabolized, it accumulates in melanoma cells thus providing concentrations of boron high enough for effective treatment.



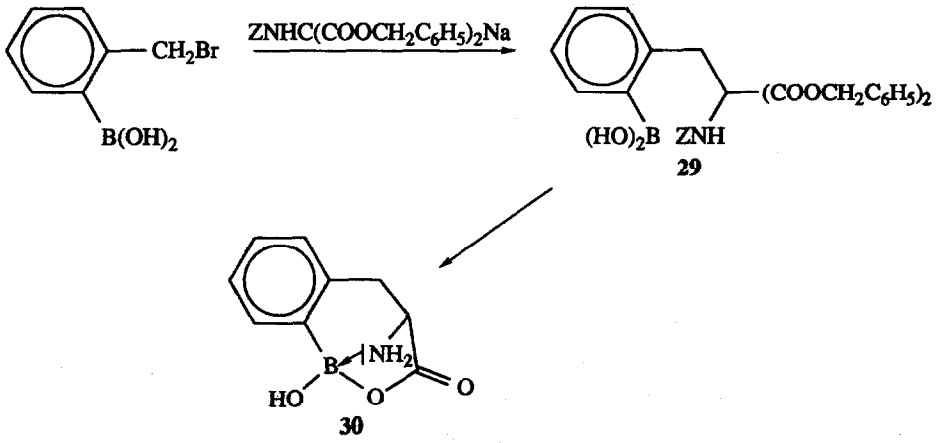
The synthesis of racemic **23** was described in the late 50's. *p*-Toluene boronic acid was converted to **24** by radical bromination followed by alkylation with the sodium salt of diethylacetylaminomalonate. Decarboxylation and deprotection steps then gave **23** [152]. Resolution of this racemate could be performed by selective hydrolysis of the corresponding ethyl esters **25** with α-chymotrypsin and optically pure **2** was thus obtained [153]. The extension of this scheme to the synthesis of ^{10}B-enriched BPA with improved deprotection yields has since been proposed [154].

Currently though, work is under way towards the synthesis of the L-isomer thus avoiding the 50% loss in material inherent in a resolution step [155-157]. In this context, asymmetric hydrogenation of a suitable dehydroalanine derivative using homogeneous catalysis has been considered.

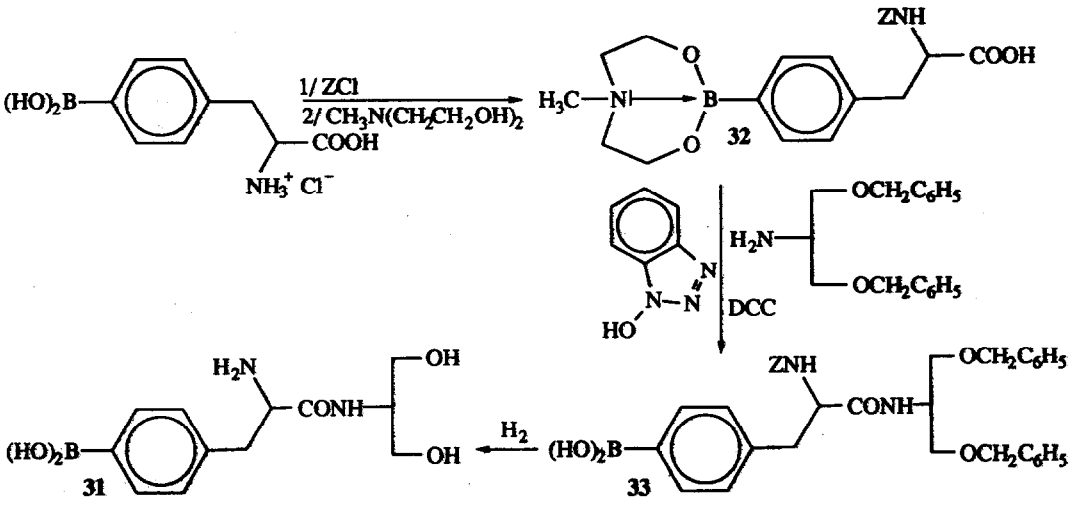


For example, *p*- formylbenzeneboronic acid **26** was protected as an -ate complex and subsequently condensed with an active methylene compound to yield **27** or **28** respectively. Hydrogenation was carried out with a chiral phosphine rhodium catalyst and the desired L-enantiomer of BPA, **23**, obtained in over 96 % enantiomeric excess [155].

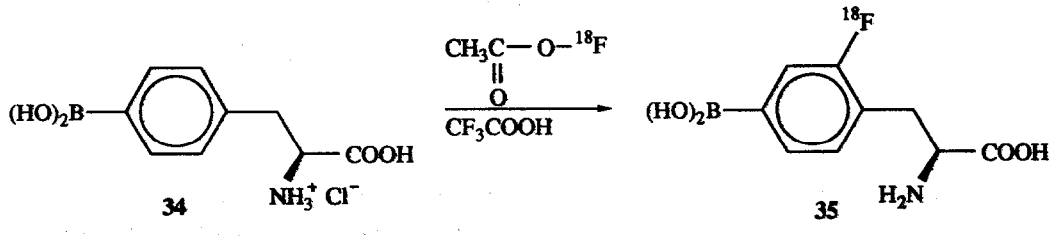
The synthesis of the *ortho*-isomer of BPA required adjustment of the protecting groups to avoid hydrolytic deboronation upon alkaline hydrolysis of the intermediate amide. Thus *o*-bromomethylbenzeneboronic acid was conventionally converted to **29** and hydrogenolysis of the benzyl esters and of the benzyloxycarbonyl (Z) groups performed. The structure actually proposed after final decarboxylation is that of an internal anhydride **30** [158].



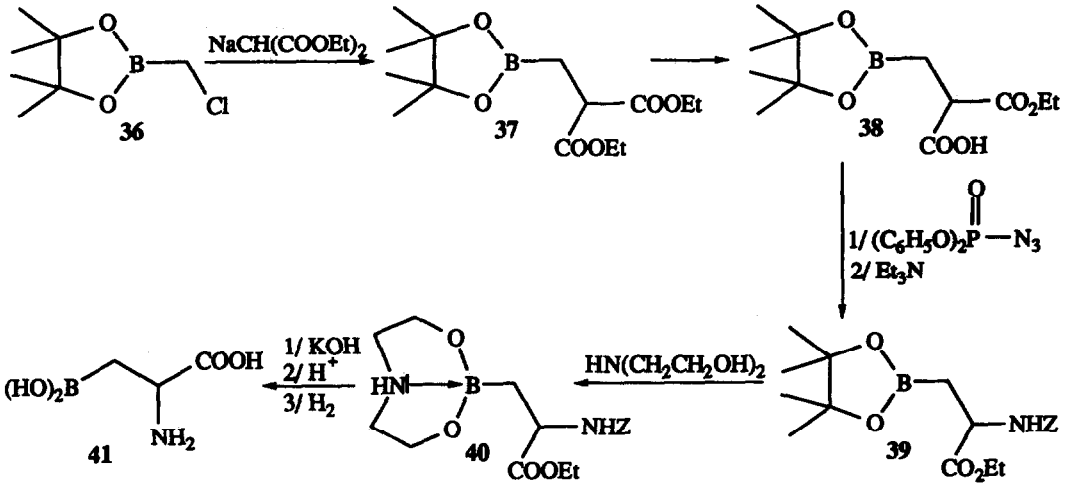
Attempts to increase the water solubility of BPA have investigated **31**. The synthesis involves protection of the amino and boronic acid groups of BPA to yield **32** followed by a peptide-like coupling with a glycerol-derived amine. Hydrogenolysis of **33** finally gives the desired BPA derivative **31** which is about 10^3 times more soluble in water than **23** [159].



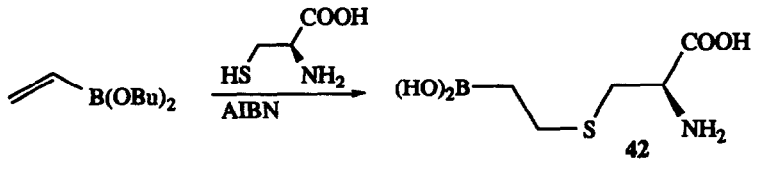
Although efforts to achieve *in vivo* localization of boron by NMR are under way [52-55], positron emission tomography (PET) is another candidate for assessment of BPA concentrations in tumors. For this purpose electrophilic fluorination of BPA hydrochloride **34** with ^{18}F -labelled acetyl hypofluorite in an acidic medium afforded **35** in over 99 % radiochemical yield. **35**, which incorporates a β-emmitter for PET utilisation, has thus been proposed as a probe for BPA tumor localisation [160-163].



Other amino acids in which side-chain functional groups have served as a basis for boron introduction are aspartic acid, cysteine, methionine and glutamic acid.

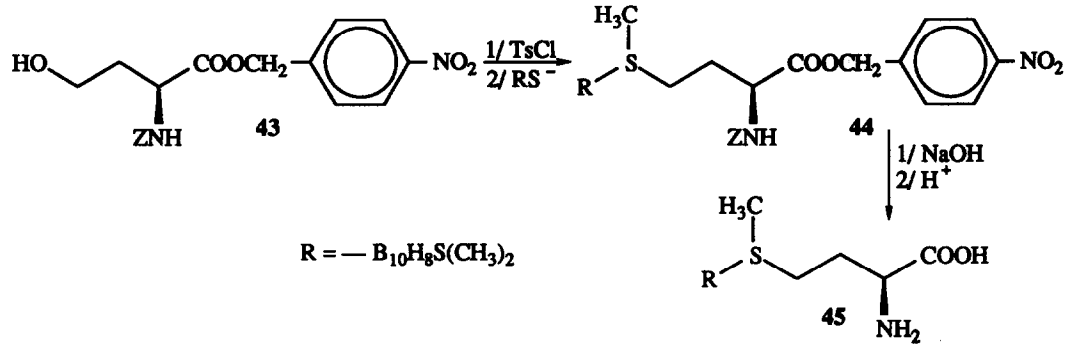


In the case of aspartic acid, the synthesis started from pinacol chloromethylboronate **36** which was alkylated with the sodium salt of diethyl malonate to give **37**. Saponification of a single ester group proceeded in excellent yield due to boron participation (through formation of an intermediate ate complex). Curtius rearrangement of **38** then afforded **39** after trapping of the intermediate isocyanate with benzyl alcohol. The deprotection of the three protecting groups was best achieved sequentially after a boron protecting group exchange as in **40**. The aspartic acid analogue **41** was thus obtained and spectroscopic studies suggested that its solution structure was best depicted as either a zwitterion or a dimer [164].

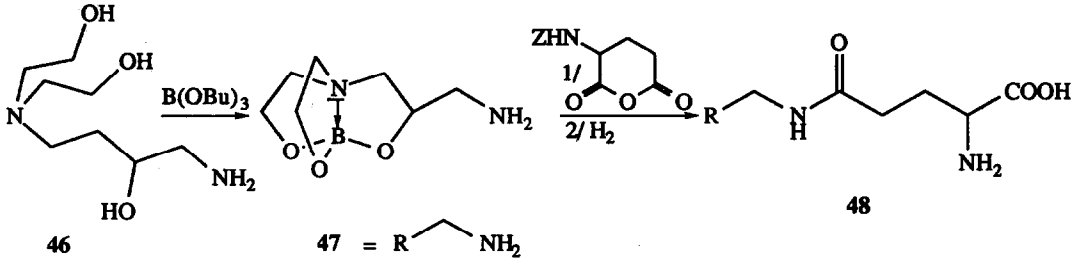


The synthesis of the cysteine boron derivative was quite straightforward since it only required a single step. Indeed, radical addition of cysteine to dibutyl vinylboronate gave **42** , the boronate esters being cleaved during recrystallisation from water [165].

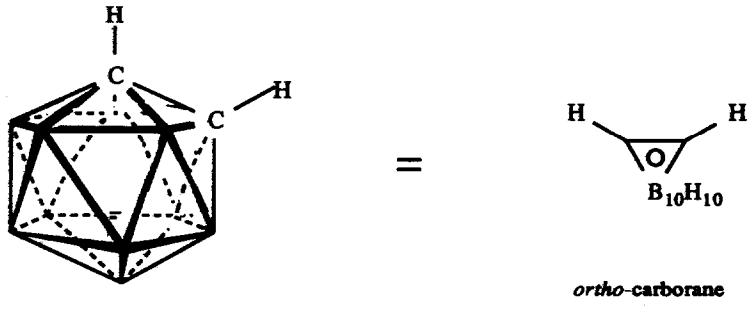
With regard to methionine, displacement of the tosylate derived from homoserine derivative **43** allowed the introduction of a polyhedral boron cluster to give **44** which was stable to the basic conditions that were later needed to deprotect the ester group when synthesising **45** [166].



Stable boron derivatives are also available by placing boron at the centre of a cage resulting in the so-called "triptych" derivatives. Thus the aminopolyol **46** reacts with tributyl borate to give stable **47**. Condensation of this triptych compound with a N-protected glutamic acid anhydride, followed by hydrogenolysis of the protecting group afforded the glutamic acid analogue **48** [167].



Other approaches to amino acid analogues incorporating boron are based on the use of boron-rich cages called carboranes. Under this name lies a family of $C_2B_{10}H_{12}$ icosahedra of general structure **49** (the more readily available ortho isomer being depicted). As the chemistry of carboranes has been extensively reviewed [168-170], it is only necessary here to emphasise the advantage of attaching them to biomolecules.

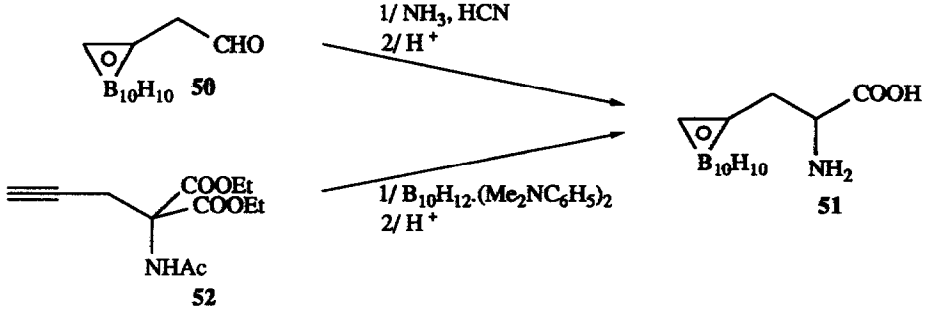


4 9 (unmarked vertices = BH)

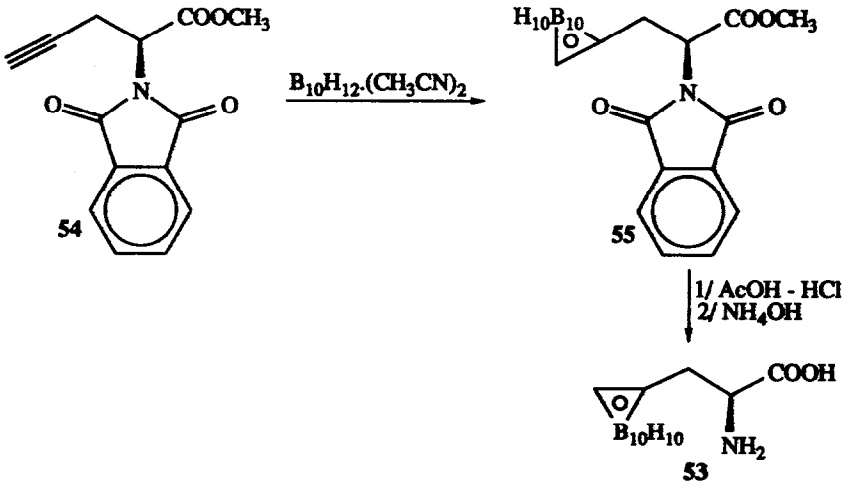
Carboranes are stable, lipophilic structures which resemble benzene in terms of reactivity and bulkiness [171-173]. Since they contain ten boron atoms, a ten-fold increase in boron concentration is constitutively obtained whenever they can be linked to a biomolecule; theoretically at least, this may help deliver much higher concentrations of ^{10}B atoms in malignant tissues, especially since ^{10}B enriched orthocarborane is now commercially available.

It is not surprising therefore that carborane-based analogues of amino acids have been prepared and in particular analogues in which an aromatic group is replaced by the boron cage.

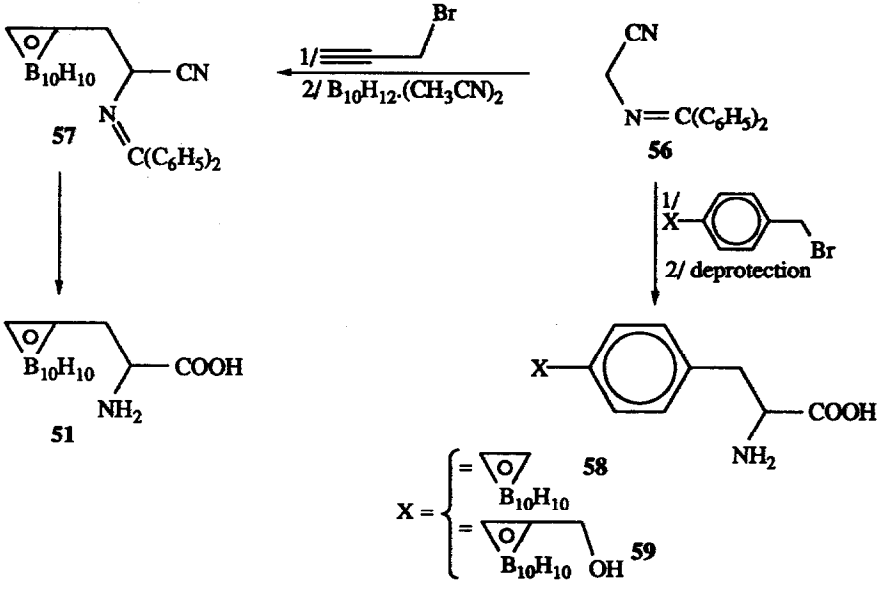
Several syntheses of racemic carboranyl alanine (which can also be viewed as an isosteric analogue of phenylalanine) have been described. A Strecker homologation of o-carboranylacetaldehyde **5 0** afforded an aminonitrile which was then hydrolysed to the racemic aminoacid **5 1** . This compound could also be obtained independantly by reaction of the triple bond of **5 2** with bis(dimethylanilino)decaborane. This was followed by acid treatment to give **5 1** . Although few details were provided, it is unfortunate that this Soviet work is rarely cited in the literature since it is the first reported example of a carboranyl aminoacid, and even of a carboranyl biomolecule [174].



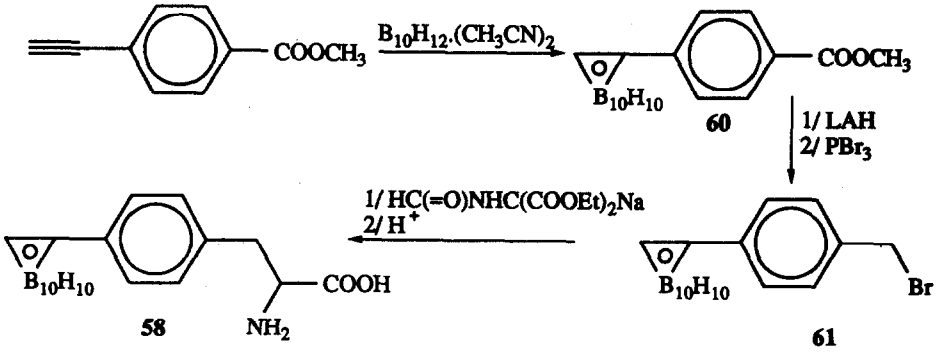
A synthesis of optically active **53** has been described, starting from a chiral propargylic glycine derivative. Thus condensation of **54** with the bisacetonitrile adduct of decaborane afforded optically active **55**, which was then deprotected to the desired **53**. Substitution of the phthaloyl nitrogen protecting group for t-butyloxy-carbonyl (Boc) resulted in doubling the overall yield of the synthesis [171,175].



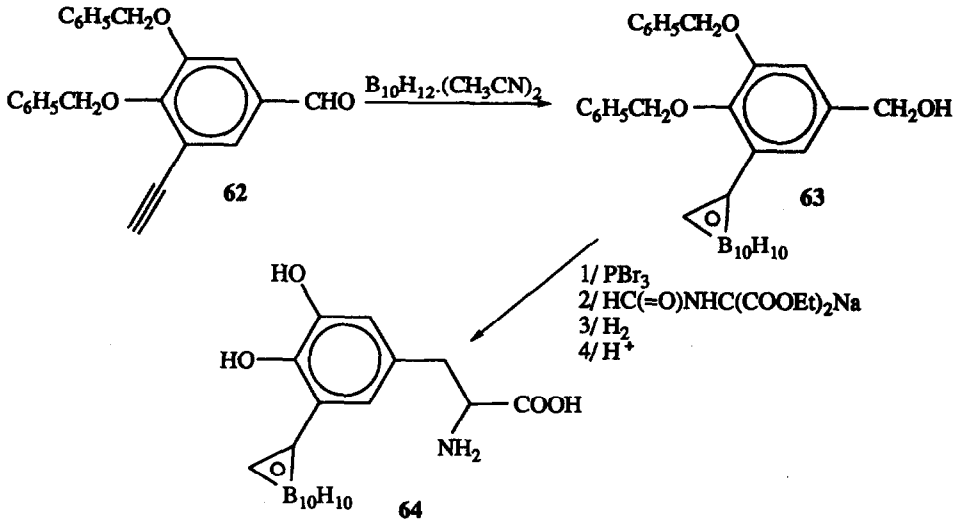
Another approach to (racemic) carboranyl alanine has been reported starting from N-(diphenylmethylene)aminoacetonitrile. Thus **56** was reacted first with propargyl bromide and then with decaborane to give the condensation product **57**. Regeneration of the amine followed by hydrolysis of the nitrile



group afforded **51** in excellent overall yield. Extension of this methodology to the condensation of carboranylated bromomethylbenzene derivatives with **56** have allowed the preparation of aromatic homologues such as **58** or **59** [176].



The former has also been obtained by the following route: addition of decaborane to methyl *p*-ethynyl benzoate gave **60** which was converted to the bromide **61**. Condensation of the latter with diethyl formamimidomalonate followed by decarboxylation and acidic cleavage of the protecting groups then gave **58** . Removal of a boron group from the cage to obtain the water soluble, charged *nido* carborane derivative was achieved with potassium hydroxide [177].

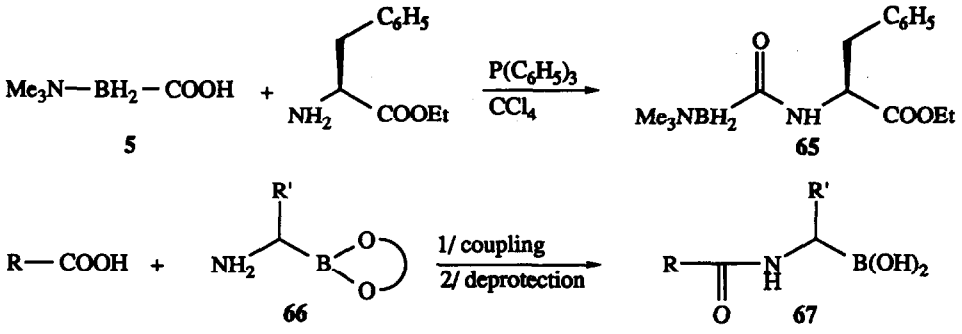


A carboranylated analogue of 3,4-dihydroxyphenylalanine has also been obtained using the same synthetic principles. Thus carboranylation of **62** occured with concomitant reduction to give the corresponding alcohol **63** instead of the expected aldehyde. Bromination followed by condensation with diethyl formamidomalonate and then decarboxylation gave the desired analogue **64** [178].

3 Peptides

Since a number of boron amino acid building blocks are now available, the preparation of boronated peptides is not surprising. Two main principles have guided development in this area: firstly, those cases in which a boronic acid replaces the amino acid carboxyl group — used mainly for enzyme inhibition applications — and secondly, the use of carboranylated vectors to increase the boron content of peptides/antibodies in BNCT; this latter approach is becoming increasingly popular.

One of the simplest dipeptides **65** has been obtained by condensing ethyl L-phenylalaninate with **5** [179]. Dipeptides and tripeptides involving glycine, alanine, isoleucine, serine or methionine residues have been prepared similarly [180].

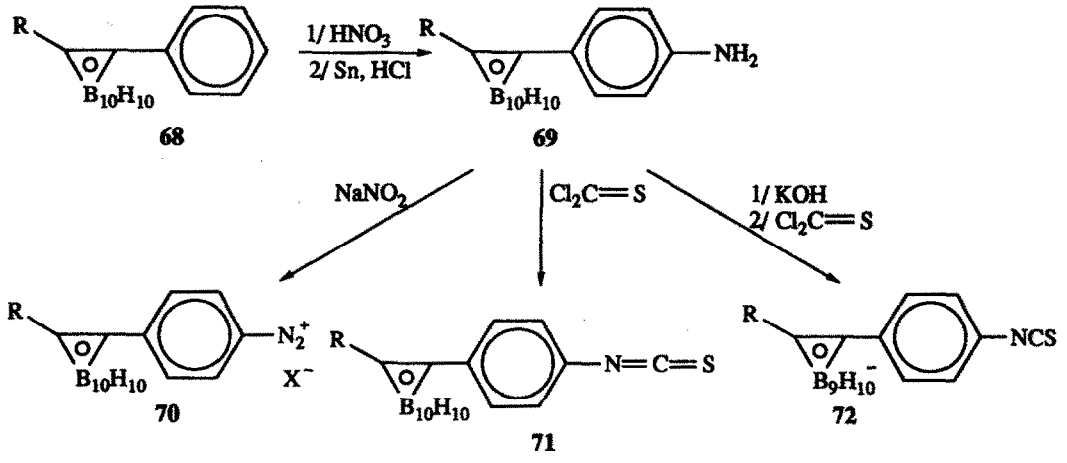


Standard coupling procedures have also been used for alpha-amino boronic acid derivatives. Thus coupling of the carboxyl terminus of an amino acid (or peptide) with the free amino group of protected boronic ester **66** proceeded uneventfully to yield **67** after deprotection. This has also been performed with aminoacids such as alanine, valine, phenylalanine, proline and arginine [148,181-186] or with "higher peptides" such as angiotensin [187]. Improvements in the building block preparations have also been reported [188].

Peptides where boron is linked to the AA side chain have been obtained by standard methodology; for exampled BPA-based peptides [153,189] or carboranylalanine[190] and ultimately carboranylated analogues of enkephalin, angiotensin, and bradykinin have been prepared [191-194].

Using antibodies is a conceptually appealing approach to selective boron delivery into tumors and is an active line of research [195-198]. Since the goal is to ensure high concentrations of boron in the cell, it is not surprising that the chemistry involved has dealt with boron clusters. Among these, dodecaboranes , carboranes , *nido*-undecaborates , and decaboranes have been proposed. The chemistry involved in modifying these boron cages to allow linking to antibody amino acid residues will be now described.

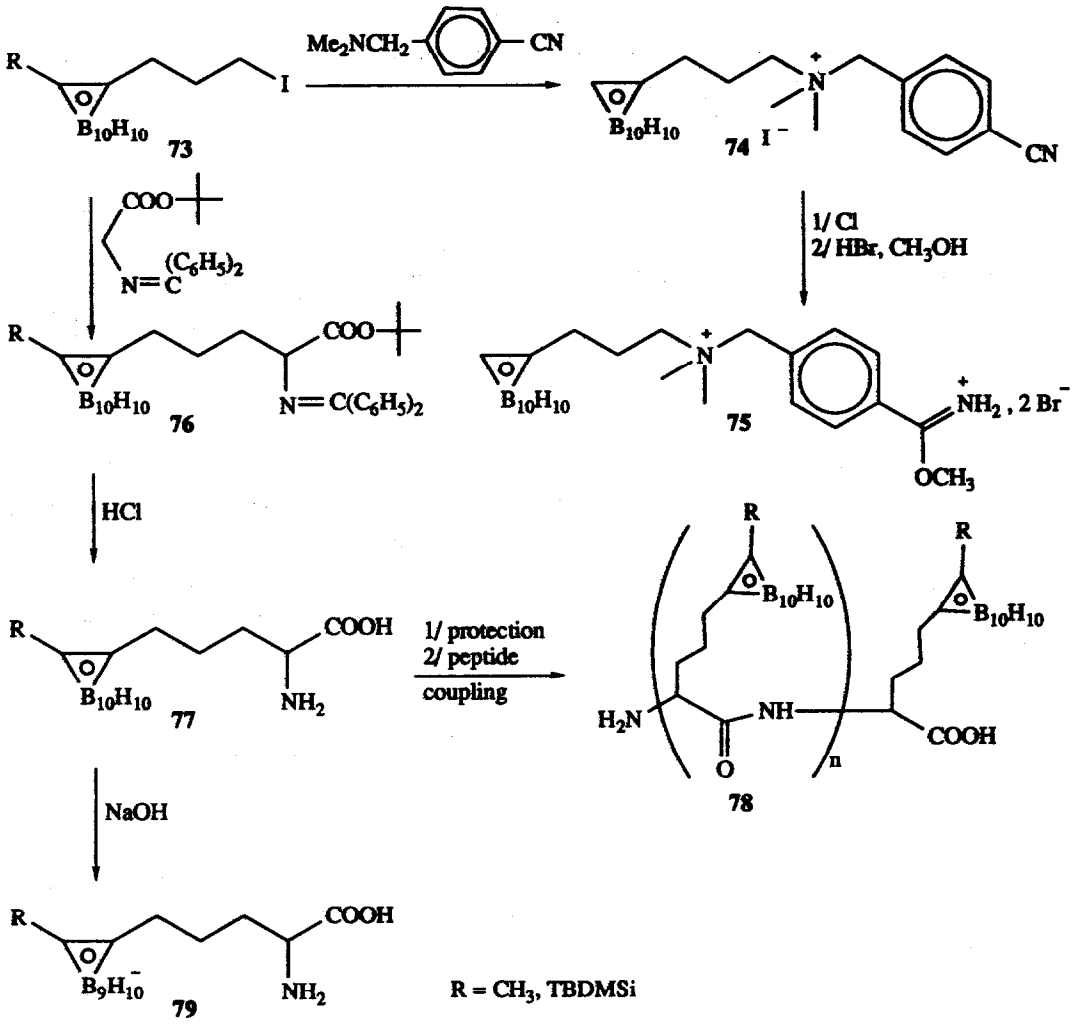
For example, phenyl *o*-carborane **68** has been nitrated and reduced to **69** prior to introduction of a diazonium leaving group using standard methodology. The resulting product **70** is stable enough to be coupled with human histocompatibility antibodies and the chemistry has been repeated to furnish the corresponding tritiated carborane [199-201].



From amine **69** the corresponding isothiocyanate **71** has been prepared to allow coupling to antibodies. This methodology has not only been conducted with the tritium labelled compound, but also with a ^{10}B enriched carborane. Base-degradation of the carborane cage afforded the water soluble *nido* derivative **72** which could be labelled with 125-iodine [202,203].

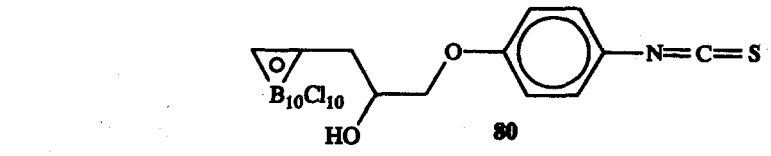
Aliphatic derivatives of carboranes have also been used to obtain a "normal reactivity" for derivatized carboranes. It was found advantageous to insert a carbon spacer between the carborane cage and the functional group which is to be reacted with the protein.

For example, the iodide **73** was reacted with p-dimethylaminomethylbenzonitrile to give **74** which can be coupled to immunoglobulin-binding material such as γ-globulins after conversion to the activated imidate **75** [204,205]. On the other hand, condensation of **73** with a protected glycine gave **76** which was then converted to **77**. This AA analogue can be self-condensed to obtain a dipeptide using suitably protected derivatives and

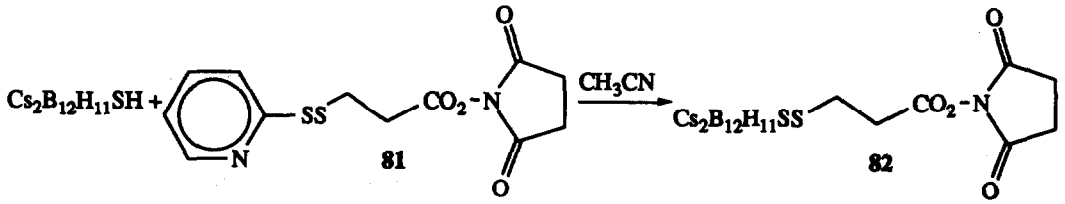


standard peptide methodology. The process can be repeated to get **78** and obtain a tetrapeptide (n = 3) which results in a segment synthesis towards boron-rich peptides [206]. These peptides may also be tagged with a fluorescent dansyl moiety before their coupling to antibodies [207-209]. Degradation of the carborane cage to obtain *nido*-undecaborate **79** and the subsequent coupling of these water-soluble compounds with antibodies has also been demonstrated.

The B-decachloroderivative of *o*-carborane has also been employed. After reaction of its lithio derivative with haloalkanes, functionalised derivatives such as the isothiocyanate **80** could be then obtained which could subsequently be bonded to macromolecules such as poly-L-lysine, concanavalin A, or human IgG [210].



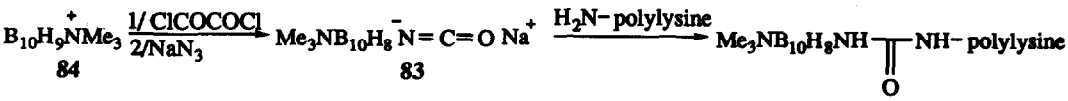
80



81 82

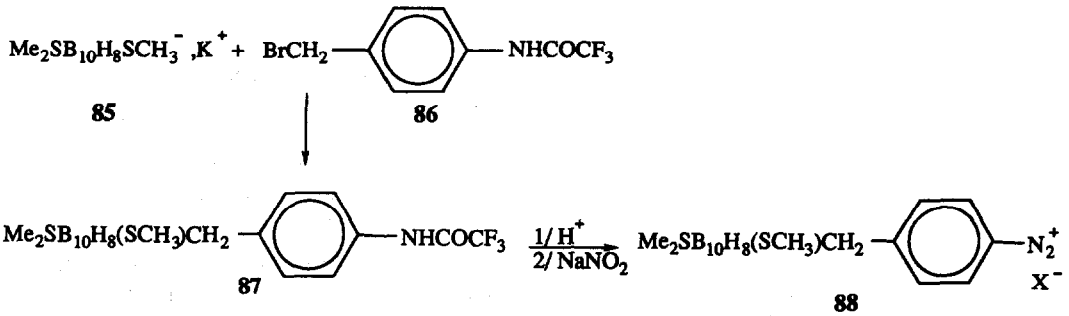
Other boron-rich cages have been attached to antibodies. For example, the caesium salt of ^{10}B enriched BSH was coupled to the heterobifunctional reagent **81**. The new disulfide thus obtained **82** could then be conjugated either to an anti-thymocyte globulin or to a colorectal cancer-directed monoclonal antibody [211].

Similarly, the isocyanate **83** derived from polyhedralborane **84** has been coupled with polylysine. The boronated urea polymer thus formed was then converted to immunoconjugates through the use of a heterobifunctional reagent as described above [212].



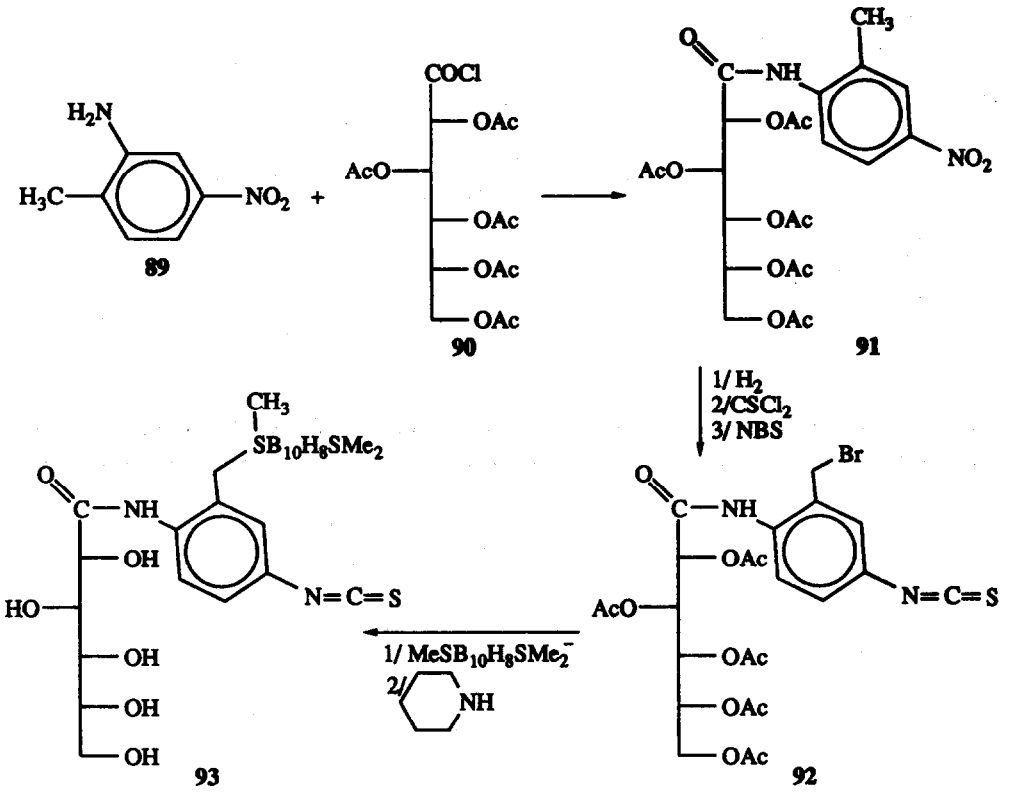
84 83

Another sulfur bearing boron polyhedron has been used. **85** was condensed with *p*-bromotoluidine derivative **86** to obtain **87**. Acidic deblocking of the trifluoracetamide afforded an amine which was then linked to bovine serum albumin after diazotation to **88** [213].



85 86 87 88

Efforts to put a more water soluble linker have also been attempted. Thus 4-nitro o-toluidine **89** was

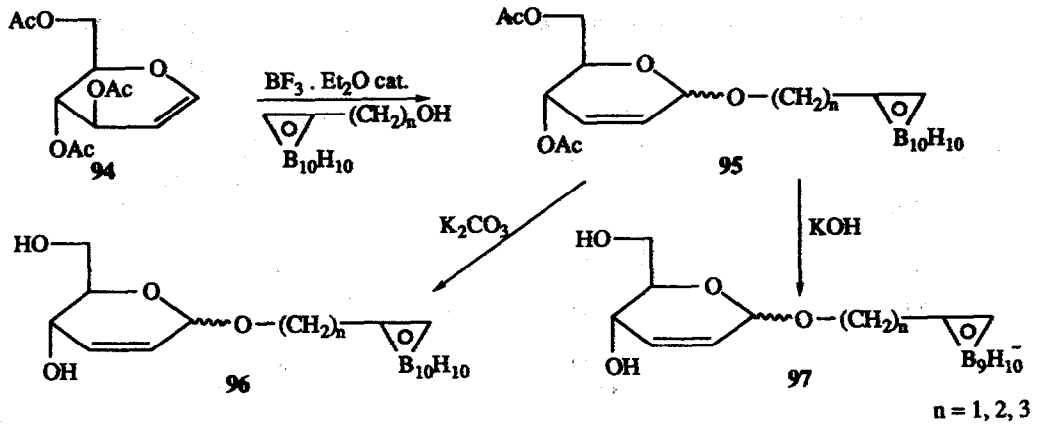


acylated with a carbohydrate derivative **90** to give **91**. Conversion of the nitro group to an isothiocyanate followed by radical bromination was carried out conventionally, which yielded **92**, before its reaction with the sulfur anion of of a polyhedral borane. Finally the ester groups of the carbohydrate were deprotected to **93** before coupling with immunoglobulin G [214]. The preservation of the isothiocyanate during the deprotection sequence is noteworthy.

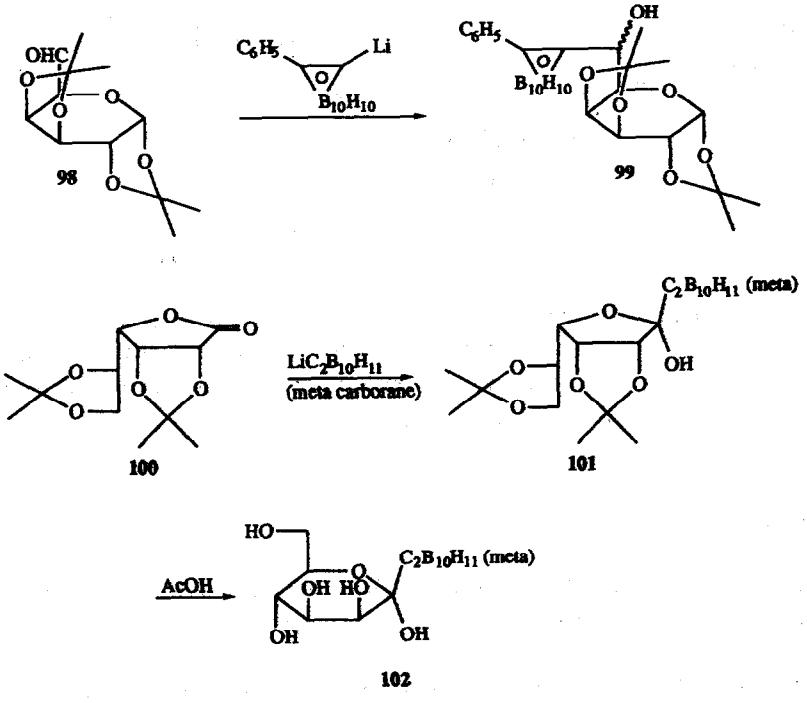
4 Carbohydrates

Carbohydrates have been used as hydrophilicity-conferring vectors, which can be of importance in the case of carboranes derivatives which by themselves are very lipophilic species.

The first reported synthesis of such water-soluble carborane derivatives was the Lewis acid catalysed glycosidation of glycal **94** with carboranyl alcohols to obtain the glycosides **95** in good yield. The neutral *closo* **96** or the charged *nido* **97** derivatives could be obtained depending on the conditions chosen for ester deprotection thus providing flexibility in this straightforward synthesis [215].



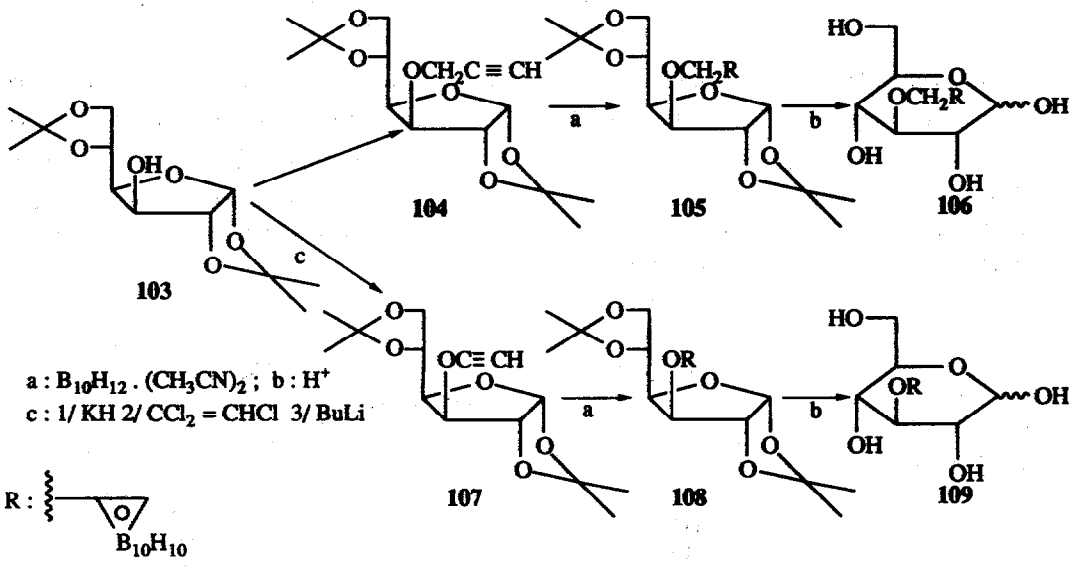
Carboranes linked to a carbohydrate moiety *via* a carbon-carbon bond have also been obtained by the direct reaction of 2-phenyl-o-carboranyllithium with carbohydrates possessing an aldehyde group such as **98**.



Thus **99** was obtained as a 2:1 mixture of epimers. The procedure was extended to other open-chain aldehydo sugars [216]. A similar approach was proposed for the mannonolactone derivative **100**. Reaction with *meta*-

carboranyl lithium afforded the condensation product in very high yield. In addition, when the anomeric mixture was left to stand the more stable beta anomer **101** (structure proven by X-ray crystallography) was formed almost exclusively. Deprotection then yielded **102**. Advantageous to this approach is the fact that a pentahydroxylated compound can be obtained in excellent overall yield [217].

Another approach to carboranated carbohydrates has been to consider the reaction of decaborane with the triple bond of a suitable acetylene derivative.

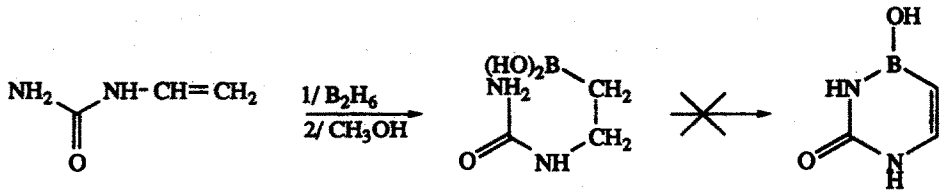


For example, propargylation of readily available diacetone-D-glucose **103** afforded **104** with carborane cage formation proceeding in good yield. **105** was then deprotected conventionally to furnish **106** [218].

A related analogue of **106** has also been prepared. After conversion of **103** to the corresponding ynol ether **107**, addition to decaborane afforded **108**. Acidic deprotection then provided **109**, a D-glucose *o*-carboranyl ether. This scheme has been shown to accomodate protecting groups other than acetals [219].

5 Nucleic bases

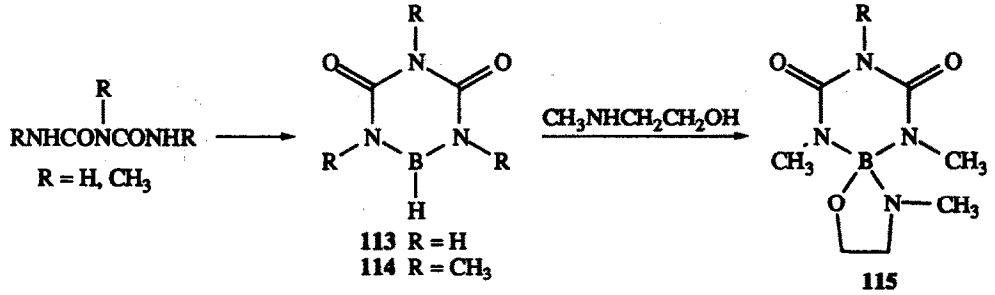
If boron could be attached to pyrimidines or purines in such a way that the resulting boronated nucleic-base could be incorporated into growing neoplasmas, significant concentrations of boron in cancerous tissues might be achieved. Various approaches to boronated nucleic bases have been proposed with this in mind.



112 111 110

Attempts to obtain **110** a compound in which boron replaces a ring carbon of uracil were hampered by the inability to cyclize **111** , itself readily obtained from N-vinylurea **112** [220].

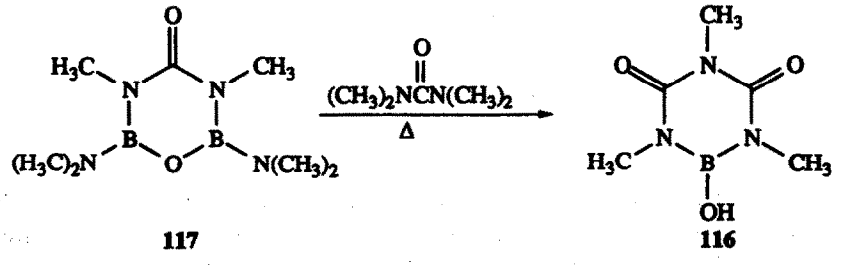
Borazauracil **113** is an isoelectronic and isosteric analogue of uracil. Its synthesis was claimed in a report [221] describing the reaction of biuret with sodium borohydride in the presence of iodine, however these results could not be subsequently reproduced by other workers [222,223]. These difficulties were attributed to the presence of labile amide hydrogen atoms so attention turned to preparing the corresponding N-methyl analogues. Although evidence for the formation of **114** was obtained, it proved necessary to form an ate complex with N-methylethanolamine to isolate a pure compound **115**.



113 R = H
114 R = CH3

115

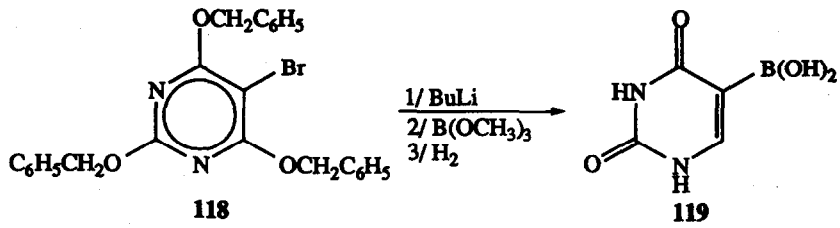
The hydroxylated analogue **116** however was shown to be thermally stable and could be obtained at high temperature by the action of tetramethylurea on **117** [224]. Such syntheses have also been effected with thiocarbonyl derivatives [225,226].



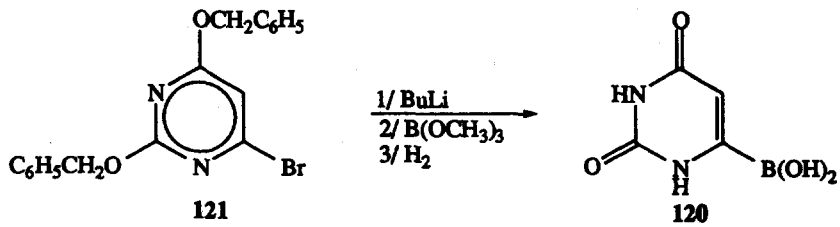
117 116

Other boron analogues of uracil have been obtained which contain a complete uracil skeleton. *i.e.* with a dihydroxyboryl group as a substituent group. When substitution is effected at position -5, the compound obtained can also be considered as an analogue of thymine.

This synthesis proceeds conventionally, with the metallation of the bromopyrimidine **118** followed by reaction with an alkyl borate. Removal of the protecting groups afforded **119** [227]. In a similar way **120** could be obtained from **121** [228,229].

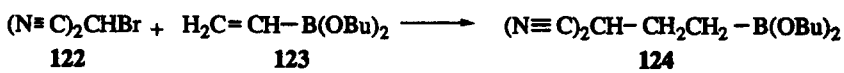


118 **119**

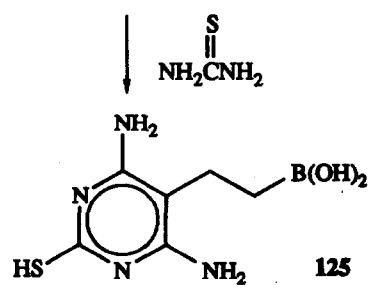


121 **120**

Another approach has been to construct the pyrimidine ring from an acyclic boronated precursor. Thus, radical-initiated addition of **122** with vinyl boronate **123** followed by reduction gave **124**. This was then condensed with thiourea to afford a boron-substituted thiopyrimidine **125** [230].



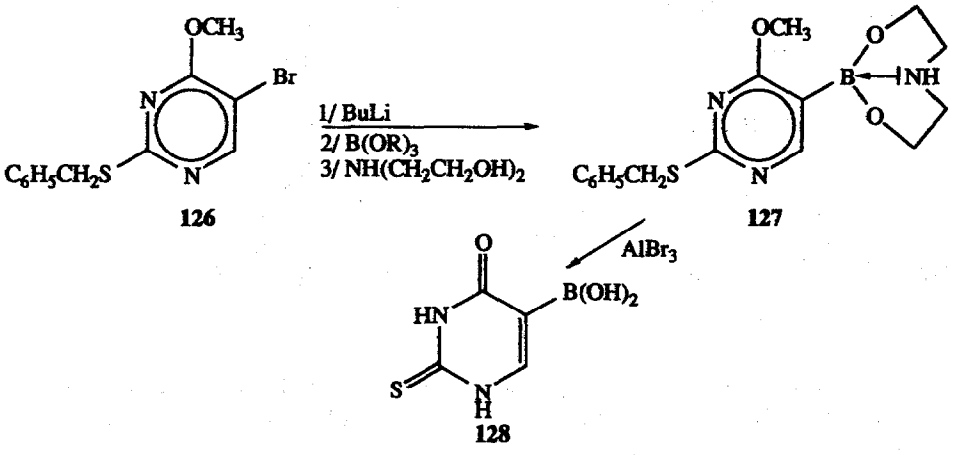
122 **123** **124**



125

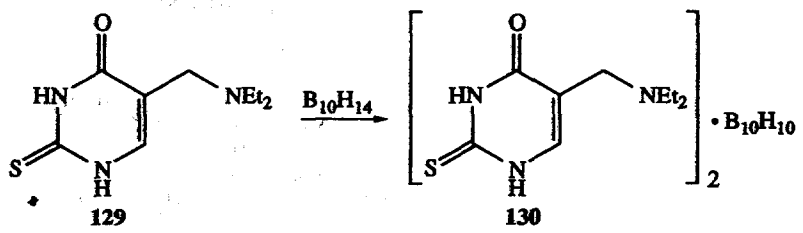
Among nucleic bases, thiouracil holds a special position since its action as a "false" precursor occurs in melanin biosynthesis. This behaviour is the reason why thiouracil boron analogues have received particular attention as synthetic targets.

Using the same process described above for uridine derivatives, metallation of a suitably protected thiopyrimidine **126** followed by boronation afforded the desired carbon-boron bond at position -5. The compound thus obtained was best isolated as its diethanolamine adduct **127**. It is of interest to note that in this case, the boronation step needed to be carried out between -85 °C and -100 °C to achieve satisfactory results. The simultaneous deprotection of all protecting groups to **128**, was carried out with aluminium tribromide and occured without cleavage of the B-C bond [231].

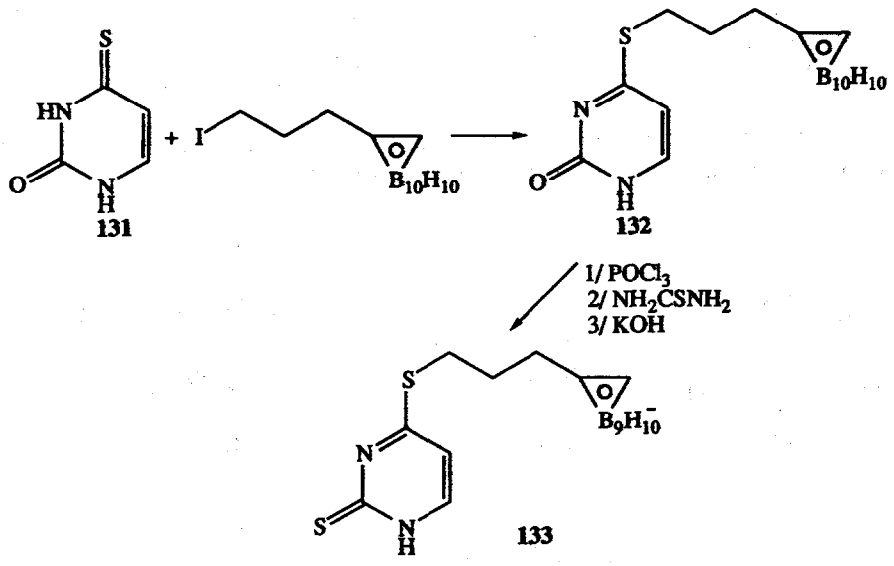


Since the reason for preparing thiouracil boron analogues was to use them as vectors for achieving high boron concentrations in cancerous cells, linking boron-rich systems such as carboranes was a logical progression.

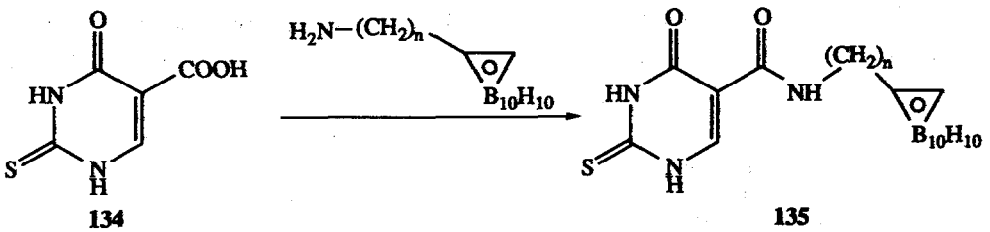
130, a decaborane salt of the amino derivative of thiouracil **129**, in which the basic nitrogen atom acts as a ligand to the decaborane ring system, has thus been synthesised[232].



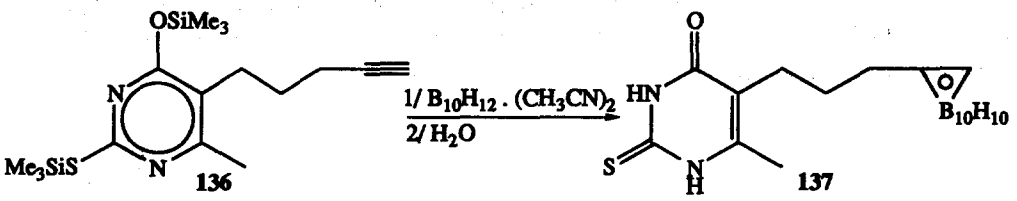
S-Alkylation of 4-thiouracil **131** with 3'-iodopropyl-o-carborane in the presence of a base has been shown to afford **132** without degradation of the carborane cage. Introduction of sulfur at position -2 and a final conversion to the *nido* derivative **133** gives a water soluble compound [233].



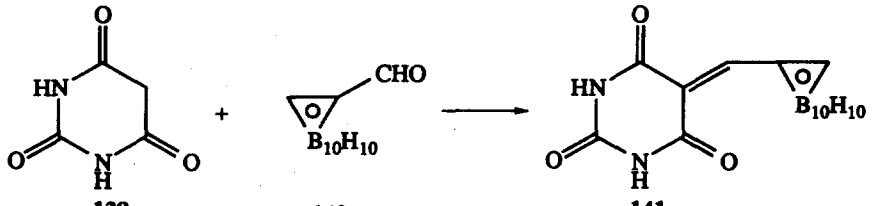
Another effective way to link a carborane moiety is to condense a carboxy functionalised thiouracil derivative such as **134** with an aminoalkylcarborane to give amide **135** [234].

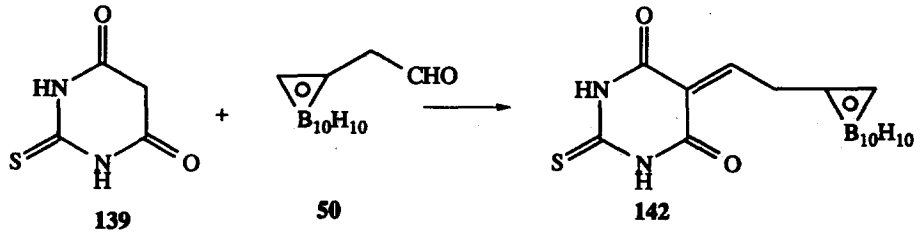


If the carborane cage is to be obtained by cycloaddition of decaborane, then an acetylenic derivative of thiourea is needed. Since the acetylenic side chain could not be introduced selectively onto the nitrogen or sulfur of a thiouracil, the derivative **136**, with pendant acetylenic groups at position -5 was obtained by total synthesis [235]. This was condensed with decaborane to give the desired carborane **137**. A carboranylated precursor in the pyrimidine series has also been described [236].

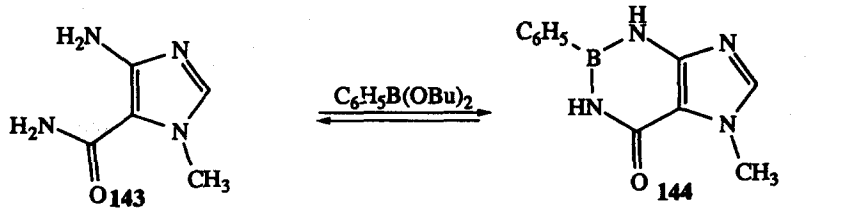


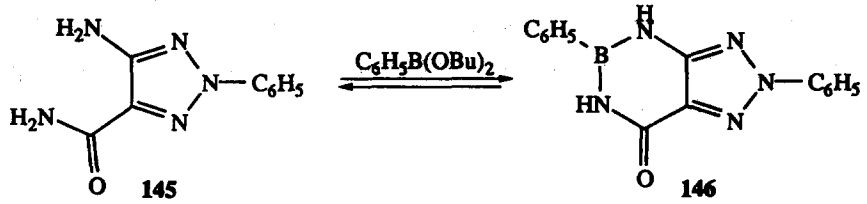
Barbituric **138** and thiobarbituric **139** acids have been shown to undergo a Knoevenagel condensation with carborane **140** or carborane acetaldehyde **50** to yield the products **141** or **142** [237].



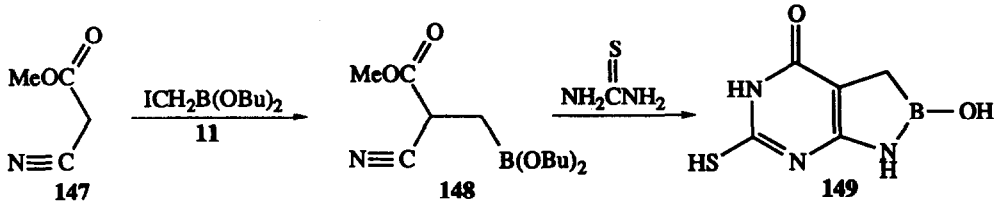


With regard to purine analogues, the introduction of boron to the ring system was first accomplished with appropriately subtituted imidazoles. Thus condensation of **143** with dibutyl phenylboronate afforded **144** [238].





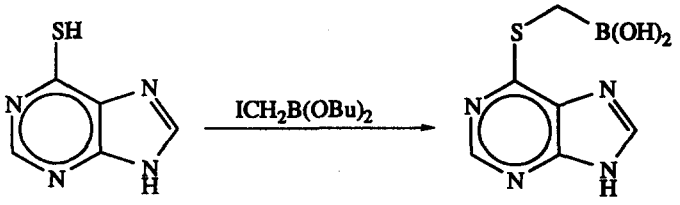
Similarly **145** was obtained from **146** [239]. Unfortunately these reactions are reversible and the boron analogues obtained are hydrolytically unstable. Such chemistry has also been extended to other deazapurine boro derivatives including analogues with boron located in the imidazole ring (thus starting with pyrimidine derivatives); however in this case too, the analogues obtained are relatively unstable [240-245].



147 **148** **149**

A stable derivative has nevertheless been obtained for the deazapurine series. Condensation of dibutyl iodomethylboronate **11** with methylcyanoacetate **147** afforded **148** which was then condensed with thiourea to give the stable purine **149**. It is of interest to note that this condensation was unsuccessful when guanidine replaced thiourea [246].

Boron has also been introduced as a substituent of the ring system and this approach has been realised by the successful S-alkylation of thiopurine **150** with dibutyl iodomethyl boronate **11**. This condensation took place in refluxing acetonitrile thus allowing the use of neutral conditions to give the stable purine analogue **151** [246].

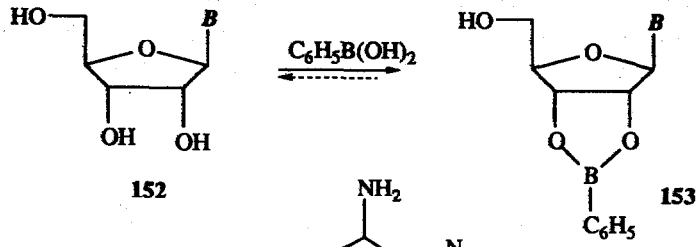


150 **151**

6 Nucleosides

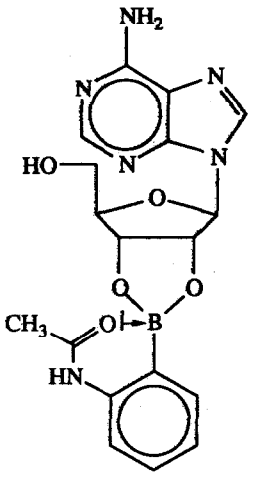
Nucleosides represent an additional way to selectively incorporate compounds into cancerous cells [247]. Given the development of techniques for linking boron to either a carbohydrate or a nucleic base, it is not surprising that both types of chemistry have been exploited in the synthetic approaches to boron-bearing nucleosides.

At first, efforts were directed to prepare boronic esters with hydroxyl groups at positions -2' and -3' of a ribonucleoside. Phenylboronic acid could thus be reacted with **152** to give crystalline derivatives **153** quite efficiently. However, these esters were found to be readily hydrolysed (complete in 10-15 min. at pH 6.5) and



152 153

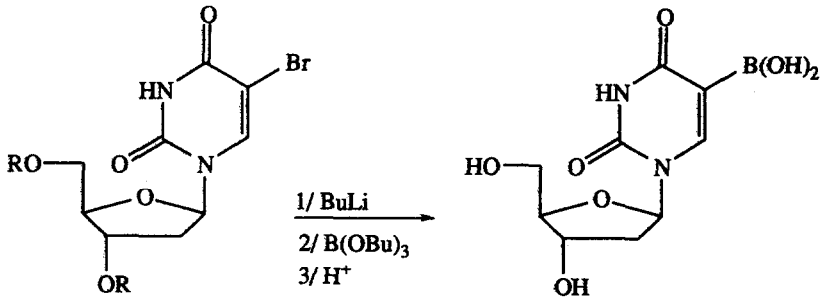
B : nucleic base



154

therefore impossible to use in physiological media [248]. Attempts to stabilise the boronate against hydrolysis have succeeded with the preparation of **154** in which anchimeric participation of the acetamido substituent acts effectively as an electron donor to the boron centre [249].

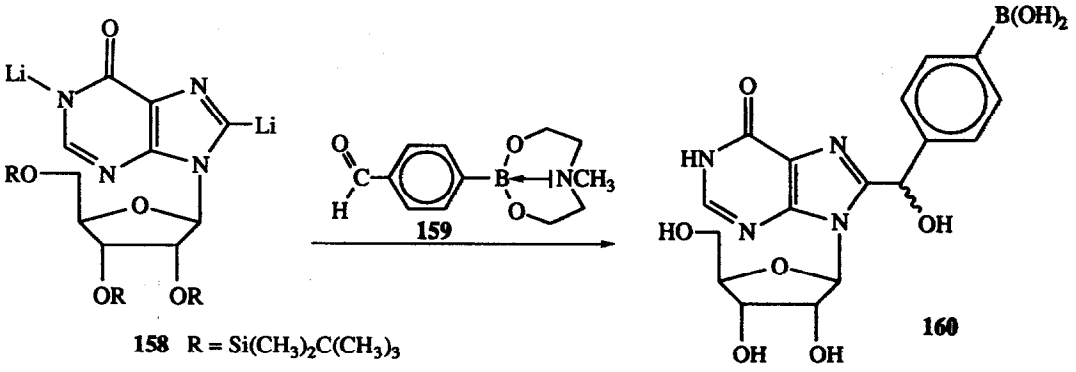
Boron has also been directly attached to th nucleic base. Thus 5-bromo-2'-deoxy-uridine **155** was converted to its O-trimethylsilyl (TMS) derivative **156** which was submitted to halogen-lithium exchange and then reacted with butyl borate to afford **157** , albeit in low yield [228,229].



155 R = H
156 R = $Si(CH_3)_3$

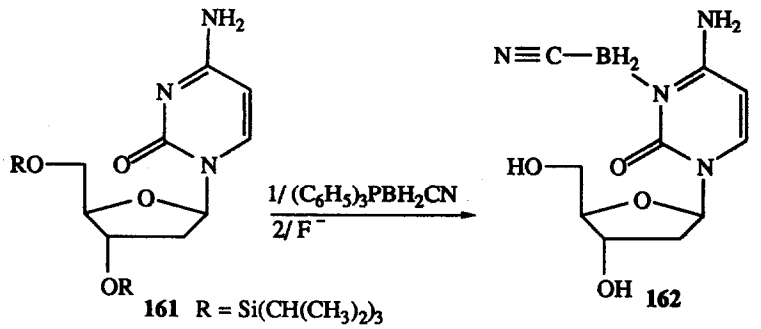
157

Another approach has been used for the ribonucleotide series through the condensation of the bislithio derivative **158** with a protected boronobenzaldehyde such as **159**. This type of boron protection was crucial for condensation to occur; **160** was isolated as a mixture of diastereoisomers and the reaction was applied to several nucleosides [250].



158 R = $Si(CH_3)_2C(CH_3)_3$

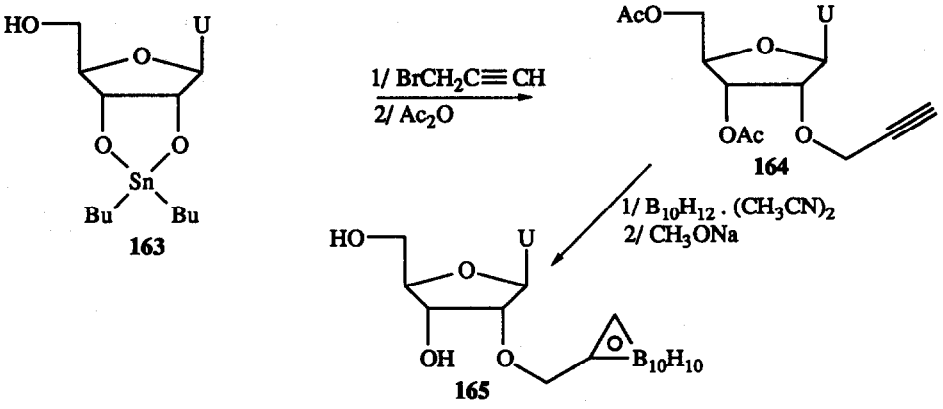
The formation of cyanoborane adducts of nucleosides represents another type of boron incorporation. These derivatives are readily obtained by the reaction of nucleosides , such a **161**, with triphenylphosphine cyanoborane to give **162** [251]. The reaction has been applied to various deoxyribonucleosides [252-255].



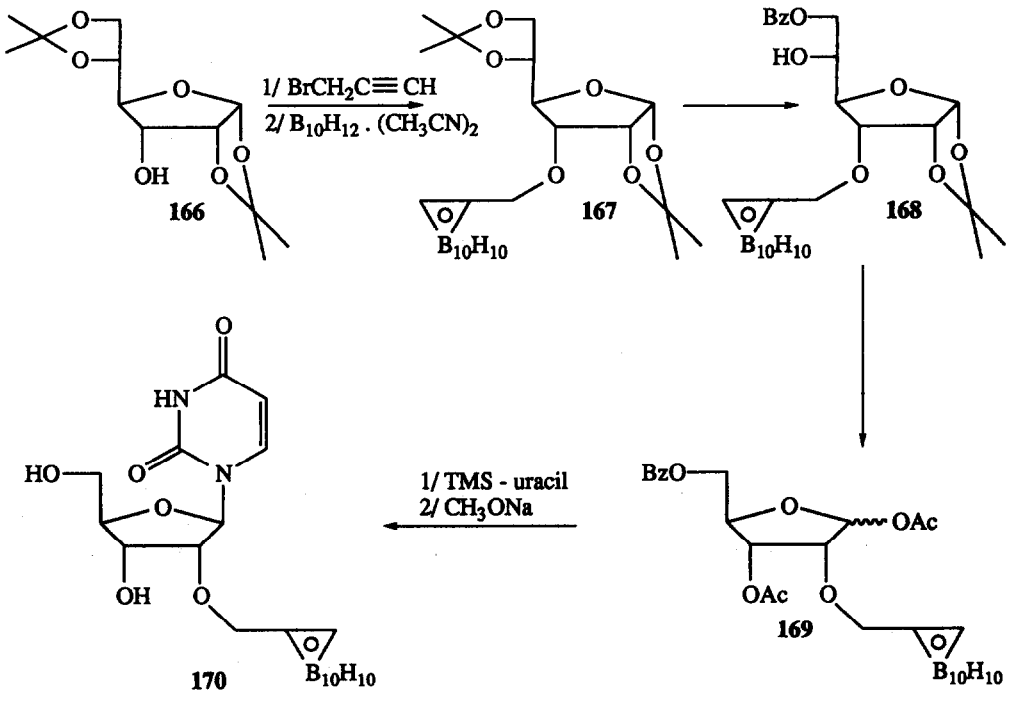
161 R = $Si(CH(CH_3)_2)_3$ **162**

Carboranes have also been linked to nucleosides. For example regioselective alkylation of the stannylidene derivative **163** of uridine, followed by acylation afforded the propargyl ether **164**. The addition of decaborane to the triple bond under the usual conditions, followed by deprotection of the hydroxyl groups then gave **165** [218,256,257].

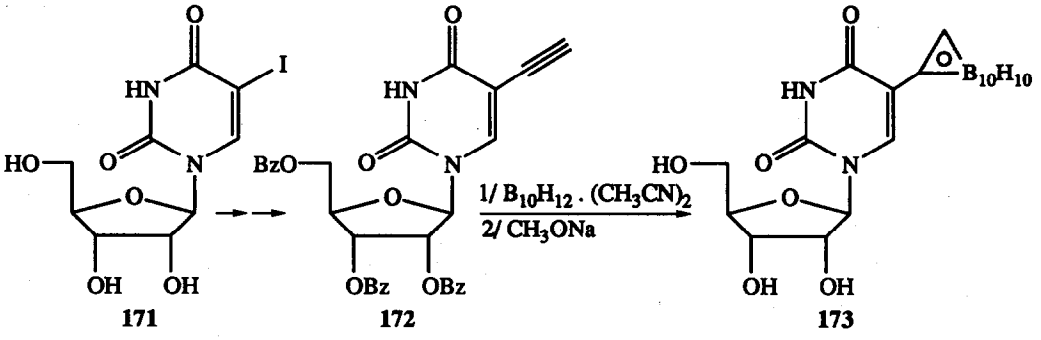
An amplification of this approach, which could allow the introduction of any desired nucleic base has also been described. For this purpose a common carboranylated ribose precursor was employed.



It was obtained by propargylation of the allofuranose derivative **166** followed by condensation with decaborane in the manner just described above. Selective hydrolysis of the 5,6-ethylidene acetal of **167** followed by blocking of the terminal hydroxyl group then gave **168**. After removal of the acetal, periodate cleavage, and acetylation, **169** could be isolated. This synthon was submitted to condensation with a N-trimethylsilyl derivative of uracil under standard conditions to afforded the desired nucleoside **170**. The versatility of this approach is to be underlined since in principle this condensation can be undertaken with other nucleic bases [258].

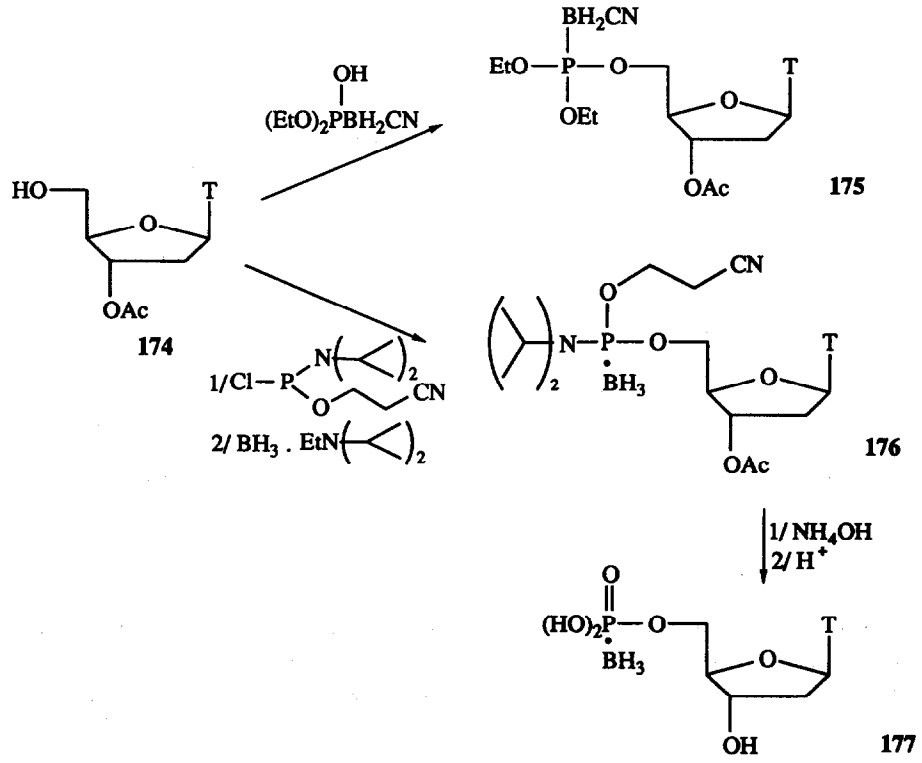


Other efforts to attach a carborane to nucleosides are based on derivatizing the uridine moiety. After conversion of 6-iodouridine **171** to the protected acetylenic derivative **172**, the cycloaddition of decaborane could be satisfactorily achieved, best results being obtained using propionitrile as the Lewis acid ligand donor.



171 **172** **173**

Unblocking then afforded **173** [259-261]. Enhancing the water solubility by linking the carborane to a glycerol-derived dendrimer has also been achieved [262].



174 **175** **176** **177**

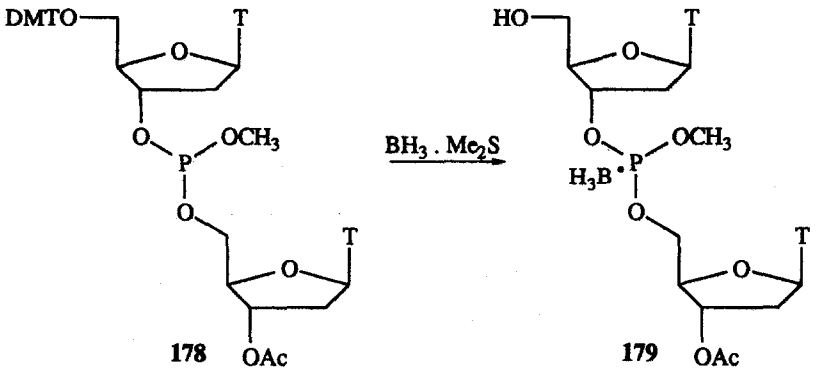
7 Nucleotides

When considering the possible action of boronated nucleotides in antisense and blocking gene expression, it is desirable to possess analogues with boron present on the phosphate internucleotide bond, thus lowering the chances of altering base pairing.

For example, 3'-O-acetyl thymidine **174** was condensed with diethylphosphitecyanoborane in the presence of DCC to yield **175** [263].

On phosphitylation of **174** , followed by reaction with a borane-amine complex, **176** was obtained. Removal of protecting groups then gave **177** which displayed an increased hydrolytic stability due to the presence of the P-B bond [264].The boranophosphates thus obtained are isoelectronic and isostructural with methylphosphonates which are stable to the action of nucleases.

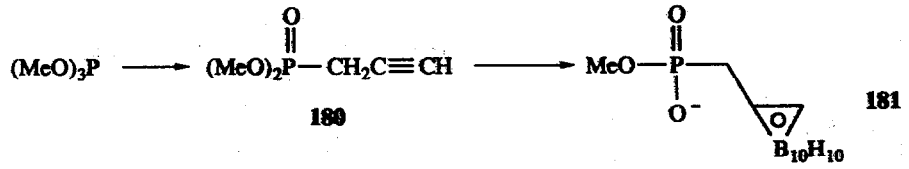
The preparation of boranophosphate analogues of di and tri nucleotides are a first step towards boronated oligonucleotides.To achieve these compounds the dinucleotide phosphite intermediate **178**, obtained using standard oligonucleotide chemistry, was boronated with excess borane dimethylsufide. The reaction occured with concomitant deprotection of the 5'-OH group and yielded **179**; repetition of this assembly process with another mononucleotide gives a trinucleotide [265,266].

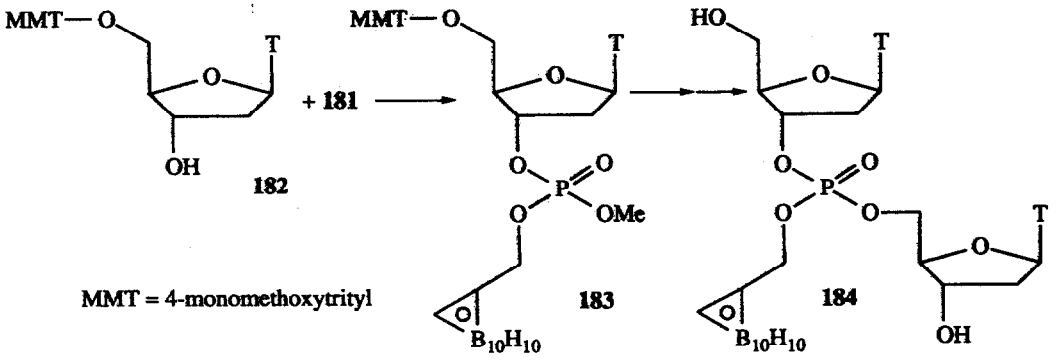


DMT = 4,4'-dimethoxytrityl

A carboranyl dinucleotide is also known and its synthesis was made possible by the preparation of a carboranyl phosphonate. Trimethylphosphite, submitted to an Arbuzov-like condensation with propargyl bromide affords **180**. When reacted with decaborane, an *o*- carborane was formed in which selective liberation

of one phosphorus protecting group to give **181** has occured. The subsequent condensation of this compound with a 5'-OH blocked thymidine **182** led to formation of the mononucleotide **183**. Hence a dinucleotide **184** could subsequently be obtained using classical oligonucleotide assembly methodology [267].





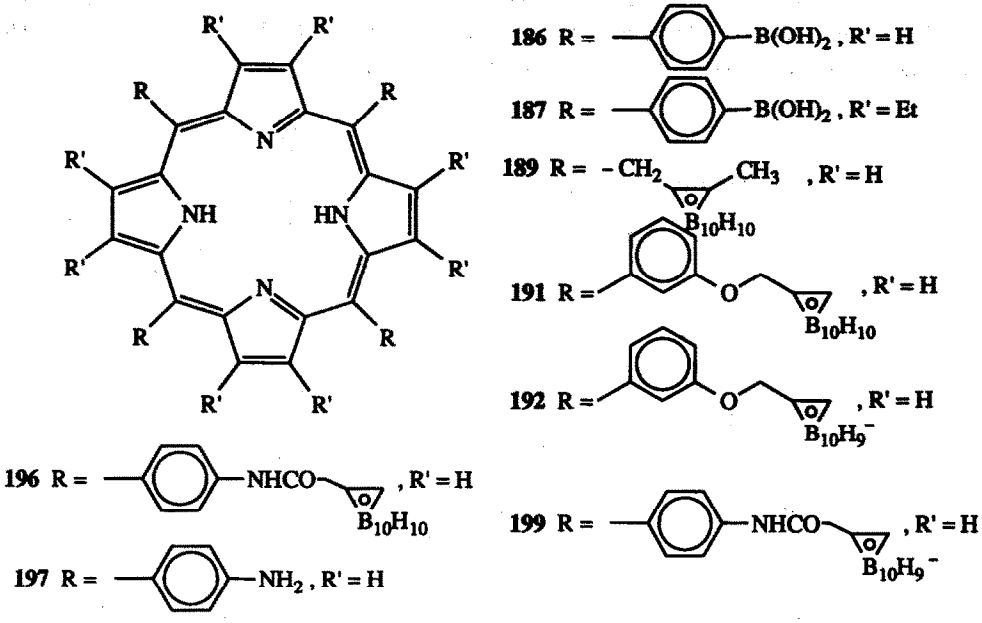
MMT = 4-monomethoxytrityl

8 Porphyrins

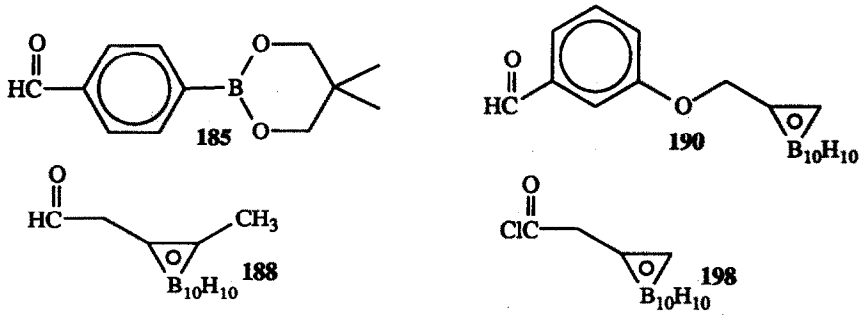
Porphyrins are known to concentrate in tumor tissues and if enriched in boron they could provide a suitable way to achieve high boron concentration in cancerous cells (it is worth noting here that porphyrins themselves, are actively involved in another type of bimodal treatment — namely photodynamic therapy — in which, acting as photosensitizers, they produce singlet oxygen upon their exposure to (red) light). Enrichening porphyrins with boron , mostly through attachments to carboranes, has thus received attention from several groups.

In this respect, one straightforward method is to prepare a boronated porphyrin by condensing several boronated sub-units (as opposed to derivatisation of non-boronated porphyrins).

Thus, the boron trifluoride etherate catalysed condensation of pyrrole with a protected boronic benzaldehyde **185** afforded **186**. The octaethyl derivative **187** was similarly obtained by the condensation of tetraethyldipyrromethane with the same aldehyde. Both **186** and **187** have been designed so as to subsequently confer water solubility *via* interaction of the boronic acid moiety with carbohydrate derivatives [268].

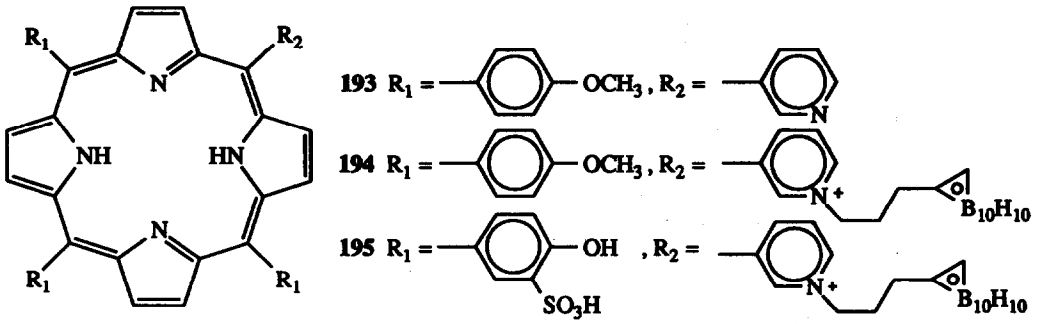


Considering carborane derivatives, a Rothemund condensation of aldehyde **188** with pyrrole afforded porphyrin **189**. The presence of a methyl group on the carborane was believed to lower the solubility in the reaction media thus facilitating product isolation; indeed, in the absence of a methyl group, the isolated yield of the corresponding porphyrin was 10 times lower [269,270] .

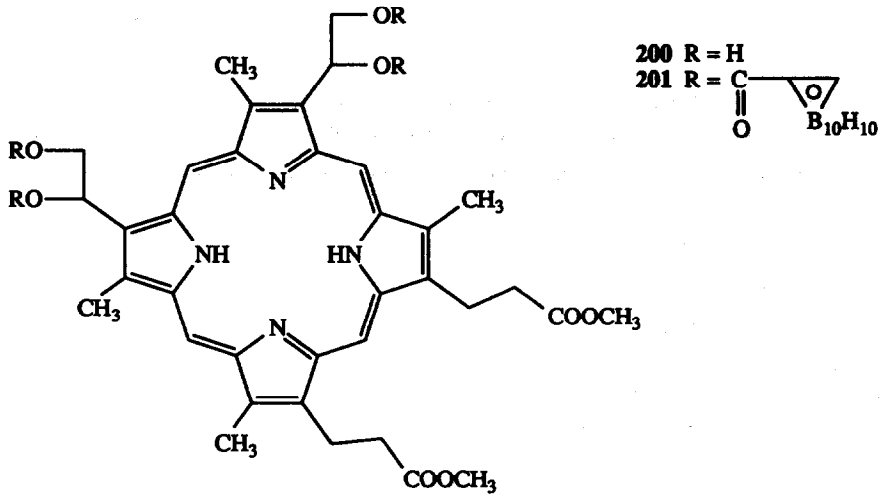


When pyrrole was condensed with aldehyde **190** under mild conditions **191** was obtained in excellent yield. This was followed by carborane degradation to the *nido* compound **192** [271].

With regard to derivatisation of non-boronated porphyrins (the second approach to boron analogues) quaternization of the pyridine rings of **193** with 3'-iodopropyl-carborane afforded **194**. This was subsequently

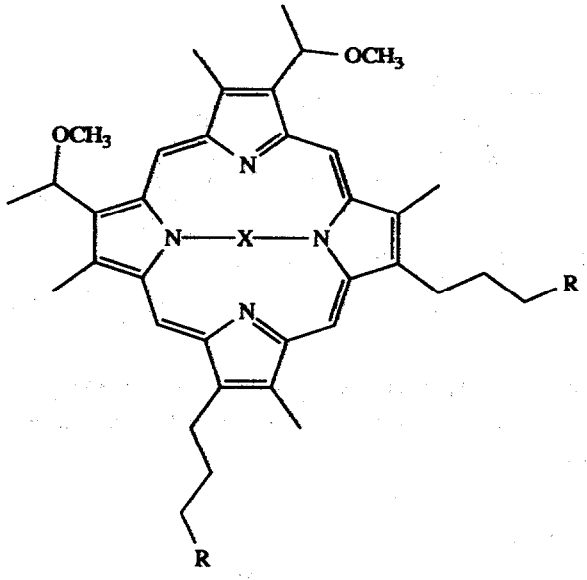


sulfonated to **195** in order to improve its solubility in water and hence its cellular uptake [272]. **196** was obtained through formation of an amide bond between a polyamino porphyrin **197** and **198**. Degradation of this carborane afforded the charged *nido* species **199** [273,274].

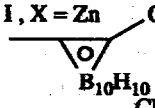


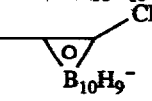
Similarly, esterification of **200** with carboranecarboxylic acid afforded **201** [275].

The attachment of carboranes to porphyrins has also been achieved using hydrocarbon chains. Reacting the lithio derivative of 2-methyl carborane with the diiodide **202** following zinc removal gave **203**. This was then degraded to amphiphilic **204** [276].

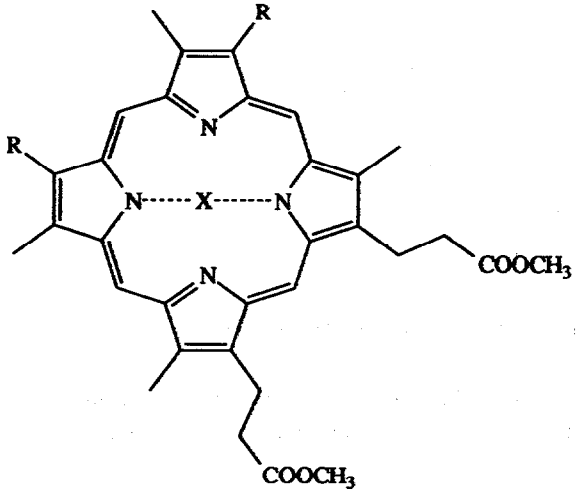


202 R = I, X = Zn

203 R =  , X = H_2

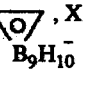
204 R =  , X = H_2

The mercuric derivative **205** has been used to attach vinyl carboranes. This was achieved with a very large excess of the carborane under Pd catalysis to give **206** after the zinc had been removed. Degradation to the *nido* derivative **207** in order to confer water solubility was subsequently performed [271,277].



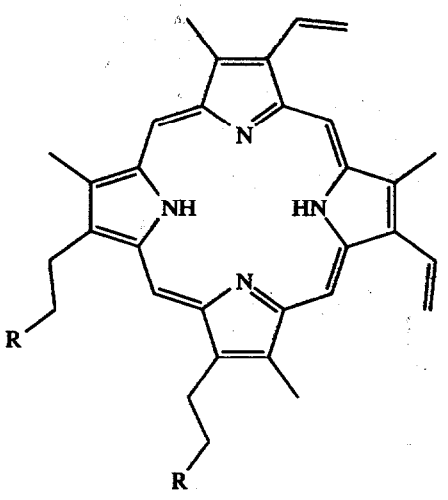
205 R = —HgCl, X = Zn

206 R = —CH=CH—  , X = H_2

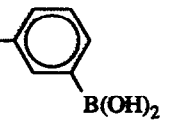
207 R = —CH=CH—  , X = H_2

A family of boronated porphyrins have been prepared which are designed to recognise various

monosaccharides and signal their presence by colour changes. i.e. interactive recognition. **208** was prepared merely by creation of an amide bond between **209** and *m*-aminophenylboronic acid [278].



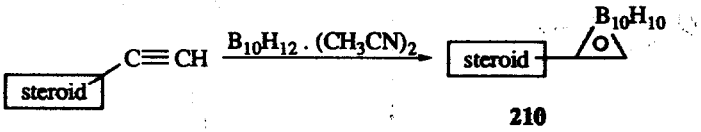
209 R = COOH
208 R = CONH



9 Miscellaneous

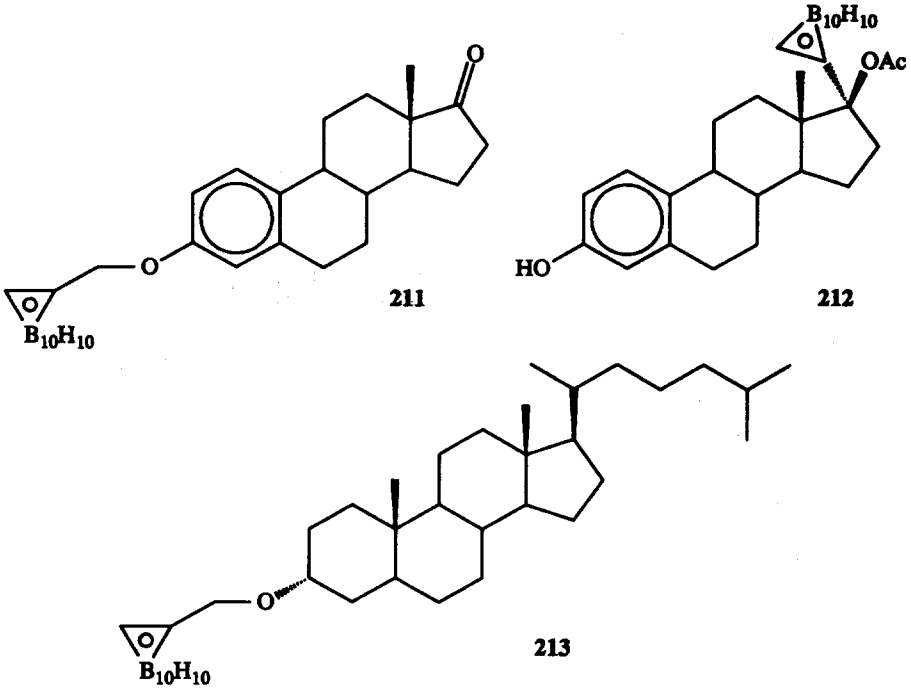
Boronated analogues of hormones, neurotransmitters and of other pharmacologically active agents are collected in this paragraph.

Steroids have also been considered worthwhile vectors for incorporating boron into cancerous cells, and conceptually, such carboranated derivatives **210** can be obtained by the reaction of acetylenic steroids with decaborane.

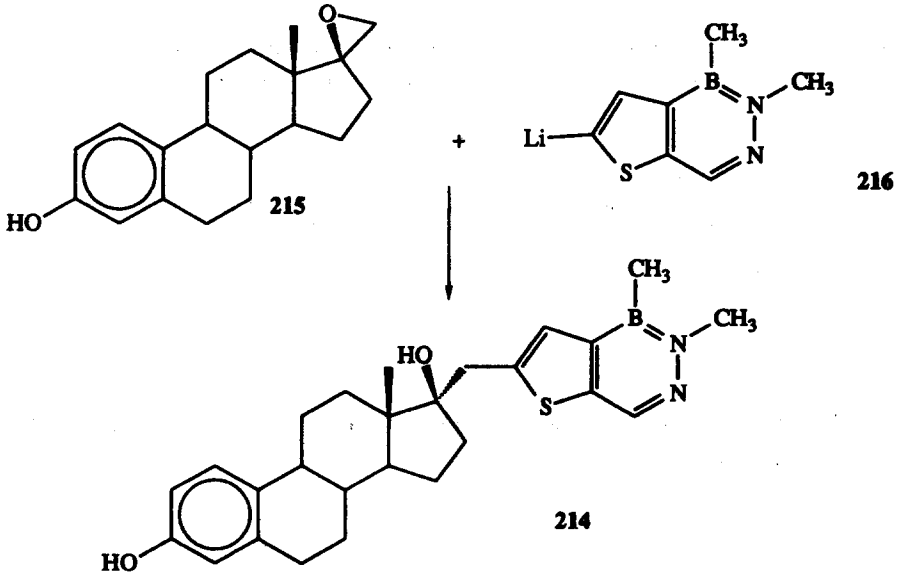


210

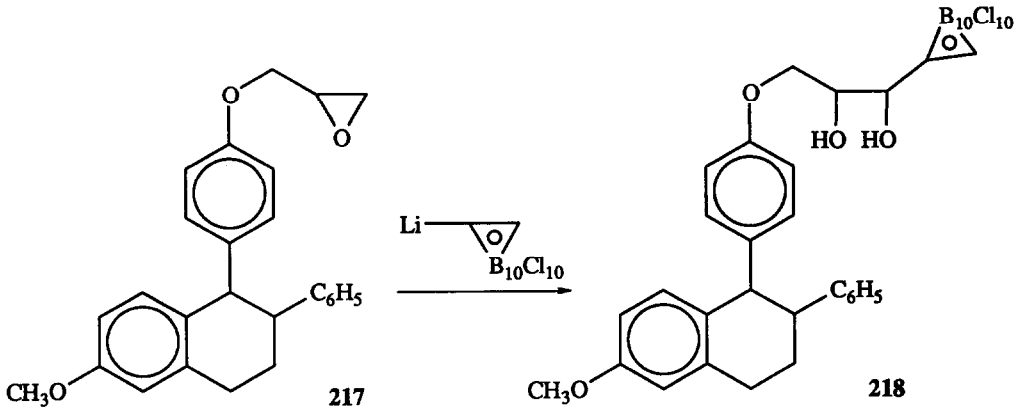
This has been effected in the estrone series for **211** and **212** [279,280]. X-ray crystallography of the cholesterol derivative **213** has been reported [281,282].



Another type of boron containing steroid has been described; **214** was obtained by oxirane cleavage of **215** using a thiophenylborazine-derived anion **216**, however it was found to decompose with time [283].



Related to steroids are the bioactive antioestrogens; carborane-labelling of **217** has been made possible by epoxide cleavage with decachlorocarboranyllithium to obtain **218**. It is of interest to note that the methyl ether could subsequently be selectively deprotected with boron tribromide [284].



217 **218**

Boron analogues of neurotransmitters have also been considered. Thus a boronic analogue of choline has been obtained by condensing dibutyl methylboronate with the Grignard reagent derived from **219**. Quaternization of the nitrogen then afforded **220** in which the ionisable borinic acid group was shown to interact with acetylcholinesterase [285].

$$(CH_3)_2N-(CH_2)_3-Cl \quad \xrightarrow[3/\ CH_3Br]{1/\ Mg \quad 2/\ CH_3B(OBu)_2} \quad (CH_3)_3\overset{+}{N}-(CH_2)_3\,BCH_3\,(OH)$$

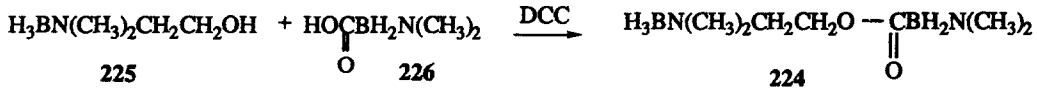
219 **220**

Whilst the borane adduct of 2-dimethylaminoethanol has been prepared, the boro analogue of choline has not been considered [286,287]. Using all possible structures of monoboronated analogs of acetylcholine, computational methods proposed that **221** should be the most stable [288]. Although **221** has not yet been prepared, a stable isomer has been characterised. Thus the isostructural and isoelectronic **222** was obtained from boronation of **223** [289]. The same methodology has also been applied to acetylthiocholine [290].

$$(CH_3)_3NBH_2CH_2O-\overset{\overset{O}{\|}}{C}CH_3 \qquad (CH_3)_2NCH_2CH_2OCOCH_3 \xrightarrow[Et_4N\,BH_4]{} H_2B-N(CH_3)_2CH_2CH_2O-\overset{\overset{O}{\|}}{C}CH_3$$

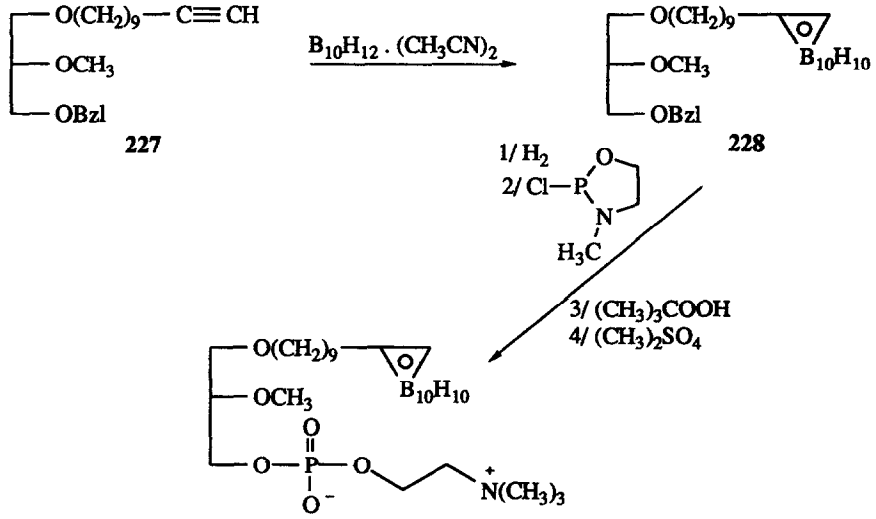
221 **223** **222**

An acetylcholine derivative **224** in which two boron atoms have been incorporated has been prepared by means of an ester linkage between **225** and **226** [291].



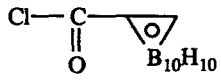
225 **226** **224**

A phosphocholine glycerolipid carborane analogue has also been prepared. Reacting decaborane with the acetylenic bond of **227** afforded **228**, which was conventionally transformed into **229** [292]. The anticholinesterase activity of carboranylated thiophosphates has also been presented [293,294].



227 **228** **229**

The possibility of attaching a carborane to a fatty acid has been examined. Condensing a carborane carboxylic acid (or an equivalent such as **230**) with a fatty-acid derived alcohol allowed the obtention of such analogues. By taking into account the base-sensitivity and thermal stability of the reactants, a comparison of different esterification methods enabled the development of an esterification process applicable to polyunsaturated fatty alcohols such as arachidonyl alcohol **231** to finally give **232** [295].



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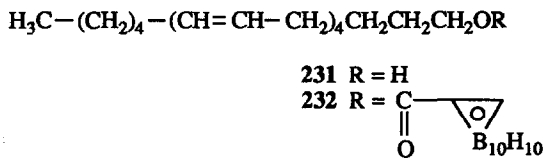

231 R = H
232 R =

Although it may become difficult to delineate the boundary between biomolecules and others, it seems appropriate to mention here that boron analogues of tetracyclines [296,297] and chlorpromazin [298-301] as well as other tumor-targeted molecules such as alkylating agents or nitro-imidazoles have also been prepared [302-307]. Other approaches for selective delivery of boron to cancerous cells involve the use of boronated liposomes [308-310].

10 Conclusion

As outlined in this report, the progress of synthetic chemistry has allowed a large number of boronated biomolecular analogues to be prepared. Their number is rapidly increasing though and the rate at which the field is expanding makes it quite likely that an update of the present review will be needed in coming years.

Indeed a 4th generation of boronated analogues, that is to say compounds which present a bioactivity of their own, is rapidly developing [312-326] ; this is already the case for quite a few of the analogues presented above. Although predicting those boronated molecules which will be of future interest remains a difficult task, it can be confidently stated that the future research can only benefit from the crosslinking of multidisciplinary fields. Indeed, other areas currently enjoying attention, which are outside the scope of this review, but which could play a major role in developing boronated biomolecules include supramolecular boron chemistry [327-333], the use of boron polymers and/or their automatic synthesis [334-336] and boron-based imaging agents [337-341].

Whatever the future, it is clear that synthetic chemistry [7] can only play a major role and "non-boronated chemists" are highly welcome to participate. Or, to put it in another way :

"Boron is not boring" !

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I apologize in advance for any omission of relevant information - contained in scientific journals - in a report which I have tried to make as comprehensive as possible.

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