Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 579–593

TETRAHEDRON

Tetrahedron report number 628

Synthesis and biological activity of α-aminoboronic acids, amine-carboxyboranes and their derivatives

Valery M. Dembitsky* and Morris Srebnik*

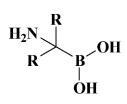
Department of Medicinal Chemistry and Natural Products, School of Pharmacy, The Hebrew University of Jerusalem, P.O. Box 12065, Jerusalem 91120, Israel

Received 8 December 2002

Contents

1. Introduction

In recent years there has been an increasing interest for new practical methods to prepare novel non-natural *R*-amino acid derivatives to serve as building blocks in combinatorial chemistry and drug discovery. Although many routes to amino acids have been developed, there is still a need for concise and convergent approaches that allow structure variability and facile incorporation of functional groups and ring systems.[1–3] As non-natural *R*-amino acid derivatives, boronic acids **1** have assumed great importance since they serve as transition state analogue of natural amino acids. Their ease of preparation and their relative stability have further increased their value.



1

The bioinorganic chemistry of boron-containing compounds is therefore an area of growing interest and has recently expanded to include purine nucleosides, psuedocryptands (which mimic the naturally occurring antibiotics boromycin and aplasmomycin), steroids, calixarenes, carbohydrates, fatty acids, porphyrins, and amino acids.[4–10] Boronic acids [$RB(OH)_2$] and boronate esters [$RB(OR_1)_2$] have been found to facilitate the transport of various ribonucleosides in and out of liposomes, an important attribute in the area of drug design.[11–13] Simple aminoboron compounds have also found some utility in boron neutron capture therapy (BNCT)[14,15] and other forms of cancer therapy.[1–4] As a result, much effort has focused on the synthesis of boron-containing amino acid and peptide derivatives.[16] Unfortunately, the incorporation of a Lewis basic amine and a Lewis acidic boronic acid functionality into the same molecule is a notoriously difficult procedure and synthetic routes to these compounds are scarce. New effective methods to prepare amino and related boron compounds will have a tremendous impact on bioinorganic and pharmaceutical chemistry.[17–22]

Serine proteases, a large and functionally diverse class of proteolytic enzymes, are prominent therapeutic targets

Keywords: α-aminoboronic acids; synthesis; serine proteases; amino-carboxyboranes inhibitors; boronic acids.

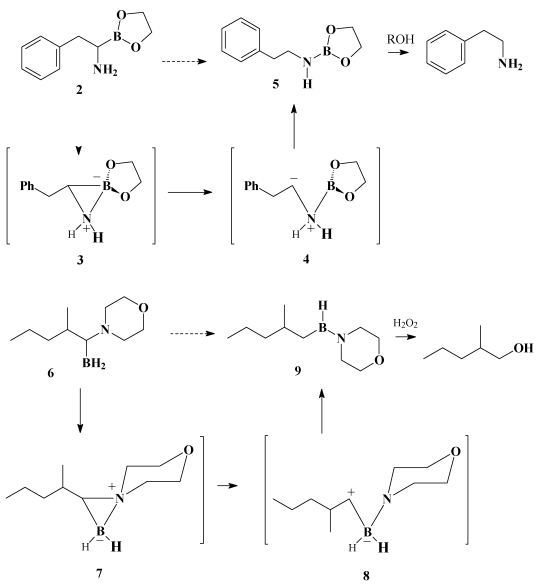
* Corresponding authors. Tel.: +972-2-675-7301; fax: +972-2-675-8201; e-mail: (M. Srebnik) msrebni@md2.huji.ac.il; (V. M. Dembitsky) dvalery@cc.huji.ac.il.

0040–4020/03/$ - see front matter © 2003 Published by Elsevier Science Ltd.
PII: S0040-4020(02)01618-6

because of their involvement in a host of physiological processes.[23] They catalyse peptide bond cleavage by acylation and deacylation of the active site serine residue in a sequence that involves two tetrahedral intermediates.[24] Most small molecule inhibitors of these enzymes form covalent adducts with the active site serine that mimic to some degree these tetrahedral intermediates. Peptide derivatives with electron-deficient ketones and aldehydes, boronic acids and phosphonylating agents have been devised as analogues of the second tetrahedral intermediate[25] with their selectivity among the various proteases related to the substrate specificity these enzymes manifest at the S1, S2, and higher, binding sites.[26]

2. Synthesis of α-aminoboronic acids

α-Aminoboronic acids or esters are unstable toward migration of boron from carbon to nitrogen and yield the corresponding amines in protic solvents.[27–29] A typical example of migration of boron from carbon to nitrogen in α-aminoboranes is rearrangement of the 1-amino-2-phenylethylboronic ester **2** to the 2-phenylethylamine derivative **3** (Scheme 1).[27] Boronic esters bearing tertiary amino groups in the α-position do not undergo this type of deboronation.[28,29] It therefore appears likely that the rearrangement occurs via intramolecular nucleophilic attack of the amino group of **2** on boron. Ring opening of **3** to **4** might then occur, or proton migration to form **5** might be concerted with ring opening.[30,31] In an analogous manner, migration of the α-aminoborane **6** would lead to the intermediate **7**, which could undergo ring opening to the zwitterion **8**, in this example concerted with, or followed by, hydride migration to form **9**.

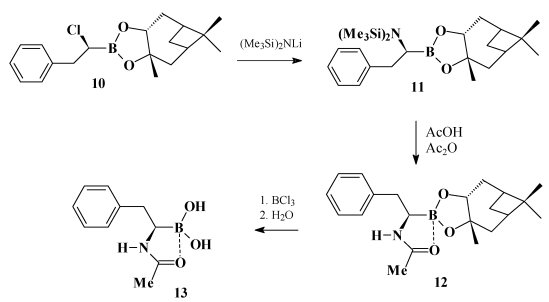


Scheme 1.

3. Synthesis of α-amidoboronic acid derivatives

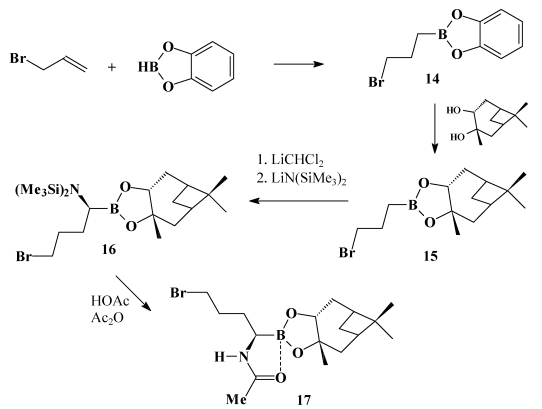
For the synthesis of α-amidoboronic acid derivatives α-haloboronic esters are usually useful.[32] Nucleophilic reactions of α-haloboronic esters with carbon nucleophiles are utilised in asymmetric synthesis with displacements of the halide atom. The asymmetric conversion of a CHCl group into a boron-carbon bond can be controlled with very high precision by the use of chiral ligands on the boron atom.

The first synthesis of the unnatural α-amidoboronic ester **13** was studied by Matteson et al.[33] (*S*)-pinanediol (*S*)-(1-chloro-2-phenylethyl)boronate **10** was prepared from the reaction of (*S*)-pinanediol benzylboronate with (dichloromethyl)lithium,[27] followed by displacement of the chloride ion from **10** with lithiohexamethyldisilazane, to provide **11**. Treatment of **11** with AcOH/Ac_2O yielded the acetoamidoboronic ester **12**, which was cleaved with BCl_3 to yield (*S*)-*N*-acetylboraphenylalanine **13** (Scheme 2). (*S*)-*N*-acetylboraphenylalanine **13** was a potent inhibitor of certain enzymes. Some other routes for the synthesis of **13** have been described.[3,32]



Scheme 2.

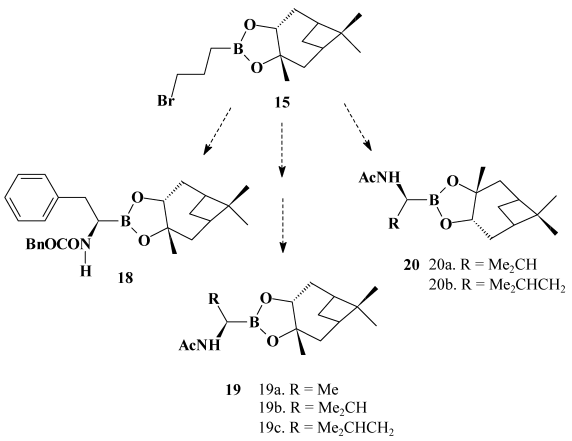
The synthesis of (*S*)-pinanediol (*R*)-(1-acetamido-4-bromobutyl)boronate **17** started from allyl bromide and catecholborane via **14** which was transesterified with (*S*)-pinanediol to **15**, and then converted to the silylated aminoboronic ester **16** by treatment with acetic anhydride and acetic acid to form **17** (Scheme 3).[34]



Scheme 3.

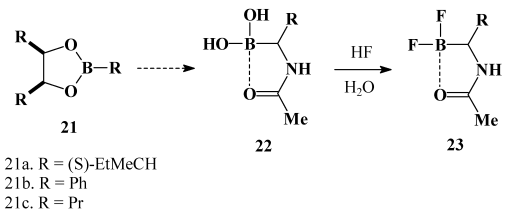
The pinane amidoboronic esters **18–20** could be synthesised by using similar chemistry (Scheme 4).[34] Enzyme inhibition studies have shown that the D-amino acid analogue **20b** was an active inhibitor of *Bacillus cereus* β-lactamase, with K_i=44 μM at pH 7.[35]

The racemic α-acetamidoboronic acids **22** have been obtained using similar chemistry. This reaction was used as the starting point for the corresponding *meso*-butanediol



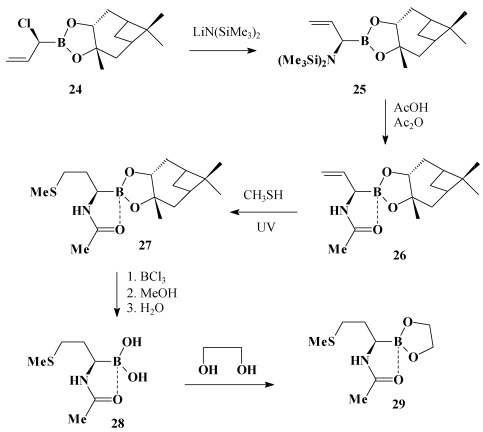
Scheme 4.

esters **21** (Scheme 5) and **22** were found to inhibit elastase and chymotrypsin.[36] The fluoro-derivatives **23** could be obtained by the treatment of **22** with aqueous hydrofluoric acid.[32]



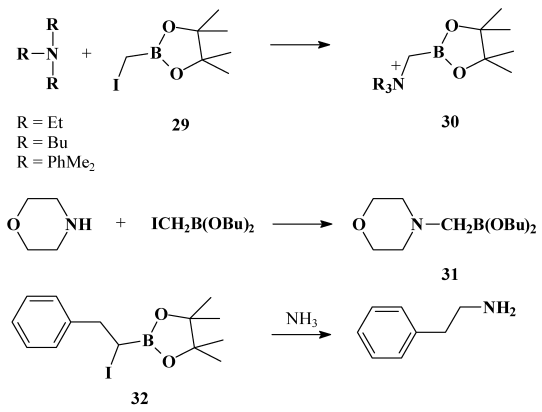
Scheme 5.

(*S*)-pinanediol (*S*)-(1-chloroallyl)boronate **24** reacted with lithiohexamethyl-disilazane to form **25** which after desilylation/acetylation formed (*S*)-pinanediol (*R*)-(1-acetamidoallyl)boronate **26** (Scheme 6). Addition of methyl mercaptan to the double bond of **26** under UV light yielded the crystalline boronic ester **27**.[37] Treatment of **27** with BCl_3 led to **28** which was esterified by ethylene glycol to form crystals of **29**.



Scheme 6.

Pinacol (iodomethyl)boronate **29** reacts with tertiary amines to form the quaternary ammonium salts **30** (Scheme 7), and dibutyl (iodomethyl)boronate with morpholine to form **31**.[31] Many attempts to react (1-halo-2-phenylethyl)boronic esters with ammonia or ammonia derivatives failed. The



Scheme 7.

reaction of (1-iodo-2-phenylethyl)-boronate **32** with aqueous ammonia gave 2-phenylethylamine (Scheme 7).[31]

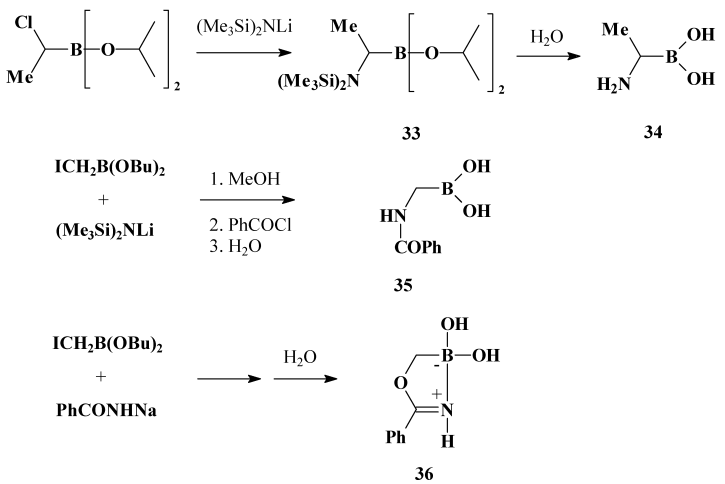
4. Asymmetric synthesis via α-haloalkylboronic esters

Free α-aminoboronic acids were synthesised and tested as potential enzyme inhibitors. The racemic boraalanine **34** was obtained in solution by hydrolysis of the boronic ester **33** (Scheme 8). It is a good inhibitor of alanine racemase from *Bacillus stearothermophilus* with K_i=20 mM (it was slow binding at K_i=0.15–0.35 min^{-1}). For D-alanine/D-alanine ligase from *Salmonella typhimurium* two binding constants for different enzyme sites were found: K_i=35 μM and K_i'=18 μM.[29] Benz(amidomethyl)-boronic **35** acid was synthesised from dibutyl (iodomethyl)boronate and lithiohexamethyldisilazane followed by benzoylation.[38] The product from the sodiobenzamide was the imido ester isomer **36**.[28]

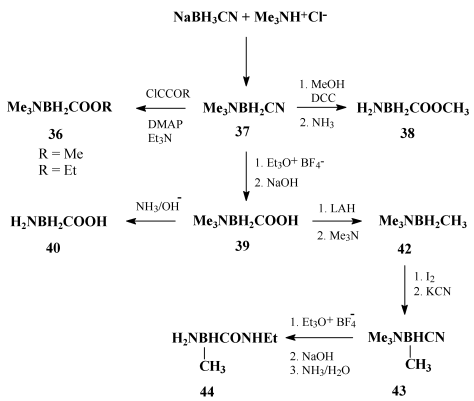
5. Synthesis of glycine α-aminoboronic acids

In the simplest amino acid, glycine, replacement of the central methylene by boron, as depicted in **40**, would give an isoelectronic and isostructural analogue. The synthesis of **40** connected with the reaction of sodium cyanoborohydride with trimethylammonium hydrochloride to give **37**. Since direct hydrolysis of the nitrile group could not be achieved, its conversion to a carboxylic acid was performed in two steps comprising the an action with Meerwein's reagent, followed by alkaline hydrolysis of the intermediate nitrilium salt.[39–41] The metal-complexing capabilities and basicity of this betaine **39** have been described.[42] Upon displacement of the trimethylamine with a large excess of liquid ammonia, the desired glycine analogue **40** was isolated.[43] The methyl ester **38** was formed from **37** in the presence of dicyclohexylcarbodiimide (DCC) which then was submitted to an amine exchange to give the glycine analogue[44] **38** (Scheme 9).

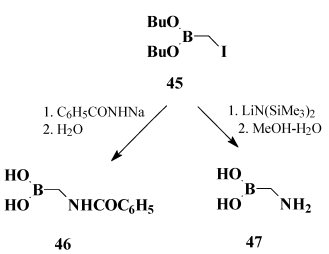
Reaction of the carboxylic acid group to give the esters **41** can be accomplished in varying yields upon reaction with chloroformates in the presence of triethylamine and 4-dimethyl-aminopyridine (DMAP). These conditions were



Scheme 8.



Scheme 9.



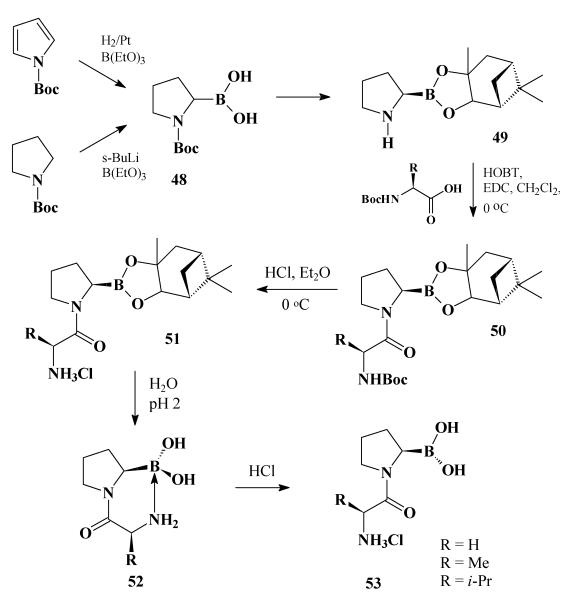
Scheme 10.

found to be more advantageous than using DCC.[45] The conversion of **39** into an alanine derivative has also been reported.[45] Lithium aluminium hydride (LAH) reduction of **39** followed by quenching with trimethylamine hydrochloride afforded **42** which was subsequently iodinated and cyanated to give **43**. The action of Meerwein's reagent followed by basic hydrolysis and amine exchange gave the desired amide **44**.[46] The initial synthetic efforts to obtain such amino acid-based inhibitors used *N*-acylated analogues of glycine. In one example, dibutyl iodomethane-boronate **45** was alkylated with the sodium salt of benzamide to give **46** (Scheme 10),[38] which shown also to be a potent inhibitor of α-chymotrypsin. The reaction of **45** with $LiN(SiMe_3)_2$ gave **47**.

6. Synthesis of proline α-aminoboronic acids

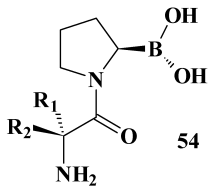
A series of prolineboronic acid (boroPro)-containing dipeptides was synthesised and assayed for their ability to inhibit the serine protease dipeptidyl peptidase IV (DPPIV).[47] The synthesis of boroproline **48** was developed by Matteson's procedure[34,48] for the preparation of aminoboronic acids. The amino boronic ester **49** was coupled with the desired Boc-amino acids in the presence of 1-(3-(dimethylamino)propyl)-3-ethyl-carbodiimide hydrochloride (EDC) to generate the fully-protected dipeptides **50**, and with HCl gave proline α-aminoboronic acids **53** via intermediates **51** and **52** (Scheme 11). The abilities of the peptides to inhibit the enzyme[47] are shown in Table 1.

A series of Boc-D-trimethylsilylalanine-proline-boro-X pinanediol derivatives **52** and **53** which are active as thrombin inhibitors have been synthesised by von Matt et al.[49,50] (Scheme 12).



Scheme 11.

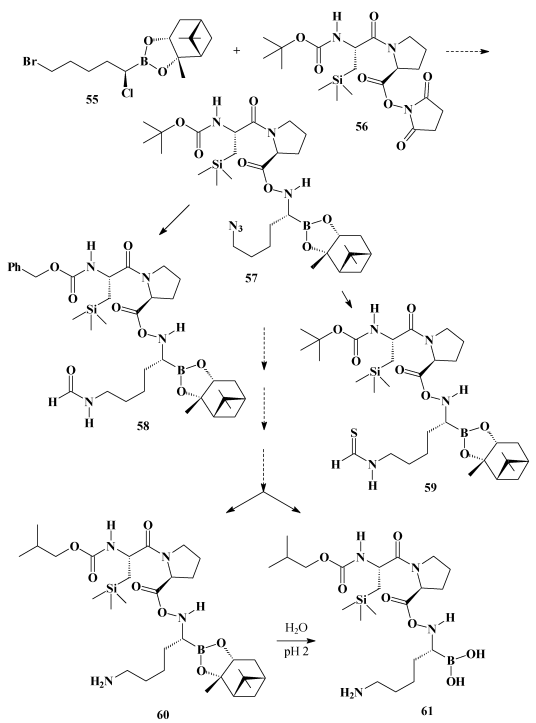
Table 1. Structure–activity relationships for $H_2N–X_{aa}$-boroPro dipeptides vs DPPIV



Compound	Amino acid	R_1	R_2	Boron configuration	IC_{50} (nM)	±SE (nM)
54a	L-Val	H	*i*-Pr	*R*	26	1
54b	L-Val	H	*i*-Pr	*S*	4000	600
54c	D-Val	*i*-Pr	H	*R*	116,000	15,000
54d	L-Ala	H	Me	*R*	15	3
54e	AiBu	Me	Me	*R*	30,000	8000
54f	L-Gly	H	H	*R*	16,000	2400
54g	L-Abu	H	Et	*R*	11	1
54h	L-Leu	H	*i*-Bu	*R*	44	2
54i	L-Ile	H	2-Bu	*R*	25	1
54j	L-tLeu	H	*t*-Bu	*R*	60	7
54k	L-Phe	H	CH_2Ph	*R*	70	7
54l	L-Phg	H	Ph	*R*	63	5
54m	L-Tyr	H	CH_2(Ph-4-OH)[a]	*R*	32	1
54n	L-Lys	H	$(CH_2)_4NH_2$	*R*	95	19
54o	L-Thr	H	CH_3CHOH	*R*	190	13
54p	L-Pro	H	$-(CH_2)_3-$	*R*	20	5
54q	L-Azet	H	$-(CH_2)_2-$	*R*	250	13
54r	L-His	H	CH_2Im	*R*	17,000	1800

[a] $CH_2C_6H_4OH$-4

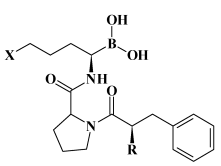
All of the thrombin inhibitors were synthesised starting from the common intermediate **57** which obtained the reaction between **55** and **56**. Hydrogenation of the azido group of **57** catalysed by palladium on carbon led to the borolysine derivatives.[51] The free amino group could be derivatised by reaction with an anhydride, acid chlorides, isocyanates and/or potassium cyanate. The thioformamide **59** could be obtained by treatment of the corresponding formamide with Lawesson's reagent. Removal of the Boc protecting group followed by reaction with benzyl chloroformate led to the compound **58**. Hydrolysis of **60** generated **61**. The X-ray structures of **58** and **61** have shown that these inhibitors bound to the active side of thrombin.



Scheme 12.

The synthesis of the thrombin inhibitor Du Pont 714 was achieved starting from 3-bromopropylboronic ester to form **62**.[32] This enzyme inhibitor was active in rabbits at dose levels of 0.1 mg kg^{-1} h^{-1}.[53,54] A methoxy group in place of guanidine on **62** also provides a potent thrombin inhibitor.[32]

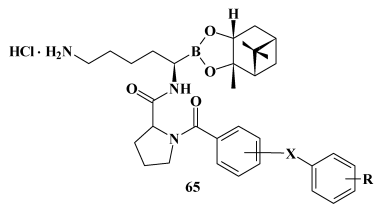
A series of conformationally-restricted boropeptide thrombin inhibitors **63** and **64** have been synthesised.[52] The potent binding affinity of the resulting inhibitors **65**, such as **65f**, may be due in part to a unique mode of binding at the thrombin active site. The thrombin binding activity data for a series of inhibitors are shown in Table 2. The synthesis of these inhibitors involved the initial preparation of the P3 benzoic acids followed by elaboration to their corresponding boropeptides.[52]



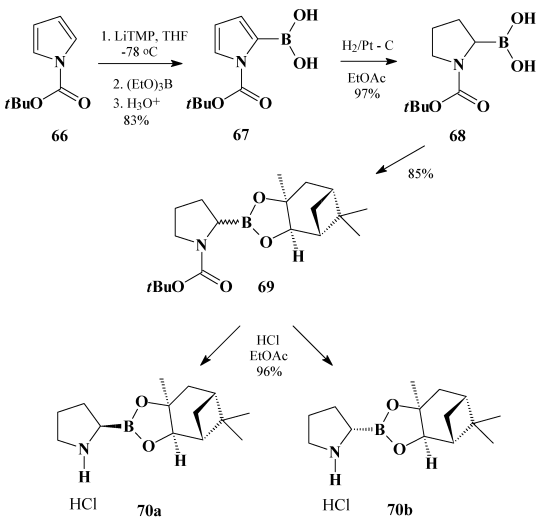
62. Du Pont 714: R = NHAc, X = NHC(NH)NH_2·HCl
63. R = NHAc, X = CH_2NH_2·HCl
64. R = H, X = CH_2NH_2·HCl

The synthesis of the pinanediol ester of prolineboronic acid was described by Kelly et al. (Scheme 13).[55] Boc-pyrrole **66**

Table 2. Boropeptide thrombin inhibitors with benzoic acid-derived residues



Compound	X	R	Position	K_i (nM)
65a	CH_2	H	*ortho*	0.29
65b	CH_2	H	*meta*	0.19
65c	CH_2	H	*para*	1.80
65d	O	H	*ortho*	0.27
65e	O	H	*meta*	0.36
65f	CH_2	2-CF_3	*meta*	0.07
65g	CH_2	2-CH_3	*meta*	0.25
65h	CH_2	2-SCH_3	*meta*	0.50
65i	CH_2	2-Br	*meta*	0.23
65j	CH_2	3-F	*meta*	0.43
65k	CH_2	3-CF_3	*meta*	0.16
65l	CH_2	4-CF_3	*meta*	0.22
65m	CH_2	3,4-(-OCH_2O-)	*meta*	0.09
65n	S	H	*meta*	<0.10
65o	S	2-CF_3	*meta*	0.45
65p	S	2-OCH_3	*meta*	0.19
65q	S	4-OCH_3	*meta*	0.42
65r	SO_2	H	*meta*	0.85
65s	SO_2	2-OCH_3	*meta*	0.58

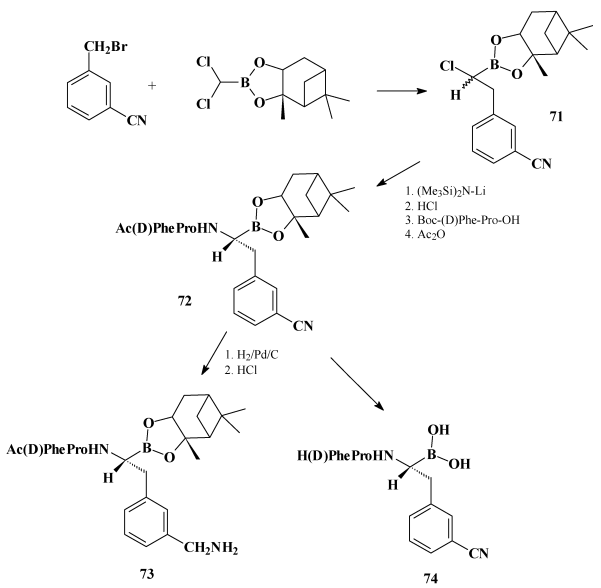


Scheme 13.

after treatment with tetramethylpiperidine gave boc-pyrrole-2-boronic acid **67**. Hydrogenolysis generated Boc-prolineboronic acid **68**, which was easily esterified with (1*S*,2*S*,3*R*,5*S*)-(+)-pinanediol to give **69**. The compound **69** was deprotected by HCl in EtOAc to form two diastereomers **70a** and **70b**.

7. Synthesis of alanine α-aminoboronic acids

Novel highly effective thrombin inhibitors have been

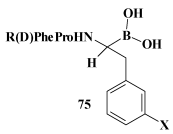


Scheme 14.

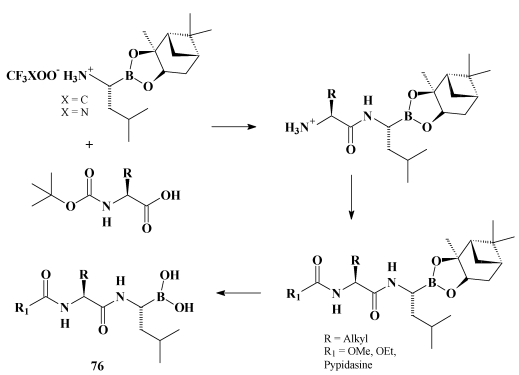
obtained by preparing boronic acid analogues **71**–**73** of the *m*-cyanoborophenylalanine analogue **74**[56] (Scheme 14). The free boronic acid **74** was isolated from the aqueous phase as a single component. The interaction of trypsin with a series of inhibitors **75** is shown in Table 3.

Potent and selective dipeptidyl boronic acid inhibitors have been demonstrated by Adams et al.[56] The synthesis of the

Table 3. Binding of peptide boronic acids to serine proteases

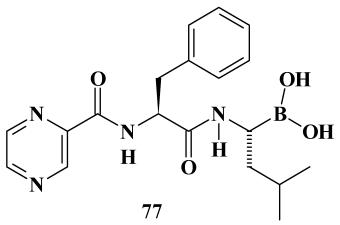


Protease	R	X X_1	or X_2	K_i for X_1 (nM)	K_i for X_2 (nM)
Thrombin	Ac	CN	H	0.79	320
Thrombin	Boc	CN	H	0.51	59
Thrombin	H	CN	H	0.48	6.3
Thrombin	Ac	CH_2NH_2		4.8	
Trypsin	Ac	CN	H	130	11,000
Trypsin	Boc	CN	H	73	5400
Trypsin	H	CN	H	5.6	1800
Trypsin	Ac	CH_2NH_2		5.6	
Pancreatic	Ac	CN	H	8600	39,000
Chymotrypsin	Ac	CN	H	49	100



Scheme 15.

Table 4. Enzyme inhibitory profile of the peptide boronic acid derivative **77**

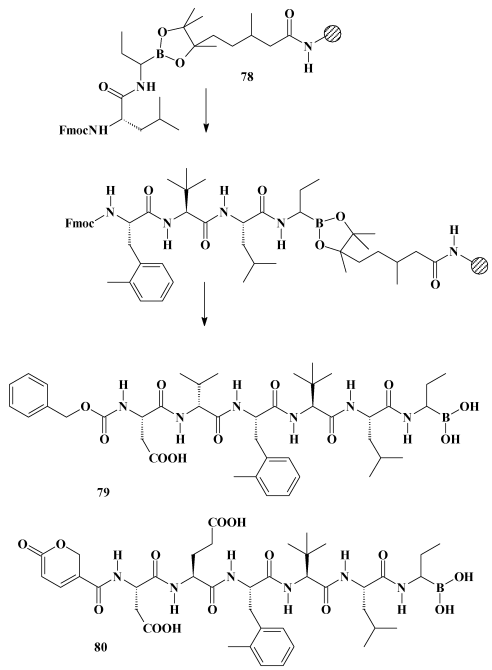


77

Enzyme	K_i (nM)
20S proteasome	0.62
Human leukocyte elastase	2300
Human cathepsin G	630
Human chymotrypsin	320
Thrombin	13,000

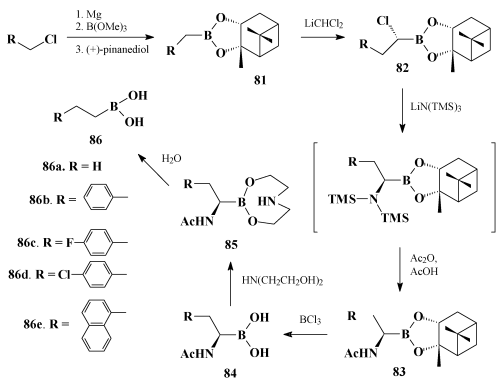
boronated dipeptide **76** was described in US Patent[57] (see Scheme 15). It was found that the boronic acid derivative **77** has inhibitor properties as indicated in Table 4.

The solid phase synthesis of the aminoboronic acids **79** and **80**, potent inhibitors of the hepatitis C virus NS3 proteinase, was demonstrated by Dunsdon et al. (Scheme 16)[58] using well known peptide boronic acid derivatives **78**.[60,61] Hepatitis C virus (HCV) is the cause of the majority of cases of transfusion-associated hepatitis. The target which requires new compounds for antiviral therapy against HCV is the the NS3 serine proteinase.[62] The amidoboronic acids **79** and **80** were found[59] to be highly potent inhibitors of the HCV NS3 proteinase.



Scheme 16.

Enantiometric 1-acetamidoboronic acids, which are *N*-acetyl trans state inhibitor analogues of the L- and D-forms of the amino acids alanine, phenylalanine, *p*-fluorophenylalanine, *p*-chlorophenylalanine, and 1-naphtryl-

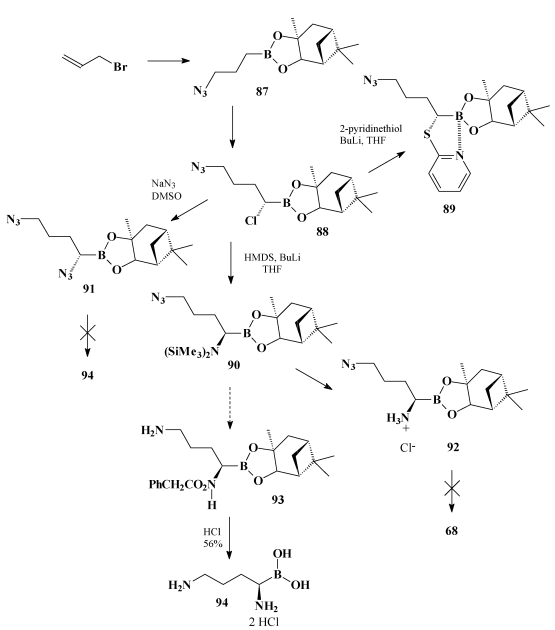


Scheme 17.

alanine were synthesised (Scheme 17) and tested as inhibitors of the serine proteases subtilisin Carlsberg and α-chymotrypsin.[63] All L-(*R*)- and D-(*S*)-1-acetamidoboronic acids were prepared according to the basic strategy developed by Matteson et al.[27,37,64] The pinanediol esters **81** gave the α-chloroboronic acids **82** in 75–95% yields with diastereoselectivites >98%. Treatment the α-chloroboronic acids **82** with lithium-hexamethyldisilazane afforted the corresponding silylated aminoboronic esters, which when heated with Ac_2O and AcOH formed the 1-acetamidoboronic esters **83**. Hydrolysis of **83** with boron trichloride gave the 1-acetamidoboronic acids **84**. Both the anhydride forms of **84** and the diethanolamine derivatives **85** are hydrolysed to the corresponding free boronic acids **86a–e**. All of the boronic acids **86a–e** are powerful competitive inhibitors of both enzymes.

8. Synthesis of ornithine α-aminoboronic acids

The asymmetric syntheses of (*R*)-1,4-diaminobutane-1-boronic acid dihydro- chloride **91** and the aminoboronic

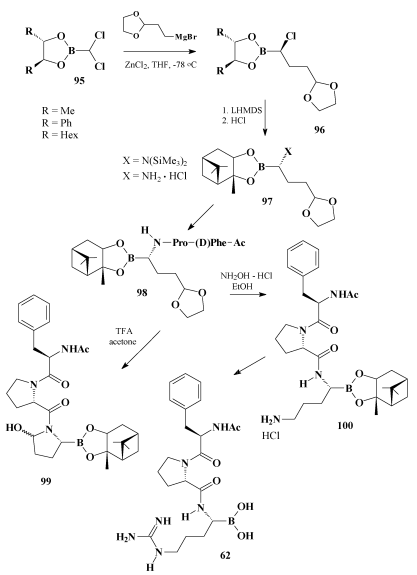


Scheme 18.

acid analogue of L-ornithine have been described[65] (Scheme 18). The 3-azidopropaneboronic ester **87** was obtained from allyl bromide and converted to the optically active (+)-pinanediol derivative **88**, which could be transformed to two compounds **89** and **90**. Attempts to obtain the (*R*)-1,4-diaminobutane-1-boronic acid **94** from **91** and **92** were unsuccessful. The *N*-protective group in **90** could be desilylated when treated with benzyl chloroformate give the monoprotected boroornithine derivative **93**, which should be a valuable precursor of the arginine boronic acid analogues.

9. Synthesis of arginine α-aminoboronic acids

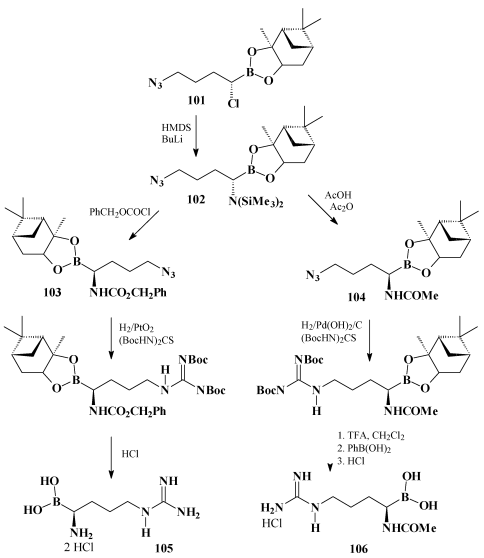
Peptides such as Du Pont 714 **62**, containing boroarginine at the primary residue are potent thrombin inhibitors.[66] The synthesis of boropeptide **100** containing a basic α-aminoboronic ester started from the dichloromethylboronic ester **95**,[67] and addition of the Grignard to **95** to give **96**. Reaction with (+)-pinanediol then provided the boronic ester **97**. The boropeptide **98** was obtained in 80% yield and it was transformed to **99** and **100**. Du Pont 714 **62** obtained from **100** was stable in water (Scheme 19).



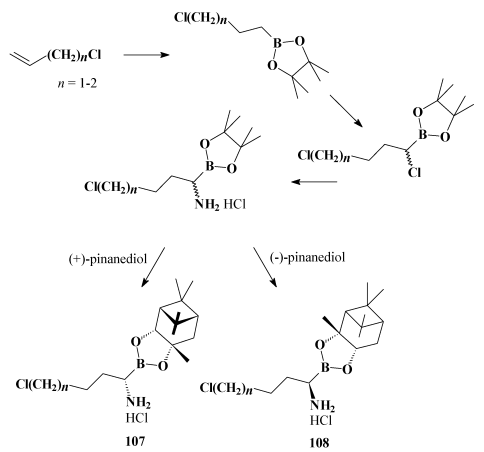
Scheme 19.

The asymmetric synthesis of an unprotected α-aminoboronic acid analogue of L-arginine **102** and its *N*-acetyl derivative **103** provided alternative substrates or inhibitors of nitric oxide synthase (Scheme 20).[68] Nitric oxide displays activities in the cardiovascular system as well as in the central and peripheral nervous systems and has considerable attracted in the past few years.[69,70] The general synthetic sequence is based on the asymmetric methodology developed by Matteson.[32] In order to introduce the amino group in the α-position of boron atom, **102** hexamethyldisilazane (HMDS) was used to displace the chloride of **101**, **103** and **104** were obtained using benzyl–chloroformate and a mixture of AcOH and Ac_2O, respectively.

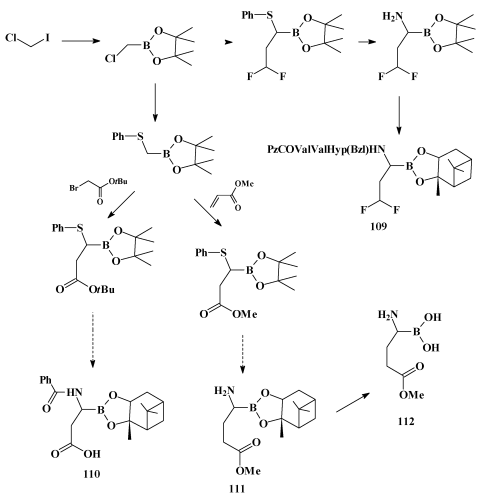
Diastereoselective crystallisation with (+) and (−)-pinanediols was demonstrated by Brosz et al.[71] Using this method, the two stereoisomers of the α-aminoboronic acids **107** and **108** (Scheme 21) could be obtained.



Scheme 20.



Scheme 21.

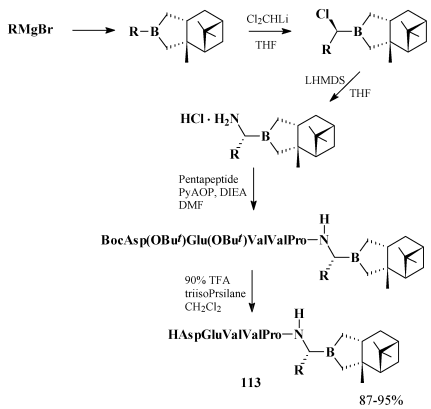


Scheme 22.

Some novel α-aminoboronic acids **109**–**112** which act as serine protease inhibitors have been synthesised[72] (Scheme 22). The methodology affords α-amino-boronic acids **109**–**112** with the general formula *R*-NHCH(R)BO_2-pinanediol where R=CH_2CHF_2, CH_2CO_2tBu, and $(CH_2)_2$-COMe.

10. Synthesis of phenethyl peptide boronic acids

A series of peptide boronic acids containing extended, hydrophobic P1 residues have been synthesised to probe the shallow, hydrophobic S1 region of HCV NS3 protease.[73] Peptide boronic acid inhibitors were synthesized using the methodology for asymmetric homologation of boronic acid pinanediol esters developed by Matteson and co-workers.[74] As shown in Scheme 23, reaction of a Grignard reagent with triisopropyl borate, followed by esterification with (+)-pinanediol affords a boronic ester. Homologation with dichloromethyllithium[75] diastereoselectively provides an (*S*)-α-chloroboronic ester. Displacement of chloride by lithium bis(trimethylsilyl)amide,[33] followed by acidolysis gives the (*R*)-α-aminoboronic ester as a stable hydrochloride salt. Coupling to the protected pentapeptide Boc-Asp(OBu^t)-Glu(OBu^t)-Val-Val-Pro-OH and deprotection with trifluoroacetic acid afforded the desired peptide boronic acids **113a**–**l**. The inhibition activity of peptide boronic acids **113a**–**l** has been demonstrated against NS3 protease, human leukocyte elastase, and human pancreatic chymotrypsin show in Table 5.

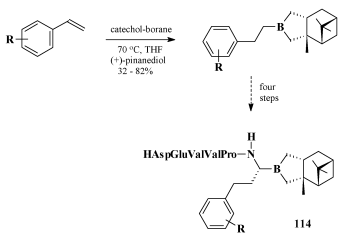


Scheme 23.

Table 5. Inhibition of NS3 protease, human leukocyte elastase, and human pancreatic chymotrypsin by peptide boronic acids **113a**–**l**

No	R	NS3 K_i (μM)	Elastase IC_{50} (μM)	Chymotrypsin IC_{50} (μM)
113a	Ethyl	0.008	0.020	>60
113b	*n*-Butyl	0.011	NT	2.1
113c	*n*-Pentyl	0.012	NT	0.38
113d	*n*-Hexyl	0.013	NT	0.42
113e	*i*-Butyl	0.008	0.060	NT
113f	*i*-Amyl	0.039	NT	0.30
113g	4-Methylpentyl	0.007	7.3	0.28
113h	Phenyl	0.9	NT	NT
113i	Benzyl	0.5	NT	0.070
113j	Phenethyl	0.008	3.5	0.075
113k	Phenpropyl	0.20	NT	NT
113l	Phenbutyl	0.010	0.4	1.9

A series of substituted phenethyl containing peptides was prepared as shown in Scheme 24. In this case, the required boronates were prepared by hydroboration of a substituted styrene with catecholborane, followed by transesterification with (+)-pinanediol.[73,76] Subsequent homologation, nitrogen substitution, and peptide coupling afforded hexapeptides **114a**–**u**. Inhibition of NS3 protease, human leukocyte elastase, and human pancreatic chymotrypsin by P1 phenethyl peptide boronic acids **114a**–**u** was observed,[73] and is shown in Table 6.



Scheme 24.

Table 6. Inhibition of NS3 protease, human leukocyte elastase, and human pancreatic chymotrypsin by P1 phenethyl peptide boronic acids **114**

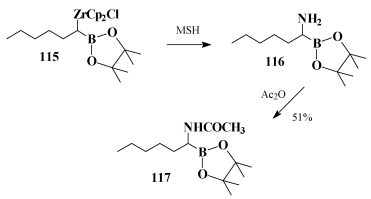
No	R	NS3 K_i (μM)	Elastase IC_{50} (μM)	Chymotrypsin IC_{50} (μM)
114a	H	0.008	3.5	0.075
114b	2-Methyl	0.82	NT	NT
114c	3-Methyl	0.034	5.7	NT
114d	4-Methyl	0.017	5.0	3.7
114e	2,4-Dimethyl	0.53	NT	NT
114f	2,5-Dimethyl	1.0	NT	NT
114g	2-Fluoro	0.018	NT	NT
114h	3-Fluoro	0.009	NT	NT
114i	4-Fluoro	0.006	0.8	0.050
114j	2,6-Difluoro	0.930	NT	NT
114k	3-Trifluoromethyl	0.025	NT	NT
114l	4-Trifluoromethyl	0.002	1.8	16.0
114m	4-Chloro	0.002	1.4	0.065
114n	4-Bromo	0.004	1.6	NT
114o	4-Phenyl	0.007	0.9	48.0
114p	4-Isopropyl	0.005	0.45	>60.0
114q	4-Cyclohexyl	0.003	0.40	>60.0
114r	4-*tert*-Butyl	0.003	0.34	>60.0
114s	4-Hydroxy	0.008	0.9	NT
114t	4-Methoxy	0.003	0.56	20.0
114u	4-Phenoxy	0.003	0.22	>60.0

Within the P1 phenethyl series, substantial effects on inhibitor potency and selectivity were observed with changes in the position and identity of the aromatic ring substituents, and the 4-trifluoromethylphenethyl **114l** P1 was identified as optimal with respect to inhibitor potency for NS3 and selectivity against elastase and chymotrypsin.[73]

11. Synthesis via zirconocene species

α-Aminoboronic esters could be synthesised via zirconocene species.[77,78] Conversion of organozirconium compounds to amines from organozirconocene chlorides has been observed[77] and, of the various electrophilic aminating reagents available for reaction with organometallic compounds[77], use the *O*-sulfonylhydroxyl-amines were found to be the most essective. They are readily available from easily

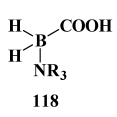
accessible starting materials in a number of high-yielding steps.[79,80] *O*-sulfonyl-hydroxylamine (MSH) has been shown to be superior to the other agents in terms of solubility in organic solvents and reactivity as an electrophilic aminating reagent.[81,82] The amination of *gem*-borazirconocene alkanes such as **115** with MSH gave compound the **116**, and subsequent treatment with Ac_2O formed the α-aminoboronic ester derivatives **117** (Scheme 25).



Scheme 25.

12. Synthesis and activity of amine-carboxyboranes and their derivatives

Amine-carboxyboranes with the common structure **118** can be regarded as isoelectronic analogues of protonated α-amino acids,[43] or more correctly, aliphatic carboxylic acids.[83] This resemblance has inspired extensive biological screening of these molecules and the promising early results led to the syntheses of a large number of ester, [84–87] amide,[88,89] peptide,[90,91] hydroxamic acid[92] and transition metal complex[93–95] derivatives of amine-carboxyboranes (A-BH_2COX, X=OR, NR_1R_2, NHOH) containing a broad range substances, among other amine-boranes, which have been reviewed recently.[96]

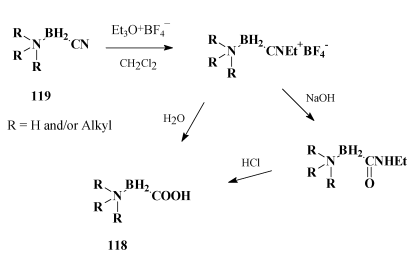


118

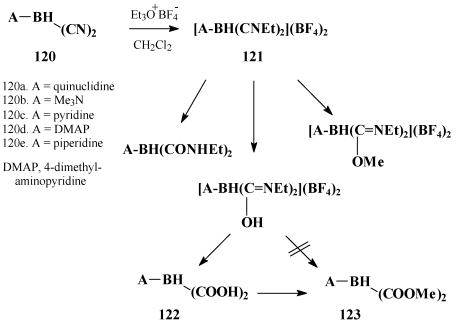
R = H, Alkyl

Today, many of these molecules are known to possess remarkable antitumuor,[97,98] anti-osteoporotic,[99] anti-inflammatory,[100] and hypolipidemic activities,[101] and their mode of action is under inverstigation.[100]

Amine-carboxyboranes with the general structure **118** (R=H or alkyl) may be regarded as boron analogues of substituted α-amino acids in their dipolar forms. As boron has one less positive charge on its nucleus than carbon, BH_2^- will be isoelectronic with CH_2 and consequently, the boron-



Scheme 26.



Scheme 27.

analogue counterparts of the α-amino acids would exist in their protonated forms in the free state.

Several routes for the synthesis of amine-carboxyboranes have been described. In one study, Das and Mukherjee[102] have demonstrated that the acid or base-catalysed hydrolysis of the amine-cyanoboranes **119** (Scheme 26) always yields the acid **118**.

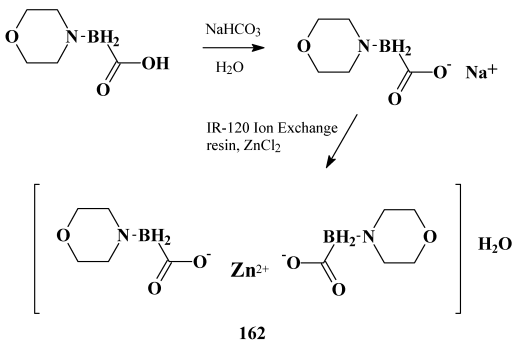
Table 7. Reaction data for R-BH_2X products and the anti-inflammatory activity of boron derivatives in CF-1 mice at 8 mg/kg

No	Compound	Days	Time (%)	Yield ED_{50}
Amine-BH_2-COOH derivatives				
124	H_3NBH_2COOH	7	75	55
125	$MeNH_2BH_2COOH$	3	88	54
126	Me_2NHBH_2COOH			59
127	Me_3NBH_2COOH	2	90	59
128	$EtNH_2BH_2COOH$	2	92	59
129	$Me_3CNH_2BH_2COOH$	2	88	
130	$H_2C{=}CHCH_2NH_2BH_2COOH$	2	82	
131	$PhCHNH_2BH_2COOH$	2	72	
132	$EtO_2CCH_2NH_2BH_2COOH$	2	60	
133	$(n\text{-}C_3H_7)_2NHBH_2COOH$			81
134	$C_{16}H_{33}NMe_2BH_2COOH$			40
135	$C_{18}H_{37}NMe_2BH_2COOH$			58
136	$H_2NNH_2BH_2COOH$			82
137	$[CH_2NMe_2BH_2COOH]_2$			58
138	$C_5H_5NBH_2COOH$	5	90	40
Amine-BH_2-COOMe derivatives				
139	H_3NBH_2COOMe	12	86	66
140	$MeNH_2BH_2COOMe$	2	92	79
141	Me_2NHBH_2COOMe	2	80	58
142	Me_3NBH_2COOMe	2	72	58
143	$H_2C{=}CHCH_2NH_2BH_2COOMe$	2	89	
144	$PhCH_2NH_2BH_2COOMe$	2	78	
145	$C_5H_5NBH_2COOMe$	5	93	
146	$EtO_2CCH_2NH_2BH_2COOMe$	2	52	
147	$CH_3(CH_2)_3NH_2BH_2COOMe$			71
148	$C_{16}H_{33}NMe_2BH_2COOMe$			71
Amine-BH2-COOEt derivatives				
149	$H_3NBH_2CONHEt$	8	90	
150	$C_{16}H_{33}NMe_2BH_2COOEt$			53
151	Me_2NHBH_2COOEt	2	82	76
152	$(BH_2CONHEt)_2$			104
153	$H_3NBH_2CONHEt$	8	90	76
154	$MeNH_2BH_2CONHEt$	2	90	51
155	$Me_2NHBH_2CONHEt$	2	91	84
156	$Me_3NBH_2CONHEt$	2	80	61
Amine-BH2-CONHR derivatives				
157	$Me_3NBH_2CONH(n\text{-}Pr)$			61
158	$Me_3NBH_2CONH(n\text{-}Bu)$			86
159	$Me_3NBH_2CONH(n\text{-}Oct)$			86
160	$Me_3NBH_2CONHC_6H_5$			72
161	$[Me_2NCH_2BH_2CONHC_2H_5]_2$			65

The amine-dicarboxyboranes **122** and their dimethyl esters **123** have been synthesised from amine-dicyanoboranes via the [amine-bis-(ethylnitrilium)-hydro-boron(2^+)]-tetrafluoroborates **121**, [amine-bis(*C*-hydroxy-*N*-ethyliminium)-hydro-boron(2^+)] cations and amine-bis(*N*-ethylcarbamoyl)boranes. The *C*-methoxy-*N*-ethyliminium groups adjacent to boron undergo an unusual hydrolysis.[103] The synthetic sequence is outlined in Scheme 27. The amine-dicyanoboranes **120a–d** were readily synthesised by base exchange.

These routes were used for the synthesis of acyclic amine-carboxyboranes which showed anti-inflammaory activity (see Table 7). The heterocyclic amine derivatives as well as amine-carbamoylboranes, carboalkoxyboranes and cyano-boranes were generally less active. Thos derivatives which demonstrated good anti-inflammatory activity **124–161** were effective inhibitors of hydrolytic lysosomal and proteolytic enzyme activities with IC_{50} values equal to 10^{-6} M in mouse macrophages, human leukocytes and Be Sal osteo-fibrolytic cells.[104]

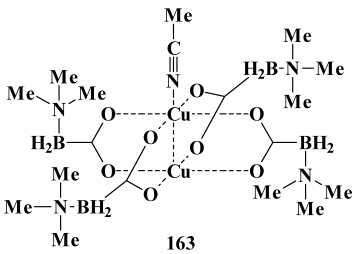
A number of metal complexes of amine-carboxyborane adducts having antitumour activity have been synthesised. Bis-μ-(morpholine-boranecarboxylato)zinc dehydrate **162** demonstrated cytotoxic activity against human $Tmolt_3$, HeLa-S^3 and MB-9812 cell growth.[105] The synthesis of the compound **162** is shown in Scheme 28.



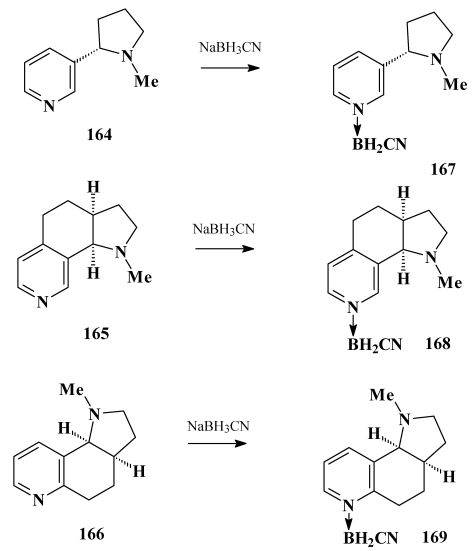
162

Scheme 28.

Another amine-carboxyborane metal complex, tetrakis-μ-(trimethylamine-boranecarboxylato)-acetonitrile dicopper **163**[105] and also **162** inhibited L_{1210} DNA, RNA and protein syntheses, with greatest inhibitory effects on DNA. The reduction in DNA synthesis correlates well with the inhibition of de novo purine synthesis and the key enzymes involved in this pathway, i.e. IMP dehydrogenase and PRPP amidotransferase.



163



164 167 165 168 166 169

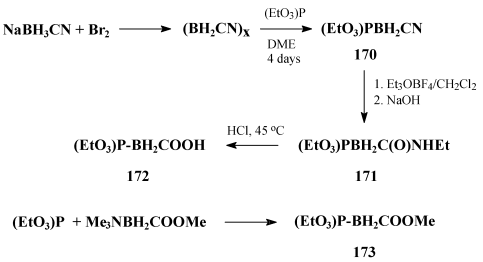
Scheme 29.

A series of boron-containing nicotine (NIC) analogues have been synthesised and evaluated for binding to α4β2 and α7 neuronal nicotinic receptors.[106] The compounds **165** and **166** were prepared according to earlier published methods.[107–109] The boron-containing analogues **167–169** were synthesised by refluxing a suspension of $NaBH_3CN$ and the hydrochloride salts of the corresponding precursors (**164–166**) in THF under N_2 overnight, according to Scheme 29. All three boron-containing analogues were found to be very stable in water. The compound **168** inhibited [^{3}H]-methyllyccaconitine binding to rat brain membranes with a similar potency compared to NIC (**167**).

13. Synthesis of boron analogues of phosphonoacetates

A general procedure has been described for exchange reactions between *N*-methyl-morpholine-borane derivatives and various organic bases involving a simple work-up to produce the exchanged products. Aqueous as well as liquid amines in the exchange reactions with *N*-methylmorpholine-BH_2X (X=COOH, COOMe, CONHEt) gave the corresponding amine-BH_2X-derivatives in good yields.[110] The method also utilises other organic bases such as phosphine, phosphate and amino acid esters in the exchange reaction which have been as obtained their borane derivatives.

Boron analogues of phosphonoacetates have been



Scheme 30.

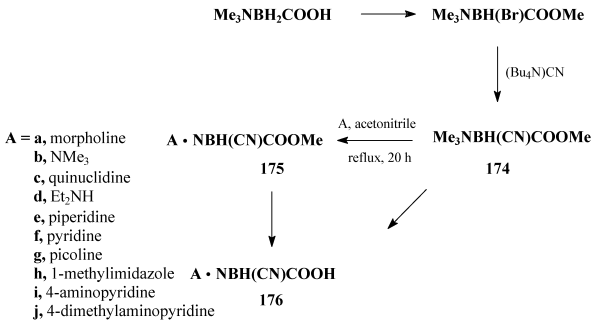
Table 8. Cytotoxicity of boron analogues of phosphonoacetates (ED_{50}, μg/ml)

No	Ehrlich carcinoma (% inhibition)	Murine L1210	Murine P388	Human HeLa	Human KB	Human glioma	Human osteo-sarcoma	Human lung	Human colon	Human $tmolt_3$
170	66	3.61		2.12	2.86	4.26	2.88	6.88	6.56	2.42
171	80	4.45	6.46							
172	39	3.47	7.26	4.41	3.87	5.29	4.18	4.48	2.65	6.16
173	97	4.15	4.98	3.96	1.75	1.60	7.25	4.80	6.96	7.64

synthesised (Scheme 30) and their antitumour and anti-inflammatory activity were studied.[110,111] Cytotoxicity data for the compounds **168–171** are shown in Table 8.

A number of amine-carboxyborane esters have been studied for their anti-hyperlipidemic activity[112] and hypolipidemic activity in rodents.[84]

The synthesis of amine–cyanocarboxyboranes—isoelectronic analogues of α-cyanocarboxylic acids—have been reported.[113] In the first step, trimethyl-carboxyborane was brominated and simultaneously esterified using *N*-bromosuccinimide in methanol.[83] The synthetic sequence outlined in Scheme 31, employing activation and then nucleophilic substitution of the boron, subsequently resulted in the preparation of several novel compounds **174–176a–j**.



Scheme 31.

14. Conclusions

A remarkable diversity of reactions has been discussed in this review. This article has also described and summarised the development of a new boron-based methodology for applications in organic synthesis of α-aminoboronic acids, amine-carboxyboranes and their derivatives. These compounds are unique among boron-containing compounds and they have a high biological activity in different fields. The investigation of the chemistry of these compounds is continuing, especially in the areas of selective reactions, synthesis, catalysis and coordination chemistry.[77,114–116]

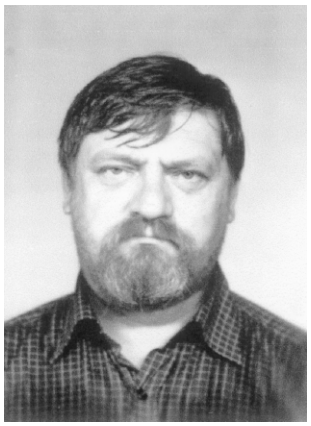
References

1. Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539.
2. Williams, R. M. *Aldrichim. Acta* **1992**, *25*, 11.
3. Williams, R. M. *Synthesis of Optically Active R-Amino Acids*; Pergamon: Oxford, 1994.
4. Graf, E.; Hosseini, M. W. *Coordinat. Chem. Rev.* **1998**, *178-180*, 1193.
5. Hiratake, J.; Oda, J. *Biosci. Biotechnol. Biochem.* **1997**, *61*, 211.
6. Lyer, R. P.; Roland, A.; Zhou, W.; Ghosh, K. *Curr. Opin. Mol. Therapeut.* **1999**, *1*, 344.
7. Imamura, M.; Sawada, S.; Kasahara-Imamura, M.; Harima, K.; Harada, K. *Internat. J. Mol. Med.* **2002**, *9*, 11.
8. Otkidach, D. S.; Pletnev, I. V. *J. Mol. Struct.: Theochem* **2001**, *536*, 65.
9. Morin, C. *Tetrahedron* **1994**, *50*, 12521.
10. Braunschweig, H.; Colling, M. *Coordinat. Chem. Rev.* **2001**, *223*, 1.
11. Dordas, C.; Brown, P. H. *J. Membr. Biol.* **2000**, *175*, 95.
12. Feakes, D. A.; Spinler, J. K.; Harris, F. R. *Tetrahedron* **1999**, *55*, 11177.
13. Malinin, V. S.; Haque, M. E.; Lentz, B. R. *Biochemistry* **2001**, *40*, 8292.
14. Spievogel, R.; Gopalaswamy, S.; Sanka, P. D.; Boyle, G.; Head, K.; Devito, K. *J. Chem. Soc., Perkin Trans.* **2000**, *2*, 557.
15. Srivastava, R. R.; Singhaus, R. R.; Kabalka, G. W. *J. Org. Chem.* **1999**, *64*, 8495.
16. Faber, K. *Biotransformations in Organic Chemistry*, 2nd ed; Springer: New York, 1995.
17. *Enzymes in Synthetic Organic Chemistry*; Wong, C. H., Whitesides, G. M., Eds.; Pergamon: New York, 1994.
18. Verlinde, C. L. M. J.; Hol, W. G.; J, . *Structure* **1994**, *2*, 577.
19. Kurinov, I. V.; Harrison, R. W. *Nat. Struct. Biol.* **1994**, *1*, 735.
20. Grutter, M. G.; Priestle, J. P.; Rahuel, J.; Grossenbacher, H.; Bode, H.; Hofsteenge, J.; Stone, S. R. *EMBO J.* **1990**, *9*, 2361.
21. Hynes, T. R.; Randal, M.; Kennedy, L. A.; Eigenbrot, E.; Kossiakoff, A. A. *Biochemistry* **1990**, *29*, 10018.
22. Yakamoto, M.; Sawaya, R.; Mohanam, S.; Rao, V. H.; Bruner, J.; Nicholson, G. L.; Ohshima, K.; Rao, J. S. *J. Neurooncol.* **1994**, *22*, 139.
23. (a) Craik, C. S.; Debouck, C. *Perspectives in Drug Discovery and Design*; Anderson, P. S., Kenyon, G. L., Marshall, G. R., Eds.; ESCOM Science Publishers BV: The Netherlands, 1995; Vol. 2. No. 3. (b) Bernkop-Schnurch, A. *J. Control. Release* **1998**, *52*, 1.
24. (a) Kraut, *J. Annu. Rev. Biochem.* **1977**, *46*, 331. (b) Polgar, L.; Halasz, P. *Biochem. J.* **1982**, *207*, 1.
25. Powers, J. C.; Harper, J. W. *Proteinase Inhibitors*, 2nd ed; Barret, A. J., Salvesen, G., Eds.; Elsevier: Amsterdam, 1986; Vol. 12, p 55.
26. Schecter, I.; Berger, A. *Biochem. Biophys. Res. Commun.* **1967**, *27*, 157.
27. Matteson, D. S.; Sadhu, K. M. *Organometallics* **1984**, *3*, 614.
28. Amiri, P.; Lindquist, R. N.; Matteson, D. S.; Sadhu, K. M. *Arch. Biochem. Biophys.* **1984**, *234*, 531.
29. Duncan, K.; Faraci, S. W.; Matteson, D. S.; Walsh, C. T. *Biochemistry* **1989**, *28*, 3541.
30. Matteson, D. S.; Cheng, T. C. *J. Org. Chem.* **1968**, *33*, 3055.

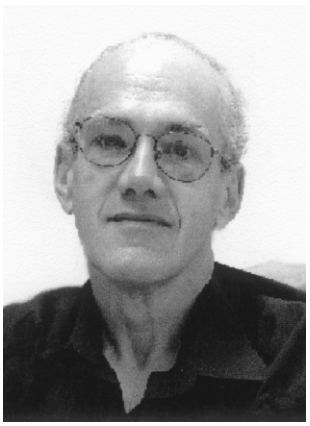
31. Matteson, D. S.; Majumdar, D. *J. Organomet. Chem.* **1979**, *170*, 259.
32. Matteson, D. S. *Stereodirected Synthesis with Organoboranes*; Springer: Berlin, 1995.
33. Matteson, D. S.; Sadhu, K. M.; Lienhard, G. E. *J. Am. Chem. Soc.* **1981**, *103*, 5241.
34. Matteson, D. S.; Jasthi, P. K.; Sadhu, K. M. *Organometallics* **1984**, *3*, 1284.
35. Philipp, M.; Maripuri, S.; Matteson, D. S.; Jeshti, P. K.; Sadhu, K. M. *Biochemistry* **1983**, *22*, A13.
36. Kinder, D. H.; Katzenellenbogen, J. A. *J. Med. Chem.* **1985**, *28*, 1917.
37. Matteson, D. S.; Michnick, T. J.; Patterson, C. D. *Organometallics* **1989**, *8*, 726.
38. Lindquist, R. N.; Nguen, A. *J. Am. Chem. Soc.* **1977**, *99*, 6435.
39. Spielvogel, B. F.; McPhail, A. T.; Hall, I. H. *Ventron Alembic* **1983**, *1*, 3.
40. Hall, I. H.; Starnes, C. O.; McPhail, A. T.; Wisian-Neilson, P.; Das, M. K.; Harchelroad, J. R.; Spielvogel, B. F. *J. Pharm. Sci.* **1980**, *69*, 1025.
41. Spielvogel, B. F.; Woinowich, L.; Das, M. K.; McPhail, A. T.; Hargrave, K. D. *J. Am. Chem. Soc.* **1976**, *98*, 5702.
42. Scheller, K. H.; Bruce, M. R.; Spielvogel, B. F.; McPhail, A. T. *Inorg. Chim. Acta* **1982**, *57*, 227.
43. Spielvogel, B. F.; Das, M. K.; McPhail, A. T.; Onan, K. D.; Hall, I. H. *J. Am. Chem. Soc.* **1980**, *102*, 6343.
44. Spielvogel, B. F.; Ahmed, F. U.; Silvey, G. L.; Wisian-Neilson, P.; McPhail, A. T. *Inorg. Chem.* **1984**, *23*, 4322.
45. Spielvogel, B. F.; Ahmed, F. U.; McPhail, A. T. *Synthesis* **1986**, 833.
46. Sood, A.; Spielvogel, B. F. *Main Group Metal Chem.* **1989**, *12*, 143.
47. Coutts, S. J.; Kelly, T. A.; Snow, R. J.; Kennedy, C. A.; Barton, R. W.; Adams, J.; Krolikowski, D. A.; Freeman, D. M.; Campbell, S. J.; Ksiazek, J. F.; Bachovcin, W. W. *J. Med. Chem.* **1996**, *39*, 2087.
48. Matteson, D. S. *Tetrahedron* **1989**, *45*, 1859.
49. Von Matt, A.; Ehrhardt, C.; Burkhard, P.; Metternich, R.; Walkinshaw, M.; Tapparelli, C. *Bioorg. Med. Chem.* **2000**, *8*, 2291.
50. Wienand, A.; Ehrhardt, C.; Metternich, R.; Tapparelli, C. *Bioorg. Med. Chem.* **1999**, *7*, 1295.
51. Metternich, R. Europ. Patent Appl., 0471651, 1992.
52. Cacciola, J.; Feving, J. M.; Alexander, R. S.; Brittelli, D. R.; Kettner, C. A.; Knabb, R. M.; Weber, P. C. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 301.
53. Knabb, R. M.; Kettner, C. A.; Timmermans, P. B. M.; Reilly, T. M. *Thromb. Haemostasis* **1992**, *67*, 56.
54. Hussain, M. A.; Knabb, R.; Aungst, B. J.; Kettner, C. *Peptides* **1991**, *12*, 1153.
55. Kelly, T. A.; Fuchs, V. U.; Perry, C. W.; Snow, R. J. *Tetrahedron* **1993**, *49*, 1009.
56. (a) Adams, J.; Behnke, M.; Chen, S.; Cruickshank, A. A.; Dick, L. R.; Grenier, L.; Klunder, J. M.; Ma, Y. T.; Plamondon, L.; Stein, R. L. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 333. (b) Adams, J. *Curr. Opin. Chem. Biol.* **2002**, *6*, 493.
57. Shenvi, A. B.; Kettner, C.A. US Patent No. 4537,773, 27.2., 1985.
58. Dunsdon, R. M.; Greening, J. R.; Jones, P. S.; Jordan, S.; Wilson, F. X. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1577.
59. Elgendy, S.; Patel, G.; Green, D.; Goodwin, C. A.; Scully, M. F.; Husman, W.; Skordalakes, E.; Kakkar, V. V.; Deadman, J. J. *Tetrahedron Lett.* **1997**, *38*, 3305.
60. Carboni, C.; Pourbaix, C.; Carreaux, F.; Delueze, H.; Maillard, B. *Tetrahedron Lett.* **1999**, *40*, 7979.
61. Kwong, A. D. *Curr. Opin. Infect. Dis.* **1997**, *10*, 485.
62. Martichonok, V.; Jones, J. B. *J. Am. Chem. Soc.* **1996**, *118*, 950.
63. Martichonok, V.; Jones, J. B. *Bioorg. Med. Chem.* **1997**, *5*, 679.
64. Matteson, D. S.; Michnick, T. J. *J. Labelled Comp. Radiopharm.* **1992**, *31*, 567.
65. Lebarbier, C.; Carreaux, F.; Carboni, B. *Synthesis* **1996**, 1371.
66. Kettner, C.; Mersinger, L.; Knabb, R. *J. Biol. Chem.* **1990**, *265*, 18289.
67. Mantri, P.; Duffy, D. E.; Kettner, C. A. *J. Org. Chem.* **1996**, *61*, 5690.
68. Lebarbier, C.; Carreaux, B.; Boucher, J. L. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2573.
69. Kerwin, Jr., J. F.; Lancaster, Jr., J. R.; Feldman, P. L. *J. Med. Chem.* **1995**, *38*, 4343.
70. Feldman, P. L.; Grifiith, O. W.; Stuehr, D. *J. Chem. Eng. News* **1993**, *71*, 26.
71. Brosz, C. S.; Calabrese, J. C.; Kettner, C. A.; Teleha, C. A. *Tetrahedron: Asymmetry* **1997**, *8*, 1435.
72. Jagannathan, S.; Forsyth, T. P.; Kettner, C. A. *J. Org. Chem.* **2001**, *66*, 6375.
73. Priestley, E. S.; De Lucca, I.; Ghavimi, B.; Erickson-Viitanen, S.; Decicco, C. P. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3199.
74. (a) Matteson, D. S.; Majumdar, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 7588. (b) Matteson, D. S.; Ray, R. *J. Am. Chem. Soc.* **1980**, *102*, 7590.
75. Matteson, D. S.; Majumdar, D. *Organometallics* **1983**, *2*, 1529.
76. Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1975**, *97*, 5249.
77. Dembitsky, V. M.; Srebnik, M. In *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; Wiley/VCH: New York, 2002; pp 230–281, Chapter 7.
78. Zheng, B.; Deloux, L.; Pereira, S.; Skrzypczak-Jankun, E.; Cheesman, B. V.; Sabat, M.; Srebnik, M. *Appl. Organomet. Chem.* **1996**, *10*, 267.
79. Tamura, Y.; Minamikawa, J. *J. Org. Chem.* **1973**, *38*, 1239.
80. Houben, J.; Schmidt, E. *Chem. Ber.* **1913**, *86*, 3616.
81. Midland, M. M.; Greer, S.; Tramontano, A.; Zderic, S. *J. Am. Chem. Soc.* **1979**, *101*, 2352.
82. Zheng, B.; Srebnik, M. *J. Org. Chem.* **1995**, *60*, 1912.
83. Györi, B.; Berente, Z.; Kovács, Z. *Inorg. Chem.* **1998**, *37*, 5131.
84. Hall, I. H.; Spielvogel, B. F.; Sood, A.; Ahmed, F.; Jafri, S. *J. Pharm. Sci.* **1987**, *76*, 359.
85. Mittakanti, M.; Morse, K. W. *Inorg.Chem.* **1990**, *29*, 554.
86. Mittakanti, M.; Feakes, D. A.; Morse, K. W. *Synthesis* **1992**, 380.
87. Gyori, B.; Berente, Z.; Emri, J.; Lazar, I. *Synthesis* **1995**, 191.
88. Mittakanti, M.; Morse, K. W. *Inorg. Chem.* **1990**, *29*, 554.
89. Das, M. K.; Mukherjee, P.; Roy, S. *Bull. Chem. Soc. Jpn* **1990**, *63*, 3658.
90. Sood, A.; Sood, C. K.; Spielvogel, B. F.; Hall, I. H. *Eur. J. Med. Chem.* **1990**, *25*, 301.
91. Karthikeyan, S.; Sood, A.; Tomasz, J.; Spielvogel, B. F.; Hall, I. H. *Amino Acids* **1995**, *8*, 323.

92. Norwood, III., V. M.; Morse, K. W. *Inorg. Chem.* **1988**, *27*, 302.
93. Norwood, III., V. M.; Morse, K. W. *Inorg. Chem.* **1987**, *26*, 284.
94. Hall, I. H.; Spielvogel, B. F.; McPhail, A. T. *J. Pharm. Sci.* **1984**, *73*, 222.
95. Carboni, B.; Monnier, L. *Tetrahedron* **1999**, *55*, 1197.
96. Norwood, III., V. M.; Morse, K. W. *Inorg.Chem.* **1986**, *25*, 3690.
97. Spielvogel, B. F.; Sood, A.; Hall, I. H. W. O. US Patent 93 09,123, 1993; *Chem. Abstr.* **1993**, *119*, 203618f.
98. Hall, I. H.; Hall, E. S.; Miller, III., M. C.; Sood, A.; Spielvogel, B. F. *Amino Acids* **1993**, *4*, 287.
99. Murphy, M. E.; Elkins, A. L.; Shrewsbury, R. P.; Sood, A.; Spielvogel, B. F.; Hall, I. H. *Met.-Based Drugs* **1996**, *3*, 31 and references therein.
100. Hall, I. H.; Rajendran, K. G.; Chen, S. Y.; Wong, O. T.; Sood, A.; Spielvogel, B. F. *Arch. Pharm. (Weinheim, Ger.)* **1995**, *328*, 39 and references therein.
101. Miller, III., M. C.; Wood, C. M.; Murphy, M. E.; Elkins, A.; Spielvogel, B. F.; Hall, I. H. *Biomed. Pharmacother.* **1998**, *52*, 169.
102. Das, M. K.; Mukherjee, P. *J. Chem. Res. (S)* **1985**, 66.
103. Berente, Z.; Gyori, B. *Chem. Commun.* **1997**, 1799.
104. Hall, I. H.; Burnham, B. S.; Chen, S. Y.; Sood, A.; Spielvogel, B. F.; Morse, K. W. *The Anti-inflammatory Activity of Boron Derivatives in Rodents*; 1995; Vol. 2. pp 1–15.
105. Miller, M. C.; Sood, A.; Spielvogel, B. F.; Hall, I. H. *Appl. Organomett. Chem.* **1998**, *12*, 87.
106. Xu, R.; Dwoskin, L. P.; Grinevich, V. P.; Deaciuc, G.; Crooks, P. A. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1245.
107. Chavdarian, C. G.; Seeman, J. I.; Wooten, J. B. *J. Org. Chem.* **1983**, *48*, 492.
108. Glassco, W.; Suchocki, J.; George, C.; Martin, B. R.; May, E. L. *J. Med. Chem.* **1993**, *36*, 3381.
109. Vernier, J.; Holsenback, H.; Cosford, N. D. P.; Whitten, J. P.; Menzaghi, F.; Reid, R.; Rao, T. S.; Saccan, A. I.; Lloyd, G. K.; Suto, C. M.; Chavez-Noriega, L. E.; Washburn, M. S.; Urrutia, A.; McDonald, I. A. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2173.
110. Mittakanti, M.; Morse, K. W. *Main Group Metal Chem.* **1996**, *19*, 727.
111. Sood, A.; Sood, C. K.; Hall, I. H.; Spielvogel, B. F. *Tetrahedron* **1991**, *47*, 6915.
112. Hall, I. H.; Spielvogel, B. F.; Das, M. K.; McPhail, A. T. *J. Pharm. Sci.* **1981**, *70*, 339.
113. Gyori, B.; Berente, Z.; Kiraly, R.; Lazar, I. *J. Chem. Soc., Perkin Trans. 1* **2002**, 300.
114. Dembitsky, V. M.; Srebnik, M. *Organometallics: Boron Compounds. The Science of Synthesis, Houben–Weyl Methods of Molecular Transformation*; Regitz, M., Kaufmann, D., Matteson, D. S., Eds.; Georg Thieme Verlag: Stuttgart, 2003; Vol. 6. Chapter 28, in press.
115. Dembitsky, V. M.; Srebnik, M. *Organometallics: Boron Compounds. The Science of Synthesis, Houben–Weyl Methods of Molecular Transformation*; Regitz, M., Kaufmann, D., Matteson, D. S., Eds.; Georg: Stuttgart, 2003; Vol. 6. Chapter 30, in press.
116. Dembitsky, V. M.; Srebnik, M. *Organometallics: Boron Compounds. The Science of Synthesis, Houben–Weyl Methods of Molecular Transformation*; Regitz, M., Kaufmann, D., Matteson, D. S., Eds.; Georg Thieme Verlag: Stuttgart, 2003; Vol. 6. Chapter 38, in press.

Biographical sketch



Valery M. Dembitsky obtained his M.S. in Organic Synthesis from the Far East State University, Vladivostok, USSR, in 1973. He holds a PhD degree in Biological Chemistry from USSR Academy of Sciences, Leningrad (before 1917 and since 1991 Saint Petersburg), in 1981. In 1989 he established Laboratory of Natural Products, Institute of Ecology of the USSR Academy of Science, Togliatti, and he was director of this Laboratory until 1993. From 1989 to 1991 he also was Associate Professor at Organic Chemistry and Biochemistry Department, Kuibyshev State University, Kuibyshev (before 1934 and since 1991 Samara), Russia. He was as visiting Professor at the Department of Scientific and Industrial Research, The Massey University, Palmerston North, New Zealand, 1990; Department of Organic and Biological Chemistry, Auckland University, Auckland, New Zealand, 1990; Department of Plant Chemistry, Institute of Organic Chemistry with Phytocentre, Bulgarian Academy of Science, 1990; Department of Natural Biogenesis, Institute of Microbiology, Czechoslovakia Academy of Science, Prague, 1989 and 1990; Department of Marine Chemistry, Institute of Oceanology, Polish Academy of Science, Sopot, Poland, 1989. During 1991–1992 he held guest Professorship at the School of Chemistry, Melbourne University, Australia, and from 1993 he started on collaboration with Professor Raphael Ikan, Department of Organic Chemistry, Hebrew University, Jerusalem. He received his D.Sc. degree in Bioorganic Chemistry and Chemistry of Natural Products from M.V. Lomonosov Moscow State Academy of Fine Chemical Technology, in 1997. Since 2000 Professor Dembitsky joined the School of Pharmacy, Hebrew University. He has published more than 220 scientific papers and 49 review articles (in English and Russian, but mostly in English). His research interests are focused in the areas of organometallic chemistry, bioorganic chemistry, chemistry of natural products, and biological imaging.



Morris Srebnik received his PhD in 1984 from the Hebrew University in Jerusalem under Professor Raphael Mechoulam. On a Lady Davis Fellowship, he joined Professor H. C. Brown's group at Purdue, where he studied the applications of organoboranes to synthesis until 1986. After a short stint at the Sigma-Aldrich Corporation he returned to Professor Brown's group. In 1990 he accepted a position at the Department of Chemistry, University of Toledo, USA. Since 1996 he is a Professor at School of Pharmacy, Hebrew University. His areas of interest include developing organometallic methodologies in synthesis centred around—boron and zirconium and lately also titanium, and investigating the potential uses of organoboranes in medicine. He also has interest in isolating new sunscreen agents from natural sources such as cyanobacteria. He is the author of more than 130 publications.