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Facile Routes To 1-Halo-1-Alkyl Boronic Esters As Precursors For Novel Thrombin Inhibitors

Said Elgendy*, Goran Claeson, Vijay V.Kakkar, Donovan Green, Geeta Patel, Christopher A. Goodwin, Jehan A. Baban, Michael F. Scully, John Deadman

Thrombosis Research Institute, Emmanuel Kaye Building, Manresa Road, Chelsea, London SW3 6LR, UK.

Abstract: Methods of synthesis are described of α-haloboronic esters by hydroboration of 1-halo-1-alkenes with catecholborane and by reaction of pinanediol dichloromethylboronate with organometallic reagents. The resulting α-haloboronic esters are synthetically useful, especially for the synthesis of peptides containing α-aminoboronic acids. The inhibitory activities of these peptides have been studied with thrombin.

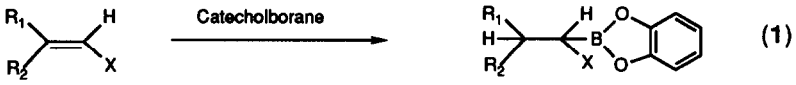
A trigonal sp^2 boron atom provides a highly electron deficient centre as an electrophile to form a strong covalent adduct with the nucleophilic catalytic centre of serine (OH) and cysteine (SH) proteases. Substrate-like inhibitors form tetrahedral sp^3 serine adducts which are stabilised by the oxyanion binding pocket of the enzyme in an analogous manner to the hemiacetal of the natural substrate[1]. X-ray crystallography of complexes of boronic acids with serine proteases[2] have shown that the inhibitors form an anti-parallel beta-pleated sheet structure with the Ser 214-Gly 219 sequence of the enzyme, in which the α-amino group of the boronate contributes to stabilisation of the complex *via* hydrogen bond formation. Consequently there has been much interest in α-aminoboronates as C-terminal derivatives of peptide based inhibitors.

Our ongoing research on thrombin has demonstrated that α-aminoboronic acids with neutral (e.g. 3-methoxypropyl P1) residues[3] are 100-1000 fold more specific for thrombin than other serine proteases and 10-100 fold more specific than the corresponding P1-boroarginine derivatives[4]. Accordingly to map the S1 site of thrombin we sought to synthesise a series of novel α-aminoboronates via their α-halo precursors. Literature routes give access to only a limited range of 1-alkyl

substituents, as by homologation of 1-alkylboronates by introduction of the α-chloro functionality[5].

The hydroboration of carbon-carbon multiple bonds has proven to be one of the most valuable synthetic techniques in organic chemistry[6]. Only two methods have been reported for the direct synthesis of α-halo boronic esters *via* hydroboration[5]. Firstly, $(MeO)_2BCHClCH_2Cl$ has been synthesized by the reaction of $(MeO)_2BH$ with *E*-1,2-dichloroethane[7]. The product obtained from the hydrolysis was contaminated with boric acid. An alternative method was hydroboration of 1-chloro-2-methylpropene with one equivalent of borane followed by hydrolysis, which yielded (1-chloro-2-methylpropyl) boronic acid. However, if the hydroboration mixture was allowed to stand in THF at room temperature for several hours, or excess of BH_3 were added, the intermediate rearranged to isobutylchloroborane[8].

In the present study, we describe the synthesis of α-haloboronic esters (**2**) by the hydroboration of 1-halo-1-alkenes (**1**) as a mixture of geometrical isomers (equation 1). As with other hydroborating agents[9,13], catecholborane hydroborates *cis*-alkenes faster than the *trans* isomers. Since we have observed little difference between the *cis* and *trans* isomers in products produced, we shall discuss each pair as a unit.



1 **2** (1)

Generally, the reaction takes place readily without solvent at elevated temperature such as in the range of 80 to 90°C. The reaction was monitored by the disappearance of the olefinic protons in the proton NMR.

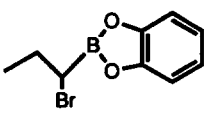
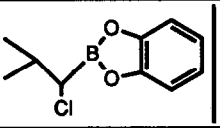
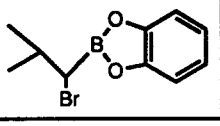
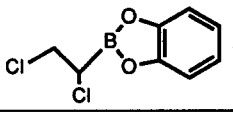
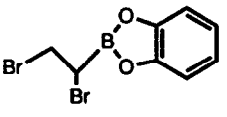
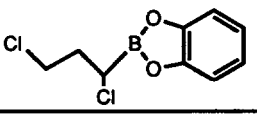
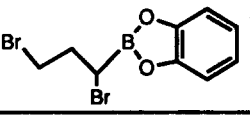
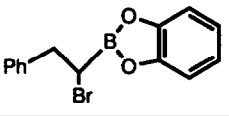
As shown in Table 1, the reactions of the chloroalkenes (entry 2,6) are slower than those of the bromo alkenes (entry 3,5,7) and the hydroboration of 1,2-dichloroethene failed, giving only the starting material (Table 1, entry 4).

In entry 8, reaction of 2-bromostyrene failed after 72 h reflux. Irradiation of the reaction mixture with ultrasound, induces reaction.

This reaction provides a new method for preparing α-haloboronic esters which is simple and economical for large scale synthesis with the following advantages:

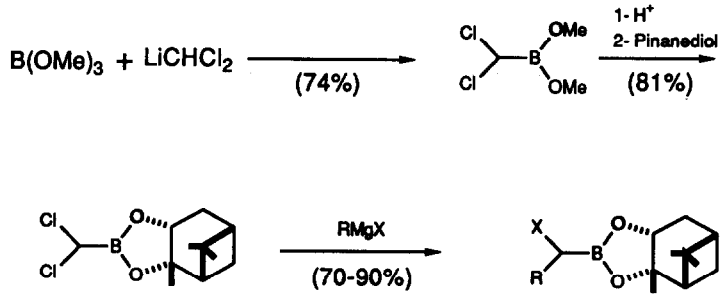
-No solvents are used.
-Unstable intermediates and cryogenic conditions are avoided.
-By optimizing the number of refluxing hours, no by-product or rearrangement is generally observed.

Table 1 Hydroboration of $R_1R_2C{=}CHX$ with catecholborane

Entry	R^1	R^2	X	Reaction Time (h)	Isolated Product	% yield
1	Me	H	Br	24		76
2	Me	Me	Cl	18		66
3	Me	Me	Br	4		82
4	Cl	H	Cl	72		—
5	Br	H	Br	30		80
6	$ClCH_2$	H	Cl	24		79
7	$BrCH_2$	H	Br	8		76
8	Ph	H	Br	20*		59

* Ultrasonic bath for two hours

Limited availability of 1-haloalkenes led us to investigate another method[5] starting from dichloromethaneboronic esters as shown in Scheme 1. This gave high yields as shown in Table 2.

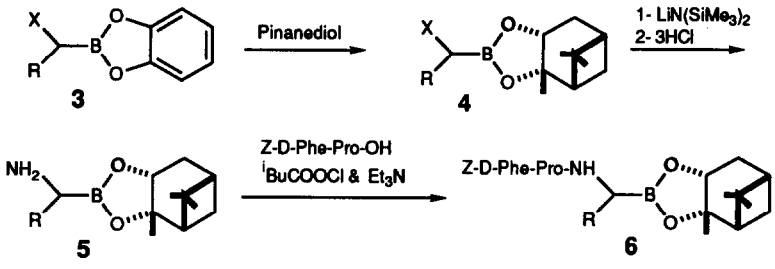


Scheme 1

Table 2 Results of the reaction of (+)-pinanediol dichloromethylboronate with RMgX

entry	R	%Yield
1	$Pent^n$	73
2	Oct^n	77
3	Cyclohexyl	82
4	$PhCH_2$	91
5	Mesityl	72

α-Haloboronates were converted to α-aminoboronates[5,10,11] as illustrated below (Scheme 2)



a, R=Et; b, R=Pr^i; c, R=$Cl(CH_2)_2$; d, R=$MeO(CH_2)_3$; e, R=$MeO(CH_2)_2$; f, R=$PhCH_2$; g, R=$BrCH_2$; h, R=CMe_2Et; i, R= $Pent^n$

Scheme 2

The reactivities of these α-aminoboronic ester containing peptides were studied with thrombin as shown in Table 3. All peptide boronic acids with more than two carbon atoms in the neutral side chain in the series Z-D-Phe-Pro were potent, competitive inhibitors of thrombin (Ki < 50 nM)

Table 3 Ki values for the thrombin inhibitors Z-D-Phe-Pro-NH-CHR-Boro-OPin

entry	R	Method of Preparation[a)]	Ki(μM)
1	Et	A	0.37
2	Pr^i	A	0.019
3	$Cl(CH_2)_2$	A	0.014
4	$MeO(CH_2)_2$	A	0.049
5	$MeO(CH_2)_3$	B	0.007
6	$PhCH_2$	C	0.012

a) A: Hydroboration of α-chloroalkene with catecholborane.
B: Homologation of the boronic esters[12].
C: Reaction of pinanediol dichloromethylboronate with RMgX.

The methoxypropyl compound gave the lowest Ki (7nM) (Table 3, entry 5). The reason for the rather high affinity of this compound (entry 5), compared to the homologue with one carbon less in the side chain (entry 4) is unclear but could possibly be related to the stabilisation through intramolecular interaction between the boron and the oxygen atom, forming the six membered ring as shown in Figure 1. Evidence for this is seen in the ^1H NMR spectra where the methylene protons are deshielded by about 0.2 ppm due to co-ordination of the oxygen to boron.

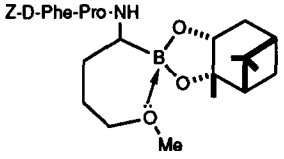


Figure 1

Experimental Section

General procedures for the manipulation of boron reagents have been outlined elsewhere[13]. Reactions involving the production of air and water sensitive compounds were carried out under a static pressure of argon or nitrogen directly from the cylinder through a glass line connected *via* a three-way tap to a vacuum pump. The preparation and purification of reagents for use in reactions of organoboron compounds have been reviewed[13].

All glassware, syringes, and needles were oven-dried at 140°C for several hours. The glassware was assembled hot and cooled under a stream of dry nitrogen or argon introduced *via* hypodermic needles inserted through serum capped inlets with outlets protected by inert oil bubblers. Manipulation of liquids was carried out under an inert atmosphere, using syringes and double-ended needle techniques. Syringes were assembled and fitted with needles while hot and then cooled as assembled units.

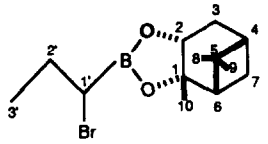
Unless otherwise stated, the apparatus for reactions at below room temperature consisted of a septum capped flask and a coated magnetic follower to enable stirring of the reaction mixture *via* an external magnetic stirrer. A bleed needle to the argon line was inserted through the cap to allow for any changes in the pressure within the vessel during reaction. Apparatus for reactions at elevated temperatures consisted of a two-necked round-bottomed flask; one neck equipped with a septum capped tap adaptor, the other with a septum capped reflux condenser carrying a nitrogen bleed.

Hydroboration of 1-halo-1-alkenes (Method A)

Catecholborane (6g, 50 mmol) was added dropwise to the 1-halo-1-alkene(50 mmol). The reaction mixture was heated at 80-90°C under argon and monitored by the disappearance of the olefinic protons in the proton NMR. The α-haloboronic ester was obtained by distillation at 90-120°C/0.05 mmHg in 59-83% yields.

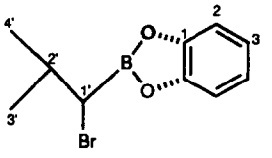
(+)Pinanediol 1-haloalkaneboronic esters were prepared by adding one equivalent of the catecholboronic ester to a solution of (+)-pinanediol in THF. The reaction mixture was left stirring at room temperature for two hours. The solvent was removed under vacuum and the residue was purified on a column of silica gel (230-400 mesh). Elution with hexane gives the desired products as colourless oils in 85-90%yield.

(+)-Pinanediol 1-bromopropylboronate (4a)



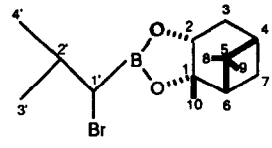
m\z 302 (M+H); δ_B 31.13; δ_H 4.34-4.39(1H, m, H-2), 3.27-3.35(1H, m, H-1'), 2.31-2.45(1H, m, H-3), 2.16-2.3(1H, m, H-7), 2.09(1H, t, *J*=5Hz, H-6), 1.91-2.09(2H, H, H-2'), 1.81-1.91(1H, m, H-4), 1.69-1.8(1H, m, H-3), 1.41(3H, s, H-10), 1.29(3H, s, H-9), 1.12-1.23(1H, m, H-7), 1.1(3H, t, *J*=7Hz, H-3'), 0.85(3H, s, H-8); δ_C 86.38(C-1), 78.3(C-2), 51.2(C-6), 39.48(C-4), 38.22(C-5), 35.3(C-3), 28.37(C-10), 27.6(C-2'), 26.9(C-9), 26.2(C-7), 23.94(C-8), 13.41(C-3'); calculated for $C_{13}H_{22}B^{79}BrO_2$ is 300.0899, observed was 300.0896.

Catechol 1-bromo-2-methylpropylboronate (3b)



m\z 256 (M+H); δ_B 32.79; δ_H 7.02-7.28(4H, m, Ph), 3.65(1H, d, *J*=7.2Hz, H-1'), 2.09-2.35(1H, m, H-2'), 1.11 -1.19(6H, q, H-3'& H-4');δ_C 147.89(C-1), 123.16(C-2), 112.85(C-3), 31.7(C-2'), 21.38(C-3'& C-4'); calculated for $C_{10}H_{12}B^{79}BrO_2$ is254.0110 , observed was 254.0119.

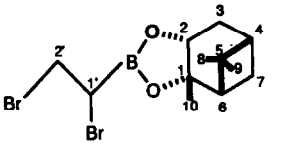
(+)-Pinanediol 1-bromo-2-methylpropylboronate (4b)



m\z 316 (M+1); δ_B 31.02; δ_H 4.34-4.39(1H, m, H-2), 3.41(1H, dd, *J*=8Hz& 1.3Hz, H-1'), 2.23-2.24(1H, m, H-2'), 2.17-2.3(1H, m, H-3), 2.06-2.15(1H, m, H-7), 2.05 (1H. t, *J*=5Hz, H-6), 1.88-1.99(1H, m, H-4), 1.55-1.8 (1H, m, H-3), ,1.4(3H, s, H-10), 1.2(3H, s, H-9), 1.03-1.11(6H, m, H-3'& H-4'), 0.9-1.1(1H, m, H-7),0.85(3H, s, H-8); δ_C 86.38(C-1), 78.3(C-2), 51.27(C-6), 39.57(C-4), 38.3(C-5), 35.44(C-3), 31.62(C-2'),

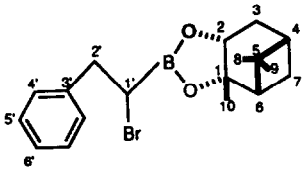
28.44(C-10), 27.01(C-9), 26.2(C-7), 24.02(C-8), 21.52(C-4'), 21.26(C-3'); calculated for $C_{14}H_{24}B^{79}BrO_2$ is 314.1046, observed was 314.1038.

(+)-Pinanediol 1,2-dibromoethylboronate (4g)



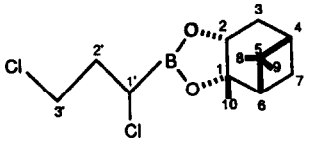
m\z 384 ($M+NH_4$); δ_B 30.68; δ_H 4.40-4.44(1H, m, H-2), 3.53-3.845(3H, m, H-1'& H-2'), 2.3-2.49(1H, m, H-3), 2.2-2.29(1H, m, H-7), 2.11(1H. t, J=5Hz, H-6), 1.9-2.01(1H, m, H-4), 1.62-1.9(1H, m, H-3), 1.43(3H, s, H-10), 1.31 -1.41(1H, m, H-7), 1.3(3H, s, H-9), 0.85(3H, s, H-8); δ_C 87.08(C-1), 78.72(C-2), 51.24(C-6), 39.5(C-4), 38.3(C-5), 35.3(C-3), 31.75(C-2'), 28.4(C-10), 27.5(C-9), 26.39(C-7), 24.04(C-8); calculated for $C_{12}H_{21}B^{79}Br_2O_2$ is 366.0001, observed was 366.0008.

(+)-Pinanediol 1-bromo-1-benzylmethylboronate (4f)



m\z 380 ($M+NH_4$); δ_B 31.80; δ_H 7.02-7.42(5H, m, Ph), 4.19-4.31(1H, m, H-2), 3.47-3.56(1H, m, H-1'), 3.1-3.32(2H, m, H-2'), 2.2-2.35(1H, m, H-3), 2.05-2.2(1H, m, H-7), 2.12(1H. t, J=5Hz, H-6), 1.71-1.95(1H, m, H-4), 1.7-1.75(1H, m, H-3), 1.32(3H, s, H-10), 1.24(3H, s, H-9), 0.95-1.04(1H, m, H-7), 0.78(3H, s, H-8); δ_C 139.1(C-3'), 129.17 (C-5'), 128.24(C-4'), 126.08(C-6'), 86.45(C-1), 78.32(C-2), 51.23 (C-6), 40.67(C-2'), 39.23(C-4), 38.21(C-5), 35.16(C-3), 28.27(C-10), 27.09(C-9), 26.37 (C-7), 23.96(C-8); calculated for $C_{18}H_{24}B^{79}BrO_2$ is 362.1053, observed was 362.1061.

(+)-Pinanediol 1,3-dichloropropylboronate (4c)



m\z 308 ($M+NH_4$); δ_B31.44; δ_H 4.2-4.39(1H, m, H-2), 3.71-3.77(2H, m, H-3'), 3.54(1H, t, J=6Hz, H-1'), 2.35-2.41(1H, m, H-3), 2.25-2.32(2H, m, H-2'), 2.2-2.25(1H, m, H-7), 2.08(1H. t, J=5Hz, H-6), 1.93-1.99(1H, m, H-4), 1.91-1.93(1H, m, H-3), 1.42(3H, s, H-10), 1.3(3H, s, H-9), 1.01-1.22(1H, m, H-7), 0.84(3H, s, H-8); δ_C 87.05(C-1), 78.74(C-2), 51.31(C-6), 42.12(C-3'),39.37(C-4), 38.27(C-5), 36.55(C-2'), 35.23(C-3), 28.40(C-10), 27.04(C-9), 26.5(C-7), 23.94(C-8); calculated for $C_{13}H_{21}B^{35}Cl_2O_2$ is 290.1012, observed was 290.1011.

Preparation of (+)-Pinanediol dichloromethylboronate

A 500 ml, 2-necked round-bottomed flask equipped with a mechanical stirrer and a septum cap was immersed in an ethanol/liquid nitrogen bath maintained at -100°C. The flask was charged with a solution of methylene dichloride (9.34g, 110 mmol) in 200 ml of THF. Pre-cooled *n*-butyl lithium (63 ml, 100 mmol) was added dropwise over a period of 40 minutes. After 0.5h at -100°C, trimethoxyborane (12.5 ml, 110 mmol) was added all at once. After another 0.5 h, the reaction mixture was hydrolyzed with 20ml of 5N HCl. The solution was allowed to reach room temperature, the organic layer separated and the aqueous layer extracted with 30ml of ether. The combined organic layers were dried($MgSO_4$), filtered and evaporated to give a white solid(20g) (which showed two peaks in the proton NMR at 5.25 and 6.15

ppm). The crude white solid(10g) was dissolved in THF(12ml) and (+)- pinanediol(6g) was added. The reaction mixture was left stirring at room temperature overnight and dried over $MgSO_4$. Removal of the solvent gave the desired product as a colourless oil (6.9g, 74%).

Preparation of α-halo boronic esters (Method C)

A solution of Grignard reagent RMgX (4mmol) in THF was added dropwise at -78°C to a solution of (+)-pinanediol dichloromethyl boronate (1g, 3.8mmol) in THF (20ml) using a dry syringe over a period of 5 minutes.

The reaction mixture was left stirring overnight (18 hours) under nitrogen. The solvent was removed and the residue dissolved in ether, washed with water and dried over $MgSO_4$. The reaction mixture was purified on a column of silica gel eluted with 10% ether/hexane to isolate the desired product as a colourless oil. The yields varied between 70-90%.

Preparation of Z-D-Phe-Pro-NH-boroMbg-OPin (6h)[14]

(+)Pinanediol 1-chloro-2,2-dimethylbutylboronate (4h)(0.55g, 1.8mmol) in THF (5ml) was added *via* a double ended needle to a solution of lithium bis(trimethylsilyl)amide (1.8ml, 1.8mmol) in THF (5ml) at -78°C under nitrogen. The reaction mixture was allowed to slowly warm to room temperature and stirred overnight. The solvent was removed under vacuum and the residue dissolved in petroleum ether (40-60°C) (25ml) to precipitate out the inorganic salt. The reaction mixture was filtered, cooled to -78°C and dry ethereal HCl(1M, 5.4ml, 5.4mmol) added. The flask was kept in the fridge overnight. The reaction mixture was filtered to isolate the α-aminoboronic ester as a white solid (0.41g, 72%).

Z-D-Phe-Pro-OH (0.45g, 1.1mmol) was dissolved in THF (7ml) and one equivalent of N-methylmorpholine (0.11g, 1.1mmol) added. The solution was cooled to -20°C and one equivalent of isobutylchloroformate(0.149, 1.1mmol) added dropwise. After 10 minutes, a solution of (+)pinanediol-1-amino-2,2-dimethylbutyl-boronate (5h) (0.348g, 1.1mmol) in THF (7ml) was transferred under nitrogen, and triethylamine (0.11g, 1.1mmol) added to the reaction flask. The reaction mixture was stirred for an hour at -20°C, followed by two hours at room temperature. Insoluble material was removed by filtration, then the solvent removed by evaporation, and the residue dissolved in ethyl acetate (30ml). The organic layer was washed with 0.2N hydrochloric acid (10ml), 5% aqueous sodium bicarbonate, saturated NaCl, and finally with water. The organic phase was then dried over anhydrous $MgSO_4$, filtered and the solvent evaporated to give a white solid. The crude product was purified on a column of silica gel eluted with hexane to give the desired product (0.59g, 81%), m\z 658 (M+1); δ_H 7.51 (1H, s, NH), 7.17-7.39(10H, m, 2Ph), 5.53(1H, d, 6.25Hz, NH), 5.11(2H, q, J=12.2Hz and 29.7Hz, O$\underline{CH_2}$Ph), 4.45-4.54(2H, m, Pro-α CH & Phe-α CH), 4.01-4.27(1H, m, Pin-H), 3.35(2H, t, J=6.6Hz, Pro-CH_2), 2.99(2H, d, J=7.55Hz, $\underline{CH_2}$Ph), 2.8(1H, m, CHB), 1.25-2.59(21H, m, Pro-2CH_2 & Pin-2CH_2, 2CH & side chain

3CH_3,CH_2), 1.35(3H, s, Pin-CH_3), 1.26(3H, s, Pin-CH_3), 0.82(3H, s, Pin-CH_3); calculated for $C_{38}H_{52}BN_3O_6$ is 608.4023, observed was 608.4018.

Preparation of Z-D-Phe-Pro-NH-boroMeg-OPin (6d)

A mixture of NaOMe (2equiv., 1.35g, 7.4 mmol) and Guanidine.HCl (1.43g, 15 mmol) in MeOH (10ml) was added to a stirred solution of Z-D-Phe-Pro-NH-boro-Ceg-OPin (6c)(2.4g, 3.7 mmol) in MeOH (12ml) over a period of two hours.

The reaction was left stirring and monitored for disappearance of the starting material by hplc. After 48h, the solvent was removed, the residue was dissolved in ethyl acetate (100ml), washed with 0.2N HCl(5ml), water, 1% $NaHCO_3$(5ml), water and dried over Na_2SO_4.

The solvent was removed and the crude product purified on a column of silica gel eluted with 10%AcOEt/$CHCl_3$ to give a white crystalline solid of the desired product (1.6g, 67%), m\z 646 (M+1); δ_B 25.52; δ_H 7.43 (1H, d, *J*=4Hz, NH), 7.21-7.34(10H, m, 2Ph), 5.7(1H, d, *J*=6 Hz, NH), 5.03-5.16(3H,m, NH & O$\underline{CH_2}$Ph), 4.2-4.58(2H, m,Pro-α CH & Phe-α CH, 4.20-4.25(1H, m, Pin-H), 3.45(2H, t, *J*=5.9Hz, $\underline{CH_2}$-OMe), 3.2(3H, s, OMe), 2.99-3.02(3H,m , CHB & $\underline{CH_2}$Ph), 1.5-2.4(10H, m, Pro-CH_2 & $\underline{CH_2}$CHB & Pin-2CH_2,2CH), 1.24-1.35(4H, m, 2Pro-CH_2), 1.4-1.62(2H, m, Pro-CH_2), 1.3(3H, s, Pin-CH_3), 1.27(3H, s, Pin-CH_3), 0.935(3H, s, Pin-CH_3); calculated for $C_{36}H_{48}BN_3O_7$ is 646.3664, observed was 646.3655.

The following compounds were synthesized as above[14]:

Z-D-Dpa-Pro-NH-boro-Val-OPin (72%); m\z 706 (M+H); δ_B 27.79; δ_H 7.45 (1H, d, 4Hz, NH), 7.21-7.35(15H, m, 3Ph), 5.24(1H, dd, *J*=6.1Hz, NH), 4.9-5.09(3H, m, Dpa-α CH & O$\underline{CH_2}$Ph), 4.42(1H, d, *J*=11.6Hz, Dpa-β H), 4.39-4.4(2H, m, Pro-CH and Pin-H), 3.69(1H, dd, *J*=8.4Hz, Pro-CH), 2.5-2.84(2H, m, CHB), 1.74-2.29(9H, m, $\underline{CH}$CHB & Pin-6H & Pro-CH_2), 1.4-1.62(2H, m, Pro-CH_2), 1.34(3H, d, Pin-CH_3), 1.25(3H, d, Pin-CH_3), 0.907(6H, dd, *J*=3.75Hz, Pr^i-2CH_3), 0.821(3H, d, Pin-CH_3); calculated for $C_{42}H_{53}BN_3O_6$ is 706.4027, observed was 706.4038.

Z-D-Phe-Pro-NH-boro-Ceg-OPin (6c) (69%); m\z 650.5 (M+H); δ_B 22.723; δ_H 7.64 (1H, s, NH), 7.09-7.33(10H, m, 2Ph), 5.7(1H, d, *J*=5.5 Hz, NH), 5.08(2H, m, O$\underline{CH_2}$Ph), 4.42-4.53(2H, m, Pro CH& Phe-α$\underline{CH}$), 4.20-4.27(1H, m, Pin-H), 3.55-3.68(3H, m, CH_2Cl & Pro-CH), 2.96-3.06(3H, m, CHB & Ph$\underline{CH_2}$), 1.58-2.29(12H, m, Pro-2CH_2& $\underline{CH_2}$CHB& Pin-2CH_2,2CH), 1.36(3H, s, Pin-CH_3), 1.26(3H, s, Pin-CH_3), 0.825(3H, s, Pin-CH_3); calculated for $C_{35}H_{46}{}^{35}ClBN_3O_6$ is 650.3168, observed was 650.3167.

Z-D-Phe-Pro-NH-boro-Mpg-OPin (6e) (76%); m\z 682 (M+Na); δ_H 8.11 (1H, s, NH), 7.17-7.39(10 H, m, 2Ph), 5.714(1H, d, *J*=5.6 Hz, NH), 4.98-5.18(2H, m, O$\underline{CH_2}$Ph), 4.42-4.51(2H, m,Pro-α CH & Phe-α CH), 4.24-4.28(1H, m, Pin-H), 3.27-3.37(2H, t, $\underline{CH_2}$-OMe), 3.23(3H, s, OMe), 3.02(2H, d, *J*=7.6Hz, $\underline{CH_2}$Ph), 2.6-2.71(1H, m, CHB)2.27-2.56(12H, m, Pro-2CH_2 & $\underline{CH_2}$CHB & Pin-2CH_2, 2CH), 1.38(3H, s, Pin-CH_3), 1.26(3H, s, Pin-CH_3), 0.835(3H, s, Pin-CH_3); calculated for $C_{37}H_{50}BN_3O_7Na$ is 682.3640, observed was 682.3650.

Z-D-Phe-Pro-NH-boro-Phe-OPina (6f) (67%); m\z 648 (M+Na); δ_H 7.55 (1H, s, NH), 6.82-7.31 (15H, m, 3Ph), 5.71(1H, d, *J*=5.4 Hz, NH), 4.9-5.1(2H, m, O$\underline{CH_2}$Ph), 4.31-4.47(2H, m,Pro-α CH & Phe-α CH), 4.24-4.28(1H, m, Pin-H), 3.4-3.8(2H, m, Pro-CH_2), 2.81-3.17(3H, m , CHB & $\underline{CH_2}$Ph)2.57-2.72(2H, m, $\underline{CH_2}$CHB), 1.42-1.59(2H, m, Pro-CH_2), 1.21(12H, s, Pinacol-4CH_3); calculated for $C_{36}H_{44}BN_3O_6Na$ is 648.3221, observed was 648.3234.

Z-D-Phe-Pro-NH-boro-Pgl-OPina (6i) (68%); m\z 606 (M+H); δ_H 7.6 (1H, s, NH), 7.19-7.3(10H, m, 2Ph), 7.48 (1H, s, NH), 4.98-5.17(2H, m, O$\underline{CH_2}$Ph), 4.47-4.6(2H, m, Pro-α CH & Phe-α CH), 3.56-3.8(2H, m, Pro-CH_2), 2.99(2H, d ,*J*=7.9Hz, $\underline{CH_2}$Ph),2.89-2.91(1H, m, CHB), 2.22-2.69(4H, m, Pro-2CH_2), 1.19(12H, s, Pinacol-4CH_3), 0.8-1.82(11H, m, Pentyl); calculated for $C_{34}H_{49}BN_3O_6$ is 606.3714, observed was 606.3707.

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14. Abbreviations:

Mpg=3-methoxypropylglycine	Mbg=2methyl-2-butylglycine
Pgl=*n*-pentylglycine	Ceg=chloroethylglycine
Meg=methoxyethylglycine	Z=benzyloxycarbonyl
OPin=pinanediol ester	OPina=pinacol ester

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