Supporting Information

Structure Guided Development of Potent Reversibly Binding Penicillin Binding Protein Inhibitors

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Contents:

Chemical synthesis

All reagents and solvents were from Aldrich or Alfa Aesar. Reactions were monitored by TLC, which was performed on precoated aluminum-backed plates (Merck, silica 60 F254). Melting points were determined using a Leica Galen III hot-stage melting point apparatus and microscope. Infrared spectra were recorded from Nujol mulls between sodium chloride discs, on a Bruker Tensor 27 FT-IR spectrometer. NMR spectra were acquired using a Bruker DPX500 NMR spectrometer. Chemical shifts (δ) are given in ppm, and the multiplicities are given as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br). Coupling constants *J* are given in Hz (± 0.25 Hz). High resolution mass spectra (HRMS) were recorded using Bruker MicroTOF. The purity of all compound synthesized were >95% as determined by analytical reverse-phase HPLC (Ultimate 3000).The chemical synthesis and characterisation of all compounds are described in the Supporting Information. The chemical synthesis of compounds **12-14**, **16** and **17** was as reported in refs. 1, 2 and 3, respectively; The chemical synthesis of compounds **15** was adapted from ref. 2.

Assay conditions

Testing of compounds for R39 inhibition was performed by monitoring the degree of hydrolysis of *N*-benzoyl-D-alanyl-thioglycolate (**S2d**) as described.[4] The inhibitors (at either 1mM or 100μM depending on their solubility) were preincubated with R39 (3.5nM) in 10mM sodium phosphate buffer (pH 7.0) containing 100mM NaCl, 100 mM D-alanine, and 0.01 mg mL^{-1} BSA for 60 min at 25°C. A substrate mixture containing **S2d** (1mM) and 5,5'-dithiobis(2-nitrobenzoic acid) (DTNB, 1mM) was then added, and the residual activity (RA) determined by measuring absorbance at 412 nm using a Power Wave microtiter plate reader (Bio-Tek Instruments, Winooski, USA). For IC_{50} determination, RA of the inhibitor was measured over a range of concentrations and the IC_{50} values determined by performing a nonlinear regression analysis using Sigma Plot (Systat software).[5] All experiments were performed in triplicate.

K_i values for inhibition of R39 were determined by steady-state competition experiments. Biphasic progress curves were observed for **29** and **30**. Steady state rates were measured over a range of concentrations (0.4μM to 6μM). Assays were conducted at 30°C in 10mM sodium phosphate buffer (pH 7.2) containing 100mM NaCl and 100mM D-alanine. After a preincubation of R39 (7nM) with boronic acid for 60 min steady state rates, v_s, were

determined by the addition of **S2d** (100µM, K_m = 0.17mM) and DTNB (1mM) using microtiter 96 well plates. K_i values are derived assuming a competitive pattern of inhibition and plotting $v_0/v_s = f(I)$, where v_0 is the initial rate in the absence of inhibitor and v_s the steady-state rate in the presence of inhibitor. K_i values can be calculated from the slope of the resulting straight line given by $K_m/((K_m + [S])\ K_i)$. The rate of the non-enzymatic hydrolysis of the **S2d** was always measured and subtracted.

Protein purification and crystallography

The *Actinomadura* R39 DD-peptidase was produced as described.[6] Crystals were grown at 20°C by hanging drop vapor diffusion. Crystals were obtained by mixing 4µL of a 25 mg mL^{-1} protein solution (containing 5mM $MgCl_2$ and 20mM Tris, pH 8), 2µL of well solution (2.0M ammonium sulfate and 0.1M MES, pH 6), 0.5µL of 0.1M $CoCl_2$ solution. Crystals were soaked in 4µL of a solution containing 3.0M ammonium sulfate and 0.1M MES, pH 6, and 0.2µL of **10** 0.1M. during 48 hours and 8µL of the same solution, and 0.2µL of **20** 0.1M during 2 hours.

Data were collected at 100 K on an ADSC Q315r CCD detector at a wavelength of 0.9797 Å on beamline BM30A at the European Synchrotron Radiation Facility (ESRF, Grenoble, France). X-Ray diffraction experiments were carried out under cryogenic conditions (100 K) after transferring the crystals into 45% glycerol, 1.8M ammonium sulfate. Intensities were indexed and integrated using Mosflm.[7] Data were scaled with SCALA of the CCP4 program suite.[8] Refinement was carried out using REFMAC5,[9] TLS,[10] and Coot.[11] The structure of R39 bound to **10** was refined to 2.4 Å with R_{cryst} and R_{free} values of 19.1% and 24.7% respectively. The structure of R39 bound to **20** was refined to 2.8 Å with R_{cryst} and R_{free} values of 21.7% and 26.4% respectively. Data statistics and refinement are given in Table S2, Supporting Information.

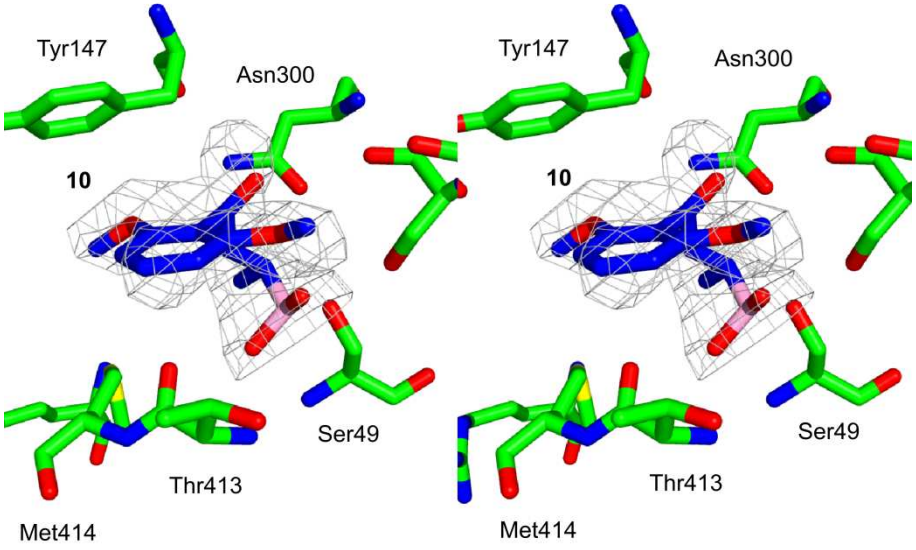
SPROUT modeling

SPROUT modeling programme used the crystal structure of **10** bound to R39 (PDB ID 2XLN). Two, apparently unutilized, hydrophobic pockets in the protein were detected using the site exploration tool. A range of small hydrophobic fragments were docked into these sites using the 'election of functional groups' tool. These were then attached to the original ligand **10** and the new ligands were evaluated using the SPROUT scoring function. This led to the development of second-generation boronic acids **18-27**. A similar approach was

applied to the crystal structure of **20** bound to R39 (PDB ID 2XK1) in the design of the third-generation boronic acids **28-30**.

Figure S1. Stereoview electron density map showing for structures of compounds **10** (blue, PDB ID 2XLN) and **20** (gold, PDB ID 2XK1) bound to R39 (green). The experimental $2F_o$-F_c electron density (contoured to 2.5σ), displayed as grey mesh, is shown for a) **10** and; b) **20**.

a)



b)

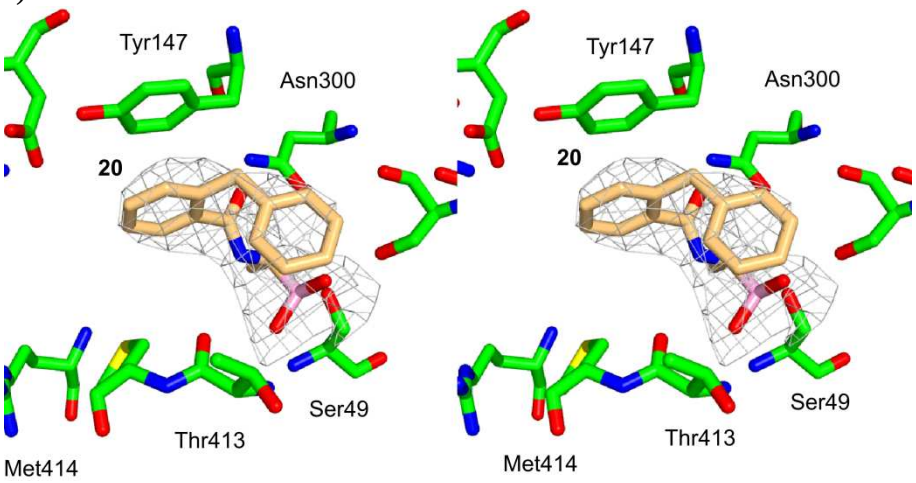


Figure S2. Identification of **20** by computational analysis. Lead compound **10** (SPROUT score = -3.21, observed IC_{50} = 33μM) was 'grown' within Pockets A and B. This process consists of five stages. A scoring system runs with each stage, guiding the 'growth' of the structure, leading to **20** (SPROUT score = -7.04, observed IC_{50} = 1.8μM).

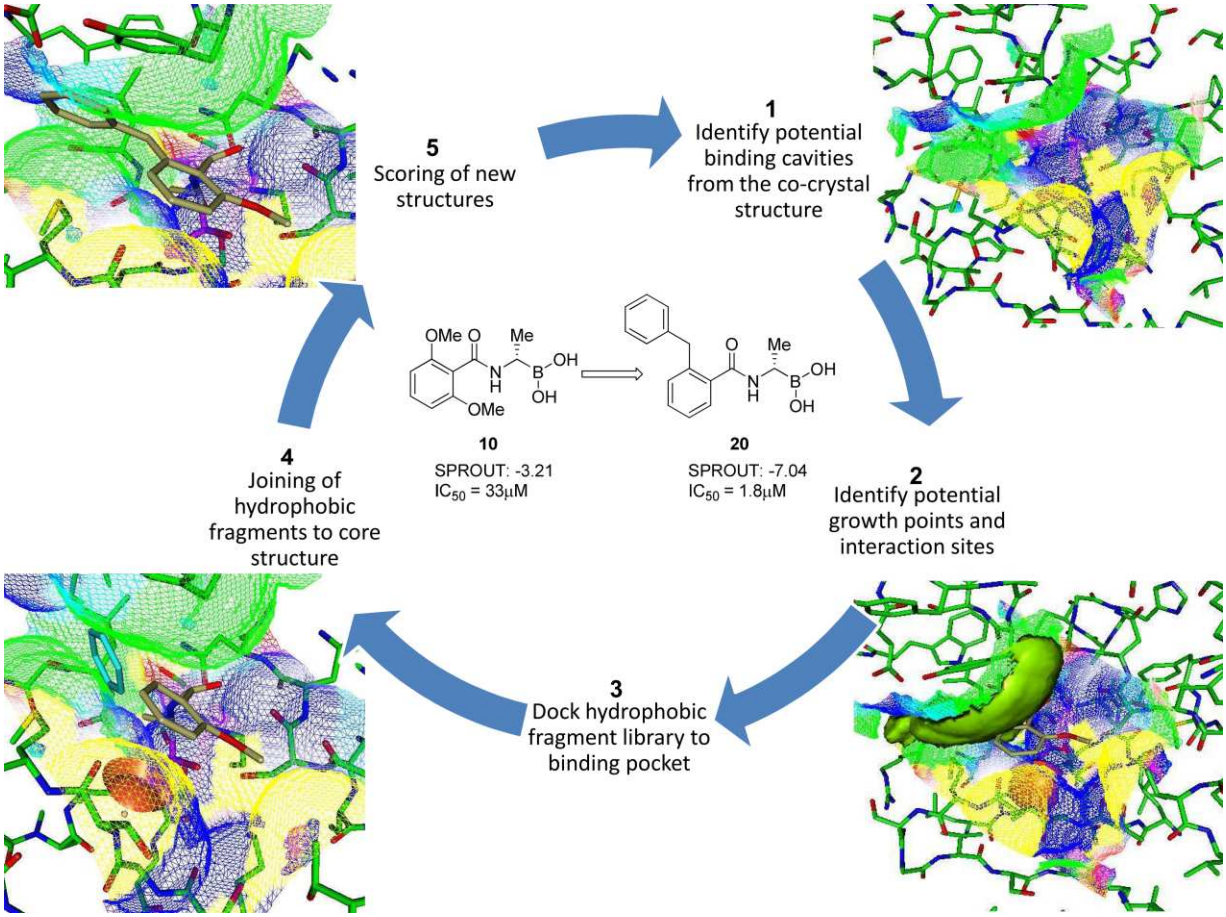
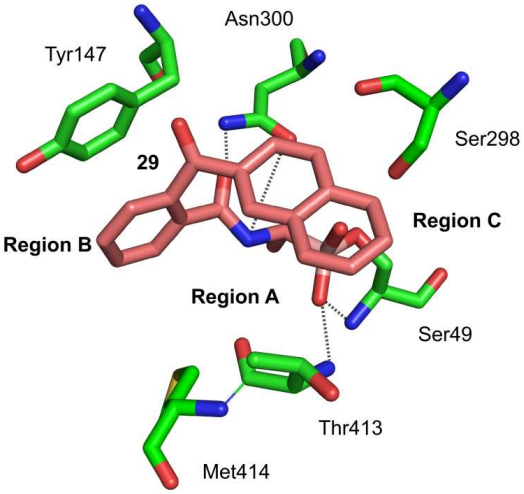
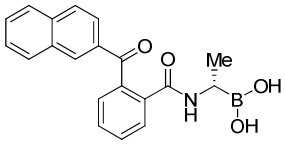


Figure S3. SPROUT modeling of a) **29** and; b) **30**. The most stable predicted conformation is shown. Apparent hydrogen-bonding interactions and hydrophobic regions are identified. Both have favourable SPROUT scores of -7.21 and -7.96, respectively compared to **20** (SPROUT scores = -7.04**)**, hence were predicted to have improved affinities.

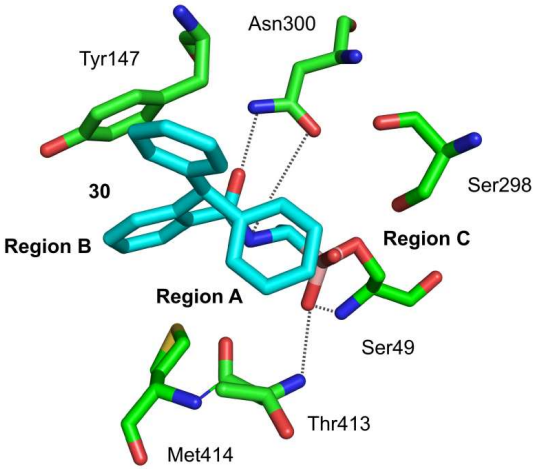
a)

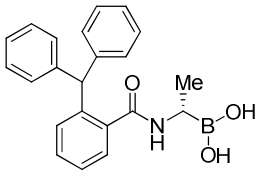




29 SPROUT = -7.21

b)





30 SPROUT = -7.96

Table S1. Inhibitory activity of trifluoromethyl ketones **1-4**, phosphonates **5-9** and boronic acids **10-17** in initial screen (1mM) against R39. Residual activities were determined in triplicate.

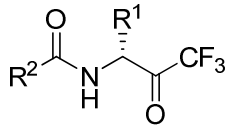
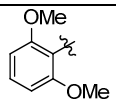
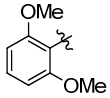
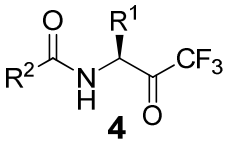
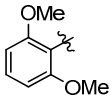
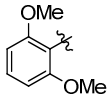
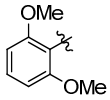
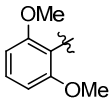
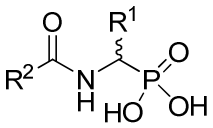
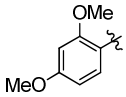
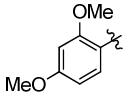
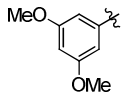
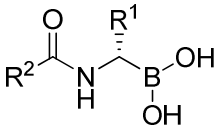
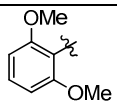
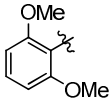
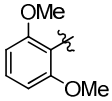
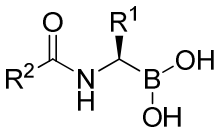
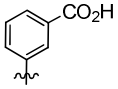
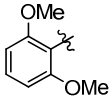
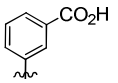
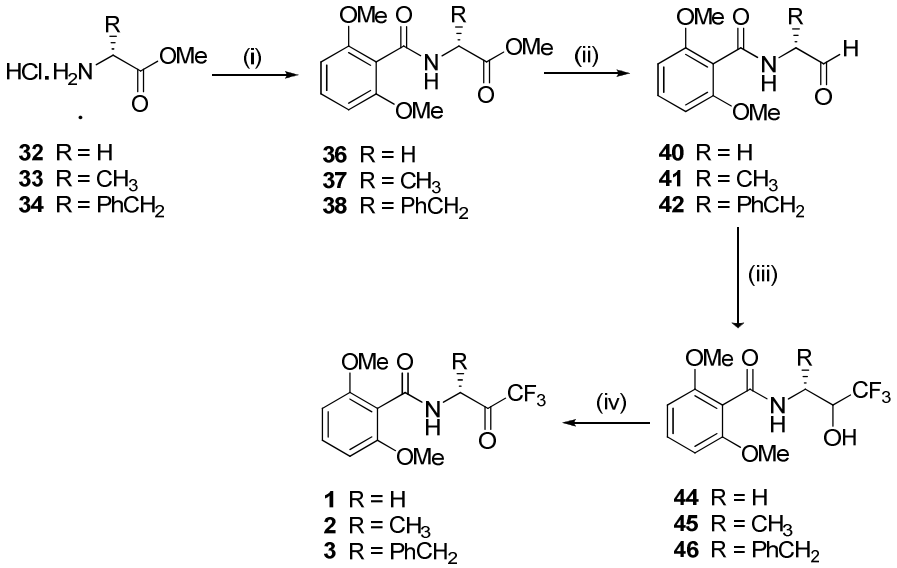
	Compound	R^1	R^2	% Residual activity
 **1-3**	**1**	H		no inhibition
	2	CH_3		no inhibition
 **4**	**3**	$PhCH_2$		no inhibition
	4	$PhCH_2$		no inhibition
Trifluoromethyl ketones	**5**	H		86 ± 3
	6	CH_3		86 ± 0
 **5-9 Phosphonates**	**7**	H		65 ± 1
	8	CH_3		76 ± 1
	9	H		70 ± 3
 **10**	**10**	CH_3		11 ± 1 (IC_{50} = 33μM)
	11	CH_3		10 ± 3 (IC_{50} = 75μM)
	12	*i*Pr		no inhibition
 **11-17 Boronic acids**	**13**	*i*Pr	$PhCH_2$	no inhibition
	14	*i*Pr		no inhibition
	15			no inhibition
	16			70 ± 10
	17	Ph		65 ± 3

Table S2. Crystallographic data and refinement statistics for structures PDB ID 2XLN and PDB ID 2XK1.

Compound	**10**	**20**
PDB code	**2XLN**	**2XK1**
Space group	$P2_1$	C2
Cell dimensions (Å,°)		a=154.9, b=92.3, c=143.8, β=92.25
Resolution range (Å)[a]	33.5-2.4 (2.53-2.4)	38.8-2.8 (2.95-2.8)
No. of unique reflections	77046	49784
Rmerge (%)[a,b]	9.6 (52.6)	8.4 (43.2)
Redundancy [a]	7.0 (6.7)	3.5 (3.5)
Completeness (%)[a]	99.6 (99.5)	99.4 (99.5)
<I>/<σI> [a]	18.1 (3.6)	12.7 (2.6)
Refinement:		
Resolution range	33.3-2.4	27.5–2.8
No. of non-hydrogen protein atoms	13394	13390
No. of water molecules	816	168
R cryst (%)	19.1	21.7
R free (%)	24.7	26.4
RMS deviations from ideal stereochemestry		
bond lengths (Å)	0.008	0.008
bond angles (°)	1.15	1.16
Mean B factor (all atoms) ($Å^2$)	24.8	48.7
Mean B factor (ligand) ($Å^2$)	36.8	57.7
Ramachandran plot:		
most favoured region (%)	91.1	85.5
additionally allowed regions (%)	8.1	13.6
generously allowed regions (%)	0.8	0.8
disallowed regions (%)	0	0.1

[a] Statistics for the highest resolution shell are given in parentheses.
[b] Rmerge = å | *I*i -*I*m | / å *I*i where *I*i is the intensity of the measured reflection and *I*m is the mean intensity of all symmetry-related reflections. Figures within brackets are for the outer resolution shell.

Scheme S1. Chemical synthesis of α-amido trifluoromethyl ketones **1-3**.



32 R = H
33 R = CH_3
34 R = $PhCH_2$

36 R = H
37 R = CH_3
38 R = $PhCH_2$

40 R = H
41 R = CH_3
42 R = $PhCH_2$

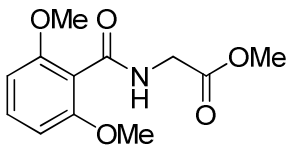
1 R = H
2 R = CH_3
3 R = $PhCH_2$

44 R = H
45 R = CH_3
46 R = $PhCH_2$

Reagents and conditions: (i) 2,6-Dimethoxybenzoyl chloride, DMAP, Et_3N, THF/ DMF, 0°C to RT; (ii) DiBAL-H, THF, -70°C to -60°C for 3 h, then HCl aq., RT; (iii) TMS-CF_3, CsF, THF, Sonication, then HCl aq.; (iv) Dess-Martin periodinane, cat. H_2O, DCM/ THF, 0°C to RT.

General procedure for the preparation of 36-38.

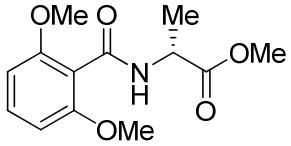
A solution of 2,6-dimethoxybenzoyl chloride (0.88 g, 4.4 mmol, 1.1 equiv.) in THF (5 mL) was added dropwise to a solution of DMAP (4-dimethylaminopyridine, 97 mg, 0.8 mmol, 0.2 equiv.) and Et_3N (1.22 mL, 8.8 mmol, 2.2 equiv.) in THF (10 mL) at 0°C. The resulting white suspension was allowed to stir for 30 mins before a solution of the corresponding amino ester hydrochloride salt (4.0 mmol, 1 equiv.) in DMF (3 mL) was added. The mixture was stir at 0°C for 30 mins, then at room temperature for overnight. The mixture was evaporated *in vacuo*, resuspended in EtOAc and washed with H_2O and 5% $NaHCO_3$. The organic phase was evaporated *in vacuo* and purified by chromatography (EtOAc/ hexane 4:1).



Methyl [(2,6-dimethoxybenzoyl)amino]acetate 36.

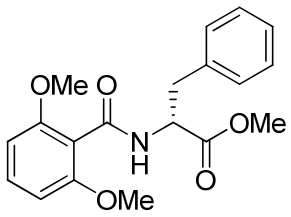
36 is a white solid (85%), mp 104-105°C. IR (nujol) υ/cm^{-1}: 3418 (amide NH), 1741 (ester CO), 1654 (amide CO). ^1H NMR (500 MHz, $CDCl_3$) δ 3.39 (3H, s, CO_2CH_3), 3.45 (6H, s,

OCH_3 x 2), 3.84 (2H, d, *J* = 5.4 Hz, CH_2), 6.24 (2H, d, *J* = 8.4 Hz, H3' and H5'), 6.79 (1H, br t, *J* = 5.2 Hz, NH), 6.93 (1H, t, *J* = 8.4 Hz, H4'). ^{13}C NMR (500 MHz, $CDCl_3$) δ 42.3 (CHB), 52.6 (CO_2CH_3), 56.4 (OCH_3 x 2), 105.3 (C3' and C5'), 116.4 (C2' and C6'), 132.4 (C4'), 159.0 (C1'), 169.4 (CO_2CH_3), 171.6 (CONH). HRMS (ESI, positive ion) $C_{12}H_{15}NNaO_5$ requires $[M+Na]^+$ 276.0842; Found 276.0843.



Methyl (2*R*)-2-[(2,6-dimethoxybenzoyl)amino]propanoate 37.

37 is a white solid (81%), mp 118-120°C. IR (nujol) υ/cm^{-1}: 3325 (amide NH), 1740 (ester CO), 1650 (amide CO). ^{1}H NMR (500 MHz, CD_3OD) δ 1.45 (3H, d, *J* = 7.1 Hz, CH_3), 3.77 (3H, s, CO_2CH_3), 3.83 (6H, s, OCH_3 x 2), 4.64 (1H, q, *J* = 7.1 Hz, CH), 6.69 (2H, d, *J* = 8.4 Hz, H3' and H5'), 7.34 (1H, t, *J* = 8.4 Hz, H4'). ^{13}C NMR (500 MHz, CD_3OD) δ 17.7 (CH_3), 48.2 (CHB), 52.8 (OCH_3 x 2), 56.7 (CO_2CH_3), 105.4 (C3' and C5'), 116.6 (C2' and C6'), 132.3 (C4'), 158.9 (C1'), 168.7 (CO_2CH_3), 174.6 (CONH). HRMS (ESI, positive ion) $C_{13}H_{18}NO_5$ requires $[M+H]^+$ 268.1179; Found 268.1179.

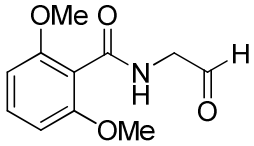


methyl (2*S*)-2-[(2,6-dimethoxybenzoyl)amino]-3-phenylpropanoate 38.

38 is a white solid (84%), mp 113-115°C. IR (nujol) υ/cm^{-1}: 3423 (amide NH), 1739 (ester CO), 1655 (amide CO). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.22 (1H, dd, *J* = 13.8, 5.1 Hz, CH_2), 3.35 (1H, dd, *J* = 13.8, 5.1 Hz, CH_2), 3.72 (3H, s, CO_2CH_3), 3.80 (6H, s, OCH_3 x 2), 5.13-5.18 (1H, m, CH), 6.37 (1H, br d, *J* = 7.2 Hz, NH), 6.55 (2H, d, *J* = 8.5 Hz, H3' and H5'), 7.20-7.29 (6H, m, phenyl-H and H4'). ^{13}C NMR (500 MHz, $CDCl_3$) δ 37.9 (CH_2), 52.3 (CO_2CH_3), 53.6 (CHB), 55.9 (OCH_3 x 2), 104.1 (C3' and C5'), 115.3 (C2' and C6'), 127.0, 128.4, 129.7, 131.0, 16.2, 157.6 (C1') 165.2 (CO_2CH_3), 171.8 (CONH). HRMS (ESI, positive ion) $C_{19}H_{22}NO_5$ requires $[M+H]^+$ 344.1492; Found 344.1493.

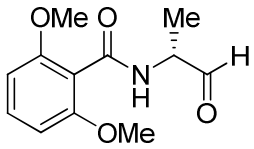
General procedure for the preparation of 40-42.

A solution of DIBAL-H (1M in THF, 18.00 mL, 1.8 mmol, 2 equiv.) was added dropwise to a solution of the above ester (0.9 mmol, 1 equiv.) in anhydrous THF (10 mL) at -70°C and resulting solution was stir at -60°C for 3 h. HCl aq. (1M, 10 mL) was then added under vigorous stirring and the mixture was allowed to warm to room temperature. The mixture was extracted with DCM, dried ($MgSO_4$), evaporated *in vacuo* and purified by chromatography (hexane/ THF/ DCM 2:1:1).



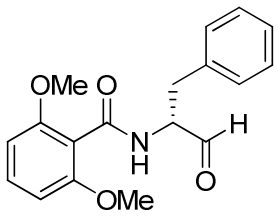
2,6-Dimethoxy-*N*-(2-oxoethyl)benzamide 40.

40 is a pale yellow oil (67%). IR (nujol) υ/cm^{-1}: 3425 (amide NH), 1731 (aldehyde CO), 1643 (amide CO). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.74 (6H, s, OCH_3 x 2), 4.28 (2H, d, J = 5.1 Hz, CH_2), 6.50 (2H, d, J = 8.4 Hz, H3' and H5'), 6.72 (1H, br s, NH), 7.21 (1H, t, J = 8.4 Hz, H4'), 9.66 (1H, s, CHO). ^{13}C NMR (500 MHz, $CDCl_3$) δ 55.0 (CHB), 56.5 (OCH_3 x 2), 104.0 (C3' and C5'), 114.7 (C2' and C6'), 131.1 (C4'), 157.7 (C1'), 165.9 (CONH), 199.3 (CHO). HRMS (ESI, positive ion) $C_{11}H_{14}NO_4$ requires $[M+H]^+$ 224.0923; Found 224.0922.



2,6-Dimethoxy-*N*-[(2*R*)-1-oxopropan-2-yl]benzamide 41.

41 is a white solid (66%), mp 130-132°C. IR (nujol) υ/cm^{-1}: 3424 (amide NH), 1732 (aldehyde CO), 1643 (amide CO). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.46 (3H, d, J = 7.3 Hz, CH_3), 3.82 (6H, s, OCH_3 x 2), 4.71-4.77 (1H, m, CH), 6.37 (1H, br s, NH), 6.57 (2H, d, J = 8.3 Hz, H3' and H5'), 7.29 (1H, t, J = 8.3 Hz, H4'), 9.67 (1H, s, CHO). ^{13}C NMR (500 MHz, $CDCl_3$) δ 14.6 (CH_3), 54.9 (CHB), 56.1 (OCH_3 x 2), 104.1 (C3' and C5'), 114.8 (C2' and C6'), 131.0 (C4'), 157.7 (C1'), 165.9 (CONH), 199.7 (CHO). HRMS (ESI, positive ion) $C_{12}H_{16}NO_4$ requires $[M+H]^+$ 238.1074; Found 238.1070.

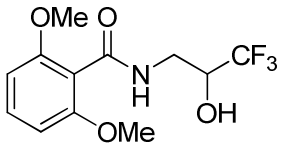


2,6-Dimethoxy-*N*-[(2*R*)-1-oxo-3-phenylpropan-2-yl]benzamide 42.

42 is a white solid (63%), mp 148-150°C. IR (nujol) υ/cm^{-1}: 3360 (amide NH), 1734 (aldehyde CO), 1644 (amide CO). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.32 (2H, d, *J* = 6.2 Hz, CH_2), 3.79 (6H, s, OCH_3 x 2), 4.90-4.94 (1H, m, CH), 6.37 (1H, br s, NH), 6.56 (2H, d, *J* = 8.6 Hz, H3' and H5'), 7.26-7.31 (6H, m, phenyl-H and H4'), 9.73 (1H, s, CHO). ^{13}C NMR (500 MHz, $CDCl_3$) δ 35.1 (CH_2), 55.9 (OCH_3 x 2), 60.0 (CHB), 104.1 (C3' and C5'), 114.8 (C2' and C6'), 126.9, 128.7, 129.7, 131.0 (C4'), 135.9, 157.7 (C1'), 165.9 (CONH), 199.2 (CHO). HRMS (ESI, positive ion) $C_{18}H_{20}NO_4$ requires $[M+H]^+$ 314.1387; Found 314.1387.

General procedure for the preparation of 44-46.

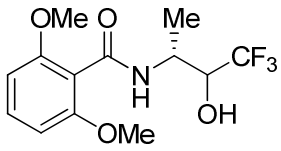
To a solution of the above aldehyde (3.0 mmol, 1 equiv.) in anhydrous THF (5 mL) was added trimethyl(trifluoromethyl)silane (0.60 mL, 3.9 mmol, 1.3 equiv.) and CsF (5 mg, 0.03 mmol, 0.01 equiv). The suspension was sonicated for 30 mins to initiate the reaction, which was indicated by the formation of a yellow colouration. The mixture was stirred at room temperature for 30 mins, HCl aq. (1M, 5 mL) was then added and the mixture allowed to stir for another 10 mins. The resulting mixture was extracted with EtOAc, washed (sat. $NaHCO_3$, brine), dried ($MgSO_4$), evaporated *in vacuo* and purified by chromatography (EtOAc/ hexane 1:1).



2,6-Dimethoxy-*N*-(3,3,3-trifluoro-2-hydroxypropyl)benzamide 44.

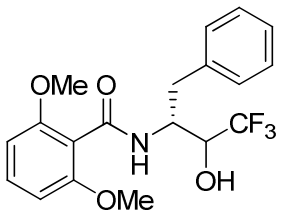
44 is a pale yellow oil (52%). IR (nujol) υ/cm^{-1}: 3235-3368 (amide NH and OH), 1640 (amide CO). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.80 (6H, s, OCH_3 x 2), 4.18-4.24 (1H, m, C*H*OH), 4.35-4.40 (2H, m, CH_2), 6.36 (1H, br s, NH), 6.55 (2H, d, *J* = 8.6 Hz, H3' and H5'), 7.28 (1H, t, *J* = 8.6 Hz, H4'). ^{13}C NMR (500 MHz, $CDCl_3$) δ 48.0 (CHB), 56.4 (OCH_3 x 2), 72.1 (CHOH), 105.0 (C3' and C5'), 117.0 (C2' and C6'), 132.1 (C4'), 158.9 (C1'), 168.5

(CONH). HRMS (ESI, positive ion) $C_{12}H_{13}F_3NO_4$ requires $[M+H]^+$ 292.0797; Found 292.0797.



2,6-Dimethoxy-*N*-[(2*R*)-4,4,4-trifluoro-3-hydroxybutan-2-yl]benzamide 45.

45 is a white solid (64%), mp 148-150°C. IR (nujol) υ/cm^{-1}: 3215-3425 (amide NH and OH), 1641 (amide CO). ^{1}H NMR (500 MHz, CD_3OD) δ 1.34 (3H, d, *J* = 7.0 Hz, CH_3), 3.82 (6H, s, OCH_3 x 2), 4.04-4.10 (1H, m, C*H*OH), 4.39-4.46 (1H, m, CH), 6.68 (2H, d, *J* = 8.3 Hz, H3' and H5'), 7.33 (1H, t, *J* = 8.3 Hz, H4'). ^{13}C NMR (500 MHz, CD_3OD) δ 17.4 (CH_3), 46.9 (CHB), 56.4 (OCH_3 x 2), 72.3 (CHOH), 105.1 (C3' and C5'), 116.9 (C2' and C6'), 132.3 (C4'), 158.9 (C1'), 168.4 (CONH). HRMS (ESI, positive ion) $C_{13}H_{17}F_3NO_4$ requires $[M+H]^+$ 308.1104; Found 308.1102.



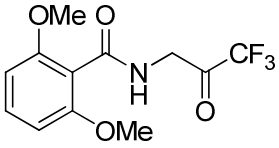
2,6-Dimethoxy-*N*-[(2*R*)-4,4,4-trifluoro-3-hydroxy-1-phenylbutan-2-yl]benzamide 46.

46 is a white solid (91%), mp 143-145°C. IR (nujol) υ/cm^{-1}: 3176-3418 (amide NH and OH), 1638 (amide CO). ^{1}H NMR (500 MHz, CD_3OD) δ 2.99 (1H, dd, *J* = 14.5, 2.9 Hz, CH_2), 3.12 (1H, dd, *J* = 14.5, 2.9 Hz, CH_2), 3.71 (6H, s, OCH_3 x 2), 4.13-4.19 (1H, m, C*H*OH), 4.56-4.61 (1H, m, CH), 6.62 (2H, d, *J* = 8.3 Hz, H3' and H5'), 7.21-7.37 (6H, m, phenyl-H and H4'). ^{13}C NMR (500 MHz, CD_3OD) δ 35.4 (CH_2), 52.0 (CHB), 56.4 (OCH_3 x 2), 72.3 (CHOH), 105.0 (C3' and C5'), 117.0 (C2' and C6'), 127.4, 129.8, 130.8, 132.0 (C4'), 139.5, 158.8 (C1'), 168.8 (CONH). HRMS (ESI, positive ion) $C_{19}H_{18}F_3NNaO_4$ requires $[M+Na]^+$ 404.1080; Found 404.1088.

General procedure for the preparation of 1-3.

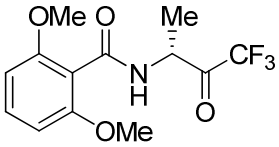
To a solution of the above trifluoromethyl alcohol (4.6 mmol, 1 equiv.) in anhydrous DCM/ THF (4:1, 30 mL) at 0^{o}C was added Dess-Martin periodinane (2.30 g, 5.4 mmol, 1.2 equiv.) and H_2O (0.1 mL in 10 mL DCM, 1.2 equiv.) and the resulting suspension was allowed to stir

at 0°C for 30 mins, then at room temperature for overnight. The mixture was washed with a mixture of NaS_2O_3 (1M) and $NaHCO_3$ sat. (1:1). The DCM layer was separated and washed (H_2O, brine), dried ($MgSO_4$), evaporated *in vacuo* and purified by chromatography (EtOAc/ hexane 4:1).



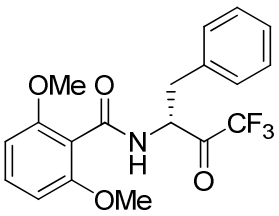
2,6-Dimethoxy-*N*-(3,3,3-trifluoro-2-oxopropyl)benzamide 1.

1 is a pale yellow oil (26%). IR (nujol) υ/cm^{-1}: 3420 (amide NH), 1754 (ketone CO), 1635 (amide CO). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.81-3.84 (2H, m, CH_2), 3.84 (6H, s, OCH_3 x 2), 6.46 (1H, br s, NH), 6.60 (2H, d, *J* = 8.4 Hz, H3' and H5'), 7.33 (1H, t, *J* = 8.4 Hz, H4'). ^{13}C NMR (500 MHz, $CDCl_3$) δ 43.1 (CHB), 56.5 (OCH_3 x 2), 105.4 (C3' and C5'), 116.6 (C2' and C6'), 132.3 (C4'), 158.9 (C1'), 163.5 (*C*OCF_3), 170.2 (CONH). HRMS (ESI, positive ion) $C_{12}H_{13}F_3NO_4$ requires $[M+H]^+$ 292.0791; Found 292.0791.



2,6-Dimethoxy-*N*-[(2*R*)-4,4,4-trifluoro-3-oxobutan-2-yl]benzamide 2.

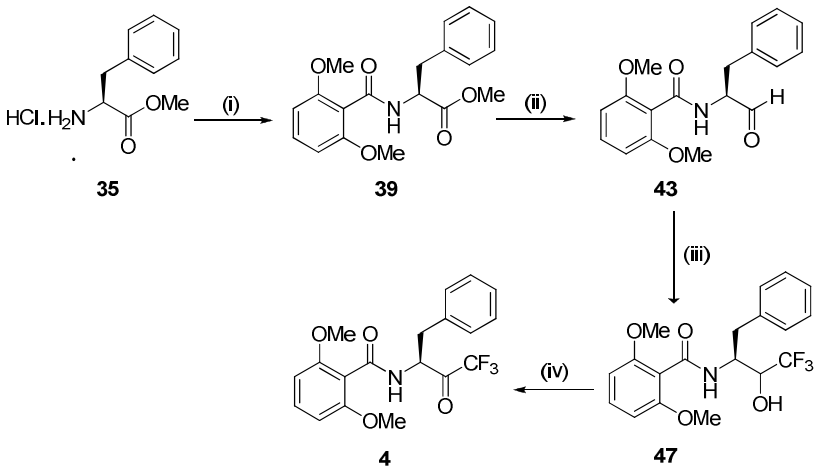
2 is a white solid (31%), mp 150-151°C. IR (nujol) υ/cm^{-1}: 3418 (amide NH), 1753 (ketone CO), 1636 (amide CO). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.56 (3H, d, *J* = 7.3 Hz, CH_3), 3.82 (6H, s, OCH_3 x 2), 5.26-5.33 (1H, m, CH), 6.37 (1H, br s, NH), 6.57 (2H, d, *J* = 8.4 Hz, H3' and H5'), 7.30 (1H, t, *J* = 8.4 Hz, H4'). ^{13}C NMR (500 MHz, $CDCl_3$) δ 16.9 (CH_3), 50.3 (CHB), 56.0 (OCH_3 x 2), 104.0 (C3' and C5'), 114.0 (C2' and C6'), 131.3 (C4'), 157.4 (C1'), 163.5 (*C*OCF_3), 168.4 (CONH). HRMS (ESI, positive ion) $C_{13}H_{15}F_3NO_4$ requires $[M+H]^+$ 306.0948; Found 306.0947.



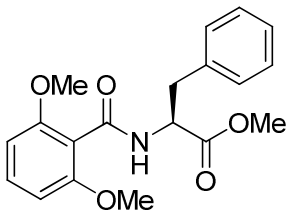
2,6-Dimethoxy-*N*-[(2*R*)-4,4,4-trifluoro-3-oxo-1-phenylbutan-2-yl]benzamide 3.

3 is a white solid (33%), mp 147-149°C. IR (nujol) υ/cm^{-1}: 3425 (amide NH), 1754 (ketone CO), 1635 (amide CO). ^{1}H NMR (500 MHz, CD_3OD) δ 3.15 (1H, dd, *J* = 14.6, 2.7 Hz, CH_2), 3.27 (1H, dd, *J* = 14.6, 2.7 Hz, CH_2), 3.71 (6H, s, OCH_3 x 2), 4.64-4.73 (1H, m, CH), 6.64 (2H, d, *J* = 8.4 Hz, H3' and H5'), 7.26-7.34 (6H, m, phenyl-H and H4'). ^{13}C NMR (500 MHz, CD_3OD) δ 35.6 (CH_2), 54.7 (CHB), 56.7 (OCH_3 x 2), 105.1 (C3' and C5'), 116.6 (C2' and C6'), 127.3, 129.3, 130.5, 132.2 (C4'), 139.6, 158.4 (C1'), 163.6 (*C*OCF_3), 169.6 (CONH). HRMS (ESI, positive ion) $C_{19}H_{21}F_3NO_4$ requires $[M+H]^+$ 384.1417; Found 384.1416.

Scheme S2. Chemical synthesis of α-amido trifluoromethyl ketones **4**.



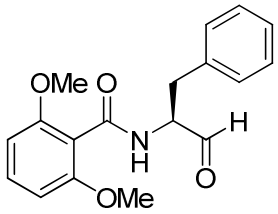
Reagents and conditions: (i) 2,6-Dimethoxybenzoyl chloride, DMAP, Et_3N, THF/ DMF, 0^{o}C to RT; (ii) DiBAL-H, THF, -70^{o}C to -60^{o}C for 3 h, then HCl aq., RT; (iii) TMS-CF_3, CsF, THF, Sonication, then HCl aq.; (iv) Dess-Martin periodinane, cat. H_2O, DCM/ THF, 0^{o}C to RT.



Methyl (2*R*)-2-[(2,6-dimethoxybenzoyl)amino]-3-phenylpropanoate 39.

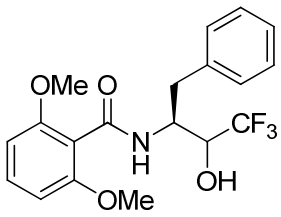
A solution of 2,6-dimethoxybenzoyl chloride (3.60 g, 17.9 mmol, 1.1 equiv.) in THF (10 mL) was added dropwise to a solution of DMAP (4-dimethylaminopyridine, 0.40 g, 3.2 mmol, 0.2 equiv.) and Et_3N (4.98 mL, 35.7 mmol, 2.2 equiv.) in THF (50 mL) at 0^{o}C. The resulting

white suspension was allowed to stir for 30 mins before a solution of L-phenylalanine methyl ester hydrochloride **35** (3.50 g, 16.2 mmol, 1 equiv.) in DMF (10 mL) was added. The mixture was stir at 0°C for 30 mins, then at room temperature for overnight. The mixture was evaporated *in vacuo*, resuspended in EtOAc and washed with H_2O and 5% $NaHCO_3$. The organic phase was evaporated *in vacuo* and purified by chromatography (EtOAc/ hexane 4:1). This gave the above as a pale yellow solid (4.62 g, 83%), mp 114-116°C. IR (nujol) υ/cm^{-1}: 3423 (amide NH), 1739 (ester CO), 1655 (amide CO). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.22 (1H, dd, *J* = 13.8, 5.1 Hz, CH_2), 3.35 (1H, dd, *J* = 13.8, 5.1 Hz, CH_2), 3.72 (3H, s, CO_2CH_3), 3.80 (6H, s, OCH_3 x 2), 5.13-5.18 (1H, m, CH), 6.37 (1H, br d, *J* = 7.2 Hz, NH), 6.55 (2H, d, *J* = 8.5 Hz, H3' and H5'), 7.20-7.29 (6H, m, phenyl-H and H4'). ^{13}C NMR (500 MHz, $CDCl_3$) δ 37.9 (CH_2), 52.3 (CO_2CH_3), 53.6 (CHB), 55.9 (OCH_3 x 2), 104.1 (C3' and C5'), 115.3 (C2' and C6'), 127.0, 128.4, 129.7, 131.0, 16.2, 157.6 (C1') 165.2 (CO_2CH_3), 171.8 (CONH). HRMS (ESI, positive ion) $C_{19}H_{22}NO_5$ requires $[M+H]^+$ 344.1492; Found 344.1497.



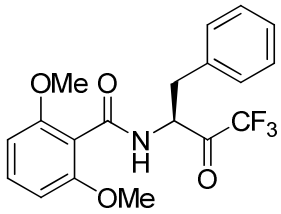
2,6-Dimethoxy-*N*-[(2*S*)-1-oxo-3-phenylpropan-2-yl]benzamide 43.

A solution of DIBAL-H (1M in THF, 24.00 mL, 2.4 mmol, 2 equiv.) was added dropwise to a solution of **39** (0.41 g, 1.2 mmol, 1 equiv.) in anhydrous THF (10 mL) at -70°C and resulting solution was stir at -60°C for 3 h. HCl aq. (1M, 10 mL) was then added under vigorous stirring and the mixture was allowed to warm to room temperature. The mixture was extracted with DCM, dried ($MgSO_4$), evaporated *in vacuo* and purified by chromatography (hexane/ THF/ DCM 2:1:1). This gave the above as a white solid (0.23 g, 62%), mp 148-150°C. IR (nujol) υ/cm^{-1}: 3360 (amide NH), 1734 (aldehyde CO), 1644 (amide CO). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.32 (2H, d, *J* = 6.2 Hz, CH_2), 3.79 (6H, s, OCH_3 x 2), 4.90-4.94 (1H, m, CH), 6.37 (1H, br s, NH), 6.56 (2H, d, *J* = 8.6 Hz, H3' and H5'), 7.26-7.31 (6H, m, phenyl-H and H4'), 9.73 (1H, s, CHO). ^{13}C NMR (500 MHz, $CDCl_3$) δ 35.1 (CH_2), 55.9 (OCH_3 x 2), 60.0 (CHB), 104.1 (C3' and C5'), 114.8 (C2' and C6'), 126.9, 128.7, 129.7, 131.0 (C4'), 135.9, 157.7 (C1'), 165.9 (CONH), 199.2 (CHO). HRMS (ESI, positive ion) $C_{18}H_{20}NO_4$ requires $[M+H]^+$ 314.1387; Found 314.1394.



2,6-Dimethoxy-*N*-[(2*S*)-4,4,4-trifluoro-3-hydroxy-1-phenylbutan-2-yl]benzamide 47.

To a solution of 43 (0.23 g, 0.7 mmol, 1 equiv.) in anhydrous THF (5 mL) was added trimethyl(trifluoromethyl)silane (0.17 mL, 1.1 mmol, 1.5 equiv.) and CsF (11 mg, 0.07 mmol, 0.01 equiv). The suspension was sonicated for 30 mins to initiate the reaction, which was indicated by the formation of a yellow colouration. The mixture was stirred at room temperature for 30 mins, HCl aq. (1M, 5 mL) was then added and the mixture allowed to stir for another 10 mins. The resulting mixture was extracted with EtOAc, washed (sat. $NaHCO_3$, brine), dried ($MgSO_4$), evaporated *in vacuo* and purified by chromatography (EtOAc/ hexane 1:1). This gave the above as a white solid (0.27 g, 96%), mp 144-146°C. IR (nujol) υ/cm^{-1}: 3176-3418 (amide NH and OH), 1638 (amide CO). ^{1}H NMR (500 MHz, CD_3OD) δ 2.99 (1H, dd, J = 14.5, 2.9 Hz, CH_2), 3.12 (1H, dd, J = 14.5, 2.9 Hz, CH_2), 3.71 (6H, s, OCH_3 x 2), 4.13-4.19 (1H, m, C*H*OH), 4.56-4.61 (1H, m, CH), 6.62 (2H, d, J = 8.3 Hz, H3' and H5'), 7.21-7.37 (6H, m, phenyl-H and H4'). ^{13}C NMR (500 MHz, CD_3OD) δ 35.4 (CH_2), 52.0 (CHB), 56.4 (OCH_3 x 2), 72.3 (CHOH), 105.0 (C3' and C5'), 117.0 (C2' and C6'), 127.4, 129.8, 130.8, 132.0 (C4'), 139.5, 158.8 (C1'), 168.8 (CONH). HRMS (ESI, positive ion) $C_{19}H_{18}F_3NNaO_4$ requires $[M+Na]^+$ 404.1080; Found 404.1079.

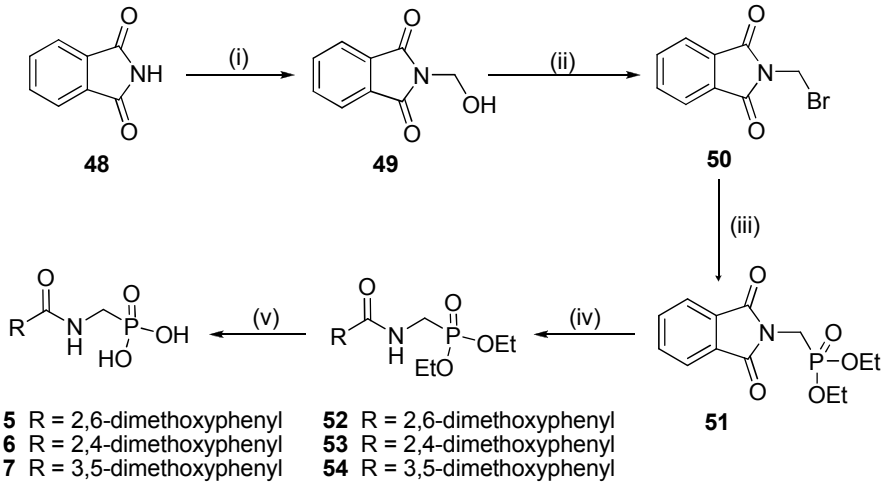


2,6-Dimethoxy-*N*-[(2*S*)-4,4,4-trifluoro-3-oxo-1-phenylbutan-2-yl]benzamide 4.

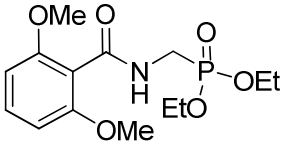
To a solution of **47** (80 mg, 0.2 mmol, 1 equiv.) in anhydrous DCM (20 mL) at 0^{o}C was added Dess-Martin periodinane (0.13 g, 0.3 mmol, 1.5 equiv.) and H_2O (5.6 μL in 1 mL DCM, 1.5 equiv.) and the resulting suspension was allowed to stir at 0^{o}C for 30 mins, then at room temperature for overnight. The mixture was washed with a mixture of NaS_2O_3 (1M) and $NaHCO_3$ sat. (1:1). The DCM layer was separated and washed (H_2O, brine), dried ($MgSO_4$), evaporated *in vacuo* and purified by chromatography (EtOAc/ hexane 4:1). This gave the above as a white solid (24 mg, 30%), mp 148-149°C. IR (nujol) υ/cm^{-1}: 3425 (amide

NH), 1754 (ketone CO), 1635 (amide CO). ^{1}H NMR (500 MHz, CD_3OD) δ 3.15 (1H, dd, *J* = 14.6, 2.7 Hz, CH_2), 3.27 (1H, dd, *J* = 14.6, 2.7 Hz, CH_2), 3.71 (6H, s, OCH_3 x 2), 4.64-4.73 (1H, m, CH), 6.64 (2H, d, *J* = 8.4 Hz, H3' and H5'), 7.26-7.34 (6H, m, phenyl-H and H4'). ^{13}C NMR (500 MHz, CD_3OD) δ 35.6 (CH_2), 54.7 (CHB), 56.7 (OCH_3 x 2), 105.1 (C3' and C5'), 116.6 (C2' and C6'), 127.3, 129.3, 130.5, 132.2 (C4'), 139.6, 158.4 (C1'), 163.6 (*C*OCF_3), 169.6 (CONH). HRMS (ESI, positive ion) $C_{19}H_{21}F_3NO_4$ requires $[M+H]^+$ 384.1417; Found 384.1417.

Scheme S3. Chemical synthesis of glycine phosphonates **5-7**.



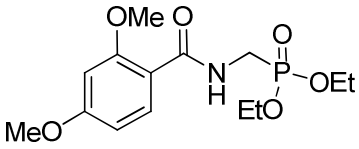
Reagents and conditions: (i) 20% Formaldehyde, reflux 1 h[12]; (ii) 30% HBr/ AcOH, 0°C, then RT 1 h[13]; (iii) $P(OEt)_3$, 90°C 1 h, then 110°C overnight[14]; (iv) hydrazine hydrate, EtOH, RT overnight, then corresponding benzoic acid, Et_3N, DPPA, DMF, 0^{o}C to RT; (v) trimethylsilyl bromide, DCM, RT overnight, then MeOH, 40°C 4 h.



Diethyl ((2,6-dimethoxybezamido)methyl)phosphonate 52.

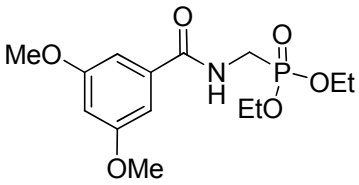
To a solution of **51**[14] (2.68 g, 9.0 mmol) in absolute EtOH (30 mL) was added hydrazine hydrate (0.54 g, 10.8 mmol) and the mixture was stirred at room temperature for overnight. It was then refluxed for 1 h and left to cool to room temperature before being placed in a refrigerator for several hours. The precipitate thus formed was removed by suction filtration. The filtrate was evaporated *in vacuo* and the resulting residue was dissolved in DMF at 0^{o}C. To this solution was added 2,6-dimethoxybenzoic acid (1.66 g, 9.0 mmol), Et_3N (2.80 mL,

20.0 mmol) and DPPA (diphenylphosphoryl azide, 2.10 mL, 9.5 mmol) and the mixture was stir at room temperature for overnight. It was then evaporated *in vacuo* and the resulting residue was resuspended in DCM. The organic phase was extracted with 1M HCl aq., washed (sat. $NaHCO_3$, brine), dried (Na_2SO_4), evaporated *in vacuo* and purified by chromatography (MeOH/ DCM) to give the above as a white solid (1.87 g, 63%), mp 98-102°C. Elem. Anal.: calcd for $C_{14}H_{21}NO_6P$ C, 50.75 %; H, 6.69%; N, 4.23%; obtained C, 50.76 %; H, 6.91%; N, 4.22%. IR (nujol) υ/cm^{-1}: 3256, 2984, 1660, 1598, 1255, 1111. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (6H, t, *J* = 7.1 Hz,), 3.08 (6H, s), 3.92 (2H, dd, *J* = 12.3, 5.9 Hz), 4.20 (4H, dd, *J* = 14.6, 7.3 Hz, 4H), 6.11 (1H, br s), 6.56 (2H, d, *J* = 8.4 Hz), 7.28 (1H, t, *J* = 8.4 Hz). ^{31}P NMR (300 MHz, $CDCl_3$) δ 23.77; HRMS (ESI, negative ion) $C_{14}H_{21}NO_6P$ $[M–H]^-$ requires 330.1107; found 330.1111.



Diethyl ((2,4-dimethoxybenzamido)methyl)phosphonate 53.

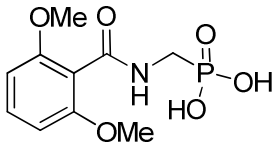
Same procedure as above: **53** is a pale yellow solid (67%), mp 77-82°C. Elem. Anal.: calcd for $C_{14}H_{21}NO_6P$ C, 50.75 %; H, 6.69%; N, 4.23%; obtained C, 50.92 %; H, 6.76%; N, 4.19%. IR (nujol) υ/cm^{-1}: 3389, 2976, 1654, 1543. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (6H, t, *J* = 7.1 Hz), 3.84 (3H, s), 3.93 (2H, dd, *J* = 12.3, 5.6 Hz), 3.95 (3H, s), 4.23-4.11 (4H, m), 6.48 (1H, d, *J* = 2.2 Hz), 6.59 (1H, dd, *J* = 8.8, 2.3 Hz), 8.07 (1H, d, *J* = 2.9 Hz), 8.15 (1H, d, *J* = 8.8 Hz). ^{31}P NMR (300 MHz, $CDCl_3$) δ 24.74. HRMS (ESI, positive ion) $C_{14}H_{23}NO_6P$ $[M+H]^+$ requires 332.1263; found 332.1252.



Diethyl ((3,5-dimethoxybenzamido)methyl)phosphonate 54.

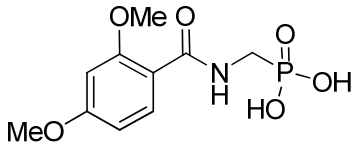
Same procedure as above: **54** is a off-white solid (60%), mp 74-80°C. Elem. Anal.: calcd for $C_{14}H_{21}NO_6P$ C, 50.75 %; H, 6.69%; N, 4.23%; obtained C, 51.06 %; H, 6.88%; N, 4.18%. IR (nujol) υ/cm^{-1}:3256, 2991, 1655, 1596, 1207. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (6H, t, *J* = 7.1), 3.78 (6H, s), 3.88 (2H, dd, *J* = 12.0, 5.9 Hz), 4.13 (4H, m), 6.55 (1H, t, *J* = 2.3 Hz), 6.94

(2H, d, *J* = 2.3 Hz), 7.05 (1H, br s). ^{31}P NMR (300 MHz, $CDCl_3$) δ 23.87. HRMS (ESI, negative ion) $C_{14}H_{23}NO_6P$ $[M–H]^–$ requires 330.1107; found 330.1116.



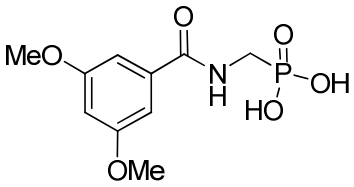
((2,6-Dimethoxybezamido)methyl)phosphonic acid 5.

Compound **52** (0.80 g, 2.4 mmol) was dissolved in anhydrous DCM (20 mL) and treated with trimethylsilyl bromide (1.32 mL, 10.0 mmol) at room temperature for 24 h. The solvent was evaporated *in vacuo*, resuspended in MeOH (10.0 mL) and stirred at 40°C for 4 h, after which it was concentrated *in vacuo* and the product precipitated with Et_2O. The resulting white solid was collected by filtration and freeze dried to give the above as a white solid (0.49 g, 74%), mp 192-195°C. Elem. Anal.: calcd for $C_{10}H_{14}NO_6P$: C, 43.64 %; H, 5.13%; N, 5.09%; obtained C, 43.75%; H, 5.23%; N, 5.02%. IR (nujol) υ/cm^{-1}: 3338, 2932, 2318, 1659, 1596, 1520, 1256, 1111. ^{1}H NMR (300 MHz, d_6-DMSO) δ 3.45 (2H, dd, *J* = 13.0, 5.7 Hz), 3.71 (6H, s), 6.64 (2H, d, *J* = 8.4 Hz), 7.28 (1H, t, *J* = 8.4 Hz), 7.83 (1H, d, *J* = 2.9 Hz). ^{31}P NMR (300 MHz, d_6-DMSO) δ 19.11. HRMS (ESI, negative ion) $C_{10}H_{13}NO_6P$ $[M–H]^–$ requires 274.0481; found 274.0477.



((2,4-Dimethoxybenzamido)methyl)phosphonic acid 6.

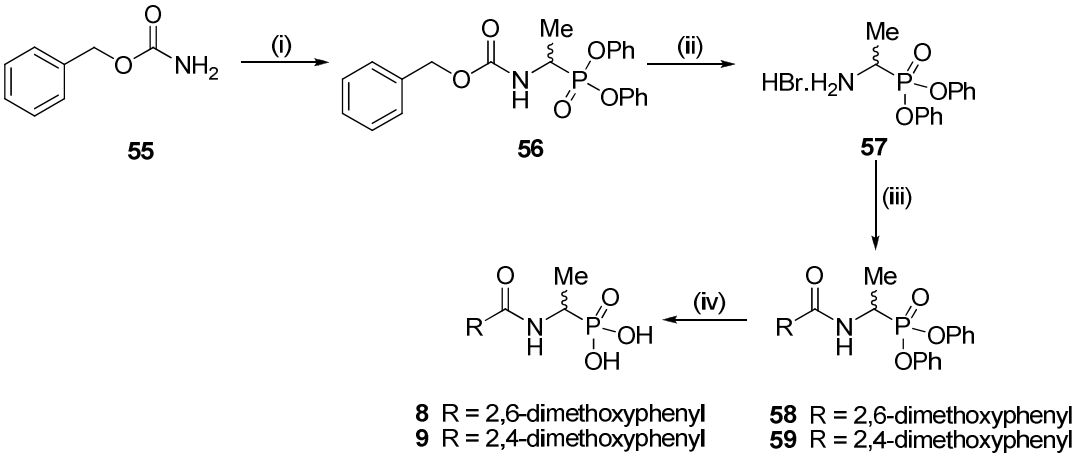
Same procedure as above: **6** is a white solid (84%), mp 198-201°C. Elem. Anal.: calcd for $C_{10}H_{14}NO_6P$: C, 43.64 %; H, 5.13%; N, 5.09%; obtained C, 43.79%; H, 5.27%; N, 5.01%. IR (nujol) υ/cm^{-1}: 3362, 2984, 2256, 1566, 1502, 1209, 1120, 1007. ^{1}H NMR (300 MHz, d_6-DMSO) δ 3.56 (2H, dd, *J* = 12.9, 5.5 Hz), 3.83 (3H, s), 3.93 (3H, s), 6.64-6.69 (2H, m), 7.91 (1H, d, *J* = 8.6 Hz), 8.08 (1H, dd, *J* = 9.8, 5.1 Hz). ^{31}P NMR (300 MHz, d_6-DMSO) δ 19.42. HRMS (ESI, negative ion) $C_{10}H_{13}NO_6P$ $[M–H]^–$ requires 274.0481; found 274.0498.



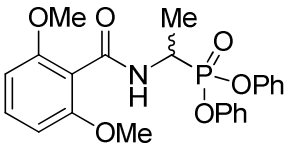
((3,5-Dimethoxybenzamido)methyl)phosphonic acid 7.

Same procedure as above: **7** is a white solid (78%), mp 200-204°C. Elem. Anal.: calcd for $C_{10}H_{14}NO_6P$: C, 43.64 %; H, 5.13%; N, 5.09%; obtained C, 43.79%; H, 5.27%; N, 5.01%. IR (nujol) υ/cm^{-1}: 3345, 2970, 2233, 1578, 1360, 1208, 1168. ^{1}H NMR (300 MHz, d_6-DMSO) δ 3.56 (2H, dd, *J* = 12.1, 6.0 Hz), 3.78 (6H, s), 6.63 (1H, t, *J* = 2.3 Hz), 7.05 (2H, d, *J* = 2.3 Hz), 8.53 (1H, t, *J* = 5.9 Hz). ^{31}P NMR (300 MHz, d_6-DMSO) δ 19.20. HRMS (ESI, negative ion) $C_{10}H_{13}NO_6P$ $[M–H]^–$ requires 274.0481; found 274.0479.

Scheme S4. Chemical synthesis of alanine phosphonates **8**-**9**.



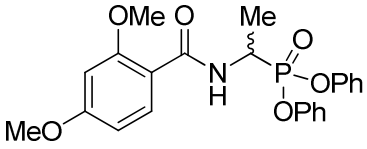
Reagents and conditions: (i) Triphenyl phosphate, acetaldehyde, benzylcarbamate, AcOH, RT 1 h, then 85°C 1h[15]; (ii) 40% HBr/ AcOH, RT 1 h[15]; (iii) Corresponding benzoic acid, Et_3N, DPPA, DMF, 0^{o}C to RT; (iv) 1M NaOH aq., dioxane, RT 2 h.



Diphenyl (1-(2,6-dimethoxybenzamido)ethyl)phosphonate 58.

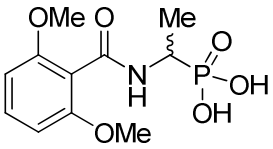
To a solution of 2,6-dimethoxybenzoic acid (1.66 g, 9.0 mmol) and **57**[15] (3.25 g, 9.0 mmol) in DMF at 0^{o}C was added Et_3N (2.80 mL, 20.0 mmol) and DPPA (diphenylphosphoryl azide, 2.10 mL, 9.5 mmol). The reaction mixture was stir at room temperature for overnight, after which it was evaporated *in vacuo* and the resulting residue was resuspended in EtOAc (250

mL). The organic phase was washed (1M HCl aq., sat. $NaHCO_3$, brine), dried (Na_2SO_4), evaporated *in vacuo* and purified by chromatography (EtOAc/ hexane) to give the above as a white solid (2.06 g, 52%), mp 170-173°C. Elem. Anal.: calcd for $C_{23}H_{24}NO_6P$: C, 62.58%; H, 5.48%; N, 3.17%; obtained C, 62.61%; H, 5.48%; N, 3.30%.. IR (nujol) υ/cm^{-1}:3267, 2934, 1665, 1594, 1531, 1473, 1315, 1254, 1113. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.47 (3H, dd, *J* = 18.1, 7.4 Hz), 3.68 (6H, s), 4.73-4.93 (1H, m), 6.68 (2H, d, *J* = 8.4 Hz), 7.17-7.25 (6H, m), 7.31 (1H, t, *J* = 8.4 Hz), 7.35-7.46 (4H, m), 8.74 (1H, d, *J* = 9.2 Hz); ^{31}P NMR (300 MHz, $CDCl_3$) δ 20.22; HRMS (ESI, positive ion) $C_{23}H_{24}NO_6P$ $[M+H]^+$ requires 442.1420; found 442.1411.



Diphenyl (1-(2,4-dimethoxybenzamido)ethyl)phosphonate 59.

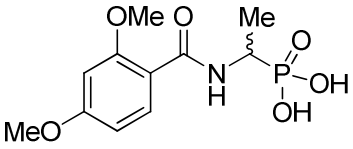
Same procedure as above: **59** is a white solid (55%), mp 158-160°C. Elem. Anal.: calcd for $C_{23}H_{24}NO_6P$ C, 62.58 %; H, 5.48%; N, 3.17%; obtained C, 62.58 %; H, 5.50%; N, 3.26%. IR (nujol) υ/cm^{-1}: 3269, 2936, 1666, 1593, 1533, 1474, 1316, 1254, 1211, 1115. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.66 (3H, dd, *J* = 17.9, 7.3 Hz), 3.82 (6H, s), 5.14 (1H, ddd, *J* = 19.2, 9.8, 7.4 Hz), 6.44 (1H, d, *J* = 8.4 Hz), 6.60 (1H, t, *J* = 2.3 Hz), 6.82 (2H, d, *J* = 2.3 Hz), 7.26 (10H, m). ^{31}P NMR (300 MHz, $CDCl_3$) δ 19.47; HRMS (ESI, positive ion) $C_{23}H_{25}NO_6P$ $[M+H]^+$ requires 442.1420; found 442.1418.



(1-(2,6-Dimethoxybenzamido)ethyl)phosphonic acid 8.

To a solution of **58** (1.77 g, 4.0 mmol) in dioxane (20 mL) was added NaOH aq. (1M, 20.0 mL) and the mixture was stirred at room temperature for 2 h, after which dioxane was removed *in vacuo*. The resulting mixture was diluted with H_2O (15 mL), acidified to pH 6 and washed with DCM. The aqueous phase was then acidified to pH 2 and stored at -10°C for overnight. The crystals thus formed were collected by suction filtration, washed with Et_2O and dried *in vacuo*. This gave the above as colourless crystals (0.75 g, 65%), mp 245-248°C. Elem. Anal.: calcd for $C_{10}H_{14}NO_6P$: C, 45.68 %; H, 5.58%; N, 4.84%; obtained C, 45.57%;

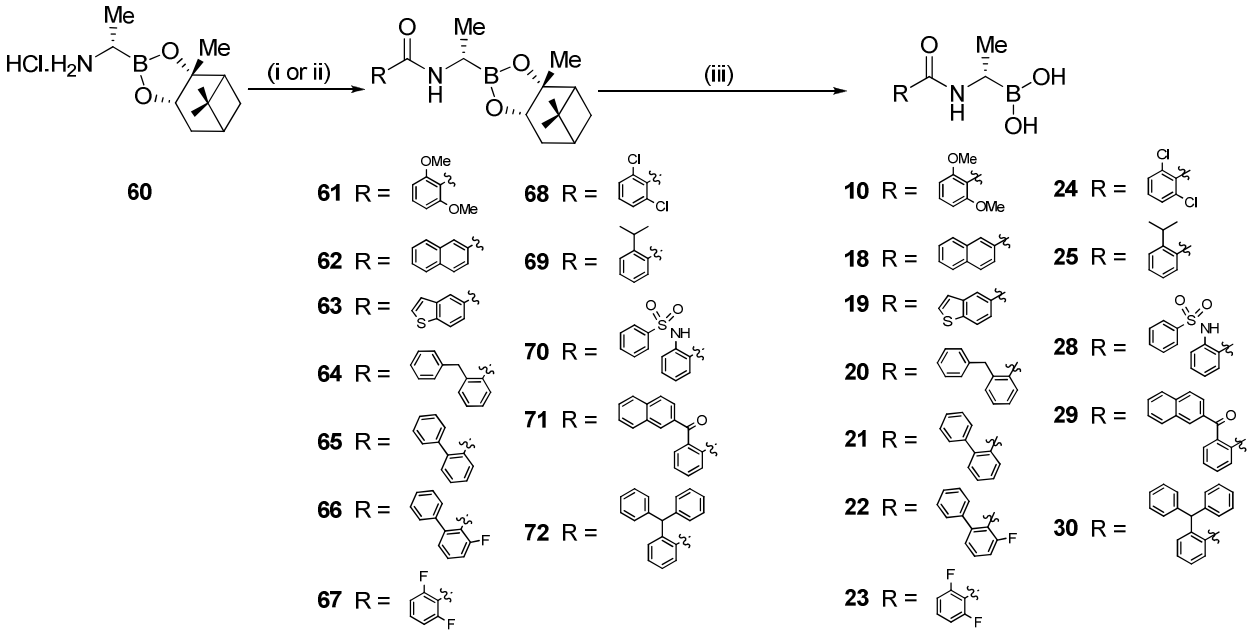
H, 5.58%; N, 4.84%. IR (nujol) υ/cm^{-1}: 3359, 2985, 2943, 2352, 1538, 1346, 1257, 1116. ^{1}H NMR (300 MHz, d_6-DMSO) δ 1.24 (1H, dd, *J* = 15.6, 7.2 Hz), 3.71 (1H, s), 4.12 (1H, ddd, *J* = 16.2, 9.0, 7.3 Hz), 6.64 (1H, d, *J* = 8.4 Hz), 7.27 (1H, dd, *J* = 11.4, 5.3 Hz), 7.53 (1H, dd, *J* = 9.0, 3.2 Hz). ^{31}P NMR (300 MHz, d_6-DMSO) δ 22.65. HRMS (ESI, negative ion) $C_{11}H_{15}NO_6P$ $[M-H]^-$ requires 288.0637; found 288.0639.



(1-(2,4-Dimethoxybenzamido)ethyl)phosphonic acid 9.

Same procedure as above: **9** is a colourless crystals (61%), mp 210-213°C. Elem. Anal.: calcd for $C_{10}H_{14}NO_6P$: C, 45.68 %; H, 5.58%; N, 4.84%; obtained C, 45.57%; H, 5.57%; N, 4.72%. IR (nujol) υ/cm^{-1}: 3379, 2980, 2948, 2676, 2319, 1600, 1376, 1332, 1269, 1210, 1020. ^{1}H NMR (300 MHz, d_6-DMSO) δ 1.27 (3H, dd, *J* = 15.7, 7.2 Hz), 3.92 (3H, s), 3.83 (3H, s), 4.22 (1H, ddd, *J* = 16.2, 8.9, 7.2 Hz), 6.62-6.71 (2H, m), 7.91 (1H, d, *J* = 9.0 Hz), 8.09 (1H, dd, *J* = 8.9, 5.1 Hz). ^{31}P NMR (300 MHz, d_6-DMSO) δ 22.65. HRMS (ESI, negative ion) $C_{11}H_{15}NO_6P$ $[M-H]^-$ requires 288.0637; found 288.0650.

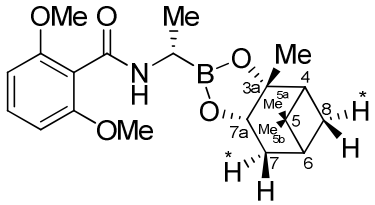
Scheme S5. Chemical synthesis of α-amido boronic acids **10, 18-25, 28-30**.



Reagents and conditions: (i) For compounds **61**, **67**, **68**; acid chlorides, DMAP, Et_3N, THF/ DMF, 0^oC to RT; (ii) For compounds **62-66**, **69-72**; aryl acids, HATU, HOBt, *N*-methylmorpholine, THF/ DMF, 0^oC to RT; (iii) KHF_2, MeOH, then chlorotrimethylsilane, MeCN/ H_2O.

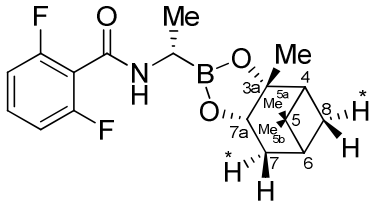
General procedure for the preparation of 61, 67 and 68.

A solution of acid chloride (3.4 mmol, 1.1 equiv.) in anhydrous THF (2 mL) was added dropwise to a mixture of DMAP (75 mg, 0.6 mmol, 0.2 equiv.) and Et_3N (0.95 mL, 6.8 mmol, 2 equiv.) in anhydrous THF (15 mL) at 0 °C. After stirring for 30 min, **60**[16] (0.80 g, 3.1 mmol, 1 equiv.) in anhydrous THF/ DMF (3:5, 8 mL) was added and the resulting suspension was stirred at 0 °C for 30 min, then at room temperature for overnight. It was then evaporated *in vacuo*, resuspended in EtOAc and washed with H_2O and 5% $NaHCO_3$. The organic phase was evaporated *in vacuo* and purified by chromatography (EtOAc/ hexane 3:7).



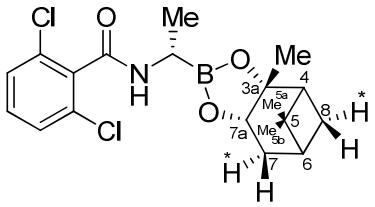
(-)-Pinanediol (*S*)-1-(2,6-dimethoxybenzamido)ethaneboronate 61.

61 is a pale yellow oil (64%). IR (nujol) υ/cm^{-1}: 3282 (amide NH), 1647 (amide CO). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (3H, s, $CH_3$5a), 1.24 (1H, d, *J* = 10.5 Hz, H8), 1.27 (3H, s, $CH_3$5b), 1.37 (3H, s, C*H*$_3$CHB), 1.41 (3H, s, CH_3C3a), 1.82-1.86 (1H, m, H7*), 1.86-1.92 (1H, m, H6), 2.00 (1H, t, *J* = 5.8 Hz, H4), 2.11-2.19 (1H, m, H8*), 2.26-2.36 (1H, m, H7), 3.11-3.20 (1H, m, CHB), 3.80 (6H, s, OCH_3 x 2), 4.23-4.31 (1H, m, H7a), 6.54 (2H, d, *J* = 8.5 Hz, H3' and H5'), 6.73 (1H, br s, NH), 7.29 (1H, t, *J* = 8.5 Hz, H4'). ^{13}C NMR (500 MHz, CDCl3) δ 16.2 (*C*H_3CB), 24.1 ($CH_3$5a), 26.3 (C8), 27.0 ($CH_3$5b), 28.5 (*C*H_3C3a), 35.7 (C7), 38.4 (C5), 39.4 (C6), 51.7 (C4), 69.1 (OCH_3 x 2), 76.6 (C7a), 84.3 (C3a), 128.1 (C3' and C5'), 130.4 (C4'), 139.0 (C2' and C6'), 142.4 (C1'), 170.0 (CONH). HRMS (ESI, positive ion) $C_{21}H_{30}BNNaO_5$ requires $[M+Na]^+$ 410.2109; Found 410.2098.



(-)-Pinanediol (*S*)-1-(2,6-difluorobenzamido)ethaneboronate 67.

67 is a white solid (91%), mp 134-135°C. Anal. ($C_{19}H_{24}BF_2NO_3$) C, H, N. IR (nujol) υ/cm^{-1}: 3283 (amide NH), 1648 (amide CO). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (3H, s, $CH_3$5a), 1.27 (1H, d, *J* = 10.5 Hz, H8), 1.30 (3H, s, $CH_3$5b), 1.36 (3H, d, *J* = 7.1 Hz, C*H*$_3$CHB), 1.43 (3H, s, CH_3C3a), 1.89 (1H, br d, *J* = 15.5 Hz, H7*), 1.89-1.95 (1H, m, H6), 2.07 (1H, t, *J* = 5.3 Hz, H4), 2.20-2.26 (1H, m, H8*), 2.32-2.39 (1H, m, H7), 3.47-3.59 (1H, m, CHB), 4.36 (1H, dd, *J* = 8.9, 1.7 Hz, H7a), 6.29 (1H, br s, NH), 6.92 (1H, d, *J* = 8.1 Hz, H3'), 6.94 (1H, d, *J* = 8.1 Hz, H5'), 7.32-7.39 (1H, m, H4'). ^{13}C NMR (500 MHz, CDCl3) δ 16.6 (*C*H_3CB), 24.0 ($CH_3$5a), 26.3 (C8), 27.1 ($CH_3$5b), 28.6 (*C*H_3C3a), 33.1 (CB), 35.5 (C7), 38.2 (C5), 39.6 (C6), 51.4 (C4), 78.2 (C7a), 86.3 (C3a), 112.0 (C3' and C5'), 131.8 (C4'), 159.2 (C2' and C6'), 160.9 (C1'), 161.3 (CONH). ^{19}F NMR (376 MHz, $CDCl_3$) -111.6. HRMS (ESI, positive ion) $C_{19}H_{24}BF_2NNaO_3$ requires $[M+Na]^+$ 386.1713; Found 386.1710.

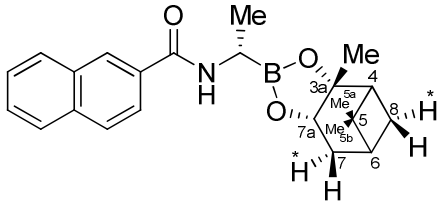


(-)-Pinanediol (*S*)-1-(2,6-dichlorobenzamido)ethaneboronate 68.

68 is a pale yellow oil (84%). IR (nujol) υ/cm^{-1}: 3272 (amide NH), 1639 (amide CO). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (3H, s, $CH_3$5a), 1.30 (1H, d, *J* = 7.07 Hz, H8), 1.34 (3H, s, $CH_3$5b), 1.43 (3H, d, *J* = 7.4 Hz, C*H*$_3$CHB), 1.47 (3H, s, CH_3C3a), 1.91-1.93 (1H, m, H7*), 1.94-1.99 (1H, m, H6), 2.11 (1H, t, *J* = 5.8 Hz, H4), 2.24-2.31 (1H, m, H8*), 2.35-2.43 (1H, m, H7), 3.57-3.65 (1H, m, CHB), 4.41 (1H, dd, *J* = 8.3, 1.8 Hz, H7a), 6.12 (1H, br s, NH), 7.23 (1H, t, *J* = 8.1 Hz, H4'), 7.29 (1H, d, *J* = 8.1 Hz, H3', H5'). ^{13}C NMR (500 MHz, CDCl3) δ 16.5 (*C*H_3CB), 24.0 ($CH_3$5a), 26.3 (C8), 27.1 ($CH_3$5b), 28.6 (*C*H_3C3a), 35.9 (C7), 38.1 (C5), 39.5 (C6), 51.3 (C4), 78.3 (C7a), 86.4 (C3a), 128.0 (C3' and C5'), 130.4 (C4'), 158.3 (C2' and C6'), 164.5 (C1'), 171.1 (CONH). HRMS (ESI, positive ion) $C_{19}H_{24}BCl_2NNaO_3$ requires $[M+Na]^+$ 418.1119; Found 418.1114.

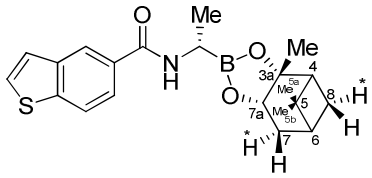
General procedure for the preparation of 62-66, **69-72.**

To a solution of aryl acid (3.7 mmol, 1.2 equiv.), HATU (*O*-(7-Azabenzotriazol-1-yl)-*N*,*N*,*N'*,*N'*-tetramethyluronium hexafluorophosphate) (1.40 g, 3.7 mmol, 1.2 equiv.) and anhydrous HOBt (1-Hydroxybenzotriazole) (0.50 g, 3.7 mmol, 1.2 equiv.) in anhydrous DMF (10 mL) at 0 °C was added *N*-methylmorpholine (1.02 mL, 9.3 mmol, 3 equiv.). After stirring for 10 min, **60**[16] (0.80 g, 3.1 mmol, 1 equiv.) in anhydrous THF/ DMF (3:5, 8 mL) was added and the resulting suspension was stirred at room temperature for overnight. The mixture was then evaporated *in vacuo*, resuspended in EtOAc and washed with 2% citric acid, sat. $NaHCO_3$, H_2O and brine. The organic phase was evaporated *in vacuo* and purified by chromatography (EtOAc/ hexane 1:4). The syntheses of the corresponding ary acids for **70** and **72** have been previously reported in refs. 17 and 18, respectively, while that for **66** and **71** are adapted from refs. 19 and 20, respectively and are described below.



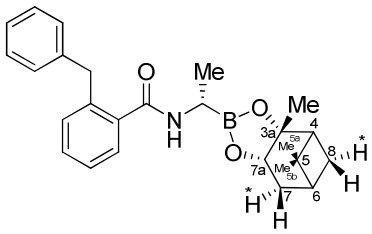
(-)-Pinanediol (*S*)-1-(naphthalene-2-carboxamido)ethaneboronate 62.

62 is a pale yellow oil (56%). IR (nujol) υ/cm^{-1}: 3283 (amide NH), 1648 (amide CO). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.81 (3H, s, $CH_3$5a), 1.00 (3H, s, $CH_3$5b), 1.15 (1H, d, *J* = 11.4 Hz, H8), 1.27 (3H, s, C*H*$_3$CHB), 1.34 (3H, s, CH_3C3a), 1.74-1.83 (1H, br d, *J* = 13.4 Hz, H7*), 1.84-1.93 (1H, m, H6), 2.00 (1H, t, *J* = 5.5 Hz, H4), 2.11-2.17 (1H, m, H8*), 2.24-2.34 (1H, m, H7), 3.16-3.26 (1H, m, CHB), 4.24 (1H, dd, *J* = 8.7, 1.6 Hz, H7a), 5.59 (1H, br s, NH), 7.07 (1H, t, *J* = 8.4 Hz, H4'), 7.16 (1H, d, *J* = 8.4 Hz, H3'), 7.30-7.42 (6H, m, phenyl side chain H and H5'). ^{13}C NMR (500 MHz, CDCl3) δ 16.0 (*C*H_3CB), 24.1 ($CH_3$5a), 26.5 (C8), 27.2 ($CH_3$5b), 28.8 (*C*H_3C3a), 36.1 (C7), 38.2 (C5), 39.9 (C6), 52.0 (C4), 73.5 (C7a), 84.5 (C3a), 127.6, 128.1, 128.8, 129.0 (phenyl side chain C and C5'), 130.0 (C2'), 130.5 (C3'), 130.9 (phenyl side chain C), 131.3 (C4'), 140.1 (C6'), 141.3 (C1'), 171.0 (CONH). HRMS (ESI, positive ion) $C_{23}H_{28}BNNaO_3$ requires $[M+Na]^+$ 400.2054; Found 400.2053.



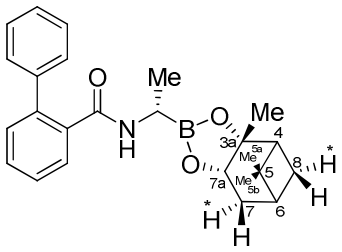
(-)-Pinanediol (*S*)-1-(1-benzothiophene-5-carboxamido)ethaneboronate 63.

63 is a pale yellow oil (57%). IR (nujol) υ/cm^{-1}: 3281 (amide NH), 1638 (amide CO). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (3H, s, $CH_3$5a), 1.24 (3H, s, $CH_3$5b), 1.26 (3H, s, C*H*$_3$CHB), 1.37 (1H, d, *J* = 11.4 Hz, H8), 1.51 (3H, s, CH_3C3a), 1.82-1.85 (1H, br d, *J* = 13.4 Hz, H7*), 1.85-1.93 (1H, m, H6), 2.01 (1H, t, *J* = 5.7 Hz, H4), 2.19-2.15 (1H, m, H8*), 2.27-2.35 (1H, m, H7), 2.82-2.90 (1H, m, CHB), 4.28 (1H, dd, *J* = 8.2, 1.7 Hz, H7a), 7.26 (1H, d, *J* = 5.0 Hz, benzothiophene H3), 7.42 (1H, d, *J* = 5.0 Hz, benzothiophene H2), 7.62 (2H, d, *J* = 8.8 Hz, benzothiophene H6 and H7), 8.25 (1H, s, benzothiophene H4), 9.20 (1H, br s, NH). ^{13}C NMR (500 MHz, CDCl3) δ 16.6 (*C*H_3CB), 24.1 ($CH_3$5a), 26.7 (C8), 27.4 ($CH_3$5b), 29.4 (*C*H_3C3a), 35.7 (CB), 36.8 (C7), 38.1 (C5), 40.1 (C6), 52.6 (C4), 76.2 (C7a), 83.5 (C3a), 122.3, 123.0, 123.7, 124.0, 124.1, 127.9, 139.0, 144.0, 170.8 (CONH). HRMS (ESI, positive ion) $C_{21}H_{26}BNNaO_3S$ requires $[M+Na]^+$ 406.1619; Found 406.1619.



(-)-Pinanediol (*S*)-1-(2-benzylbenzamido)ethaneboronate 64.

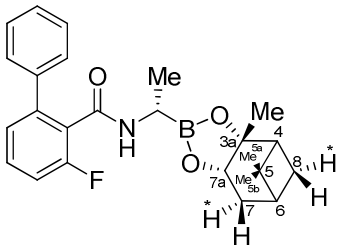
64 is a white solid (62%), mp 156-158°C. IR (nujol) υ/cm^{-1}: 3271 (amide NH), 1643 (amide CO). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84 (3H, s, $CH_3$5a), 1.20 (3H, s, $CH_3$5b), 1.26 (1H, s, H8), 1.27 (3H, d, *J* = 7.8 Hz, C*H*$_3$CHB), 1.35 (3H, s, CH_3C3a), 1.79-1.84 (1H, br d, *J* = 14.3 Hz, H7*), 1.85-1.90 (1H, m, H6), 1.98 (1H, t, *J* = 5.5 Hz, H4), 2.09-2.18 (1H, m, H8*), 2.26-2.33 (1H, m, H7), 3.01-3.08 (1H, m, CHB), 4.19 (1H, d, *J* = 4.0 Hz, CH_2Ph), 4.22-4.26 (1H, dd, *J* = 8.7, 1.8 Hz, H7a), 6.93 (1H, br s, NH), 7.14-7.21 (5H, m, benzyl H), 7.24 (1H, d, *J* = 7.7 Hz, H5'), 7.25 (1H, t, *J* = 7.7 Hz, H3'), 7.35 (1H, t, *J* = 7.7 Hz, H4'), 7.42 (1H, d, *J* = 7.7 Hz, H2'). ^{13}C NMR (500 MHz, CDCl3) δ 16.5 (*C*H_3CB), 24.2 ($CH_3$5a), 26.5 (C8), 27.4 ($CH_3$5b), 28.9 (*C*H_3C3a), 36.1 (C7), 38.0 (C5), 38.8 (benzyl CH_2), 40.0 (C6), 52.0 (C4), 73.7 (C7a), 84.6 (C3a), 126.2 (benzyl C3 and C5), 126.3 (C5'), 128.1 (C2'), 128.5 (C3'), 129.0 (benzyl C4), 131.0 (C4'), 131.1 (benzyl C2 and C6), 132.3 (benzyl C1),139.8 (C6'), 140.6 (C1'), 170.7 (CONH). HRMS (ESI, positive ion) $C_{26}H_{32}BNNaO_3$ requires $[M+Na]^+$ 440.2367; Found 440.2367.



(-)-Pinanediol (*S*)-1-(2-phenylbenzamido)ethaneboronate 65.

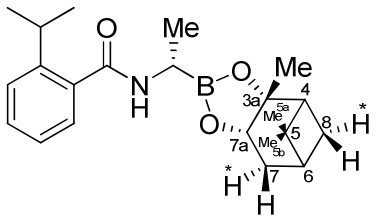
65 is a pale yellow oil (64%). IR (nujol) υ/cm^{-1}: 3215 (amide NH), 1648 (amide CO). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.83 (3H, s, $CH_3$5a), 0.93 (3H, s, $CH_3$5b), 1.25 (3H, s, C*H*$_3$CHB), 1.28 (1H, d, *J* = 10.3 Hz, H8), 1.36 (3H, s, CH_3C3a), 1.74-1.80 (1H, br d, *J* = 14.5 Hz, H7*), 1.82-1.87 (1H, m, H6), 1.97 (1H, t, *J* = 5.9 Hz, H4), 2.07-2.14 (1H, m, H8*), 2.24-2.32 (1H, m, H7), 2.77-2.84 (1H, m, CHB), 4.20 (1H, d, *J* = 8.7 Hz, H7a), 5.94 (1H, br s, NH), 7.30-7.42 (7H, m, phenyl side chain H, H3' and H5'), 7.48 (1H, t, *J* = 7.8 Hz, H4'), 7.82 (1H, d, *J* = 7.8 Hz, H2'). ^{13}C NMR (500 MHz, CDCl3) δ 15.9 (*C*H_3CB), 24.0 ($CH_3$5a), 26.4 (C8), 27.2 ($CH_3$5b), 28.8 (*C*H_3C3a), 36.2 (C7), 38.1 (C5), 39.8 (C6), 51.9 (C4), 73.4 (C7a), 84.3 (C3a),

127.6, 128.0, 128.7, 128.9 (phenyl side chain C, C3' and C5'), 129.9 (C2'), 130.4 (phenyl side chain C, C3' and C5'), 130.8 (phenyl side chain C), 131.1 (C4'), 139.6 (C6'), 140.5 (C1'), 171.1 (CONH). HRMS (ESI, positive ion) $C_{25}H_{30}BNNaO_3$ requires $[M+Na]^+$ 426.2211; Found 426.2219.



(-)-Pinanediol (*S*)-1-(2-fluoro-6-phenylbenzamido)ethaneboronate 66.

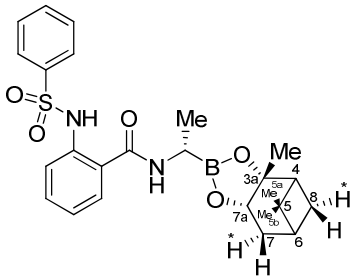
66 is a pale yellow oil (74%). IR (nujol) υ/cm^{-1}: 3271 (amide NH), 1647 (amide CO). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.81 (3H, s, $CH_3$5a), 1.00 (3H, s, $CH_3$5b), 1.15 (1H, d, *J* = 11.4 Hz, H8), 1.27 (3H, s, C*H*$_3$CHB), 1.34 (3H, s, CH_3C3a), 1.74-1.83 (1H, br d, *J* = 13.4 Hz, H7*), 1.84-1.93 (1H, m, H6), 2.00 (1H, t, *J* = 5.5 Hz, H4), 2.11-2.17 (1H, m, H8*), 2.24-2.34 (1H, m, H7), 3.16-3.26 (1H, m, CHB), 4.24 (1H, dd, *J* = 8.7, 1.6 Hz, H7a), 5.59 (1H, br s, NH), 7.07 (1H, t, *J* = 8.4 Hz, H4'), 7.16 (1H, d, *J* = 8.4 Hz, H3'), 7.30-7.42 (6H, m, phenyl side chain H and H5'). ^{13}C NMR (500 MHz, CDCl3) δ 16.0 (*C*H_3CB), 24.1 ($CH_3$5a), 26.5 (C8), 27.2 ($CH_3$5b), 28.8 (*C*H_3C3a), 36.1 (C7), 38.2 (C5), 39.9 (C6), 52.0 (C4), 73.5 (C7a), 84.5 (C3a), 127.6, 128.1, 128.8, 129.0 (phenyl side chain C and C5'), 130.0 (C2'), 130.5 (C3'), 130.9 (phenyl side chain C), 131.3 (C4'), 140.1 (C6'), 141.3 (C1'), 171.0 (CONH). ^{19}F NMR (376 MHz, $CDCl_3$) δ -115.0. HRMS (ESI, positive ion) $C_{25}H_{29}BFNNaO_3$ requires $[M+Na]^+$ 444.2117; Found 444.2114.



(-)-Pinanediol (*S*)-1-(2-(propan-2-yl)benzamido)ethaneboronate 69.

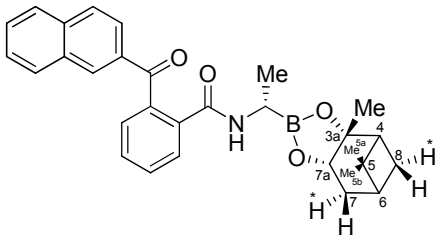
69 is a pale yellow oil (63%). IR (nujol) υ/cm^{-1}: 3271 (amide NH), 1649 (amide CO). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.80 (3H, s, $CH_3$5a), 1.15-1.27 (13H, m, isopropyl CH_3 x 2, H8, $CH_3$5b, C*H*$_3$CHB), 1.31 (3H, s, CH_3C3a), 1.72-1.80 (1H, br d, *J* = 14.3 Hz, H7*), 1.80-1.86 (1H, m, H6), 1.88-1.99 (1H, m, H4), 2.03-2.13 (1H, m, H8*), 2.21-2.29 (1H, m, H7), 2.95-

3.04 (1H, m, CHB), 3.32-3.41 (1H, m, isopropyl CH), 4.14-4.22 (1H, m, H7a), 7.03-7.08 (1H, m, H5'), 7.26 (1H, d, *J* = 7.8 Hz, H2'), 7.35 (2H, t, *J* = 7.8 Hz, H3' and H4'), 7.76 (1H, br s, NH). ^{13}C NMR (500 MHz, CDCl3) δ 16.6 (*C*H$_3$CB), 24.1 (CH$_3$5a), 26.5 (C8), 27.3 (CH$_3$5b), 28.0 (isopropyl CH$_3$), 28.9 (*C*H$_3$C3a), 29.8 (isopropyl CH), 36.4 (C7), 38.1 (C5), 39.9 (C6), 52.1 (C4), 78.3 (C7a), 83.8 (C3a), 125.6 (C5'), 126.2 (C3'), 127.3 (C2'), 127.6 (C6'), 131.2 (C4'), 164.5 (C1'), 173.1 (CONH). HRMS (ESI, positive ion) $C_{22}H_{32}BNNaO_3$ requires $[M+Na]^+$ 392.2367; Found 392.2371.



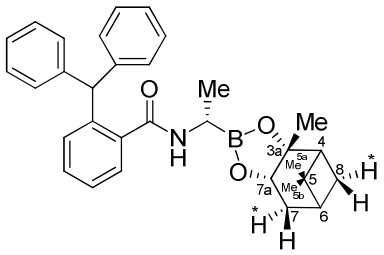
(-)-Pinanediol (*S*)-1-(2-[(phenylsulfonyl)amino]benzamido)ethaneboronate 70.

70 is a pale yellow oil (55%). IR (nujol) υ/cm^{-1}: 3350 (sulphonamide NH), 3281 (amide NH), 1633 (CO amide), 1162 (sulphonamide SO). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.83 (3H, s, CH$_3$5a), 1.21 (3H, s, CH$_3$5b), 1.24 (3H, s, C*H*$_3$CHB), 1.26 (1H, d, *J* = 11.4 Hz, H8), 1.44 (3H, s, CH$_3$C3a), 1.82-1.89 (1H, br d, *J* = 15.6 Hz, H7*), 1.85-1.93 (1H, m, H6), 2.03 (1H, t, *J* = 5.1 Hz, H4), 2.17-2.26 (1H, m, H8*), 2.29-2.37 (1H, m, H7), 3.24-3.33(1H, m, CHB), 4.34 (1H, d, *J* = 8.2 Hz, H7a), 6.51 (1H, br s, CONH), 7.00 (1H, t, *J* = 8.6 Hz, H5'), 7.28-7.41 (5H, m, SO_2Ph), 7.61 (1H, d, *J* = 8.6 Hz, H4'), 7.71 (1H, d, *J* = 8.6 Hz, H3'), 7.76 (1H, d, *J* = 8.6 Hz, H6'), 10.92 (1H, br s, SO_2NH). ^{13}C NMR (500 MHz, CDCl3) δ 16.5 (*C*H$_3$CB), 24.1 (CH$_3$5a), 26.8 (C8), 27.3 (CH$_3$5b), 29.5 (*C*H$_3$C3a), 33.2 (CB), 36.1 (C7), 38.2 (C5), 39.9 (C6), 52.0 (C4), 76.2 (C7a), 83.8 (C3a), 121.0 (C3'), 123.2 (C5'), 126.7 (SO_2Ph-C2 and SO_2Ph-C6), 128.3 (SO_2Ph-H3 and SO_2Ph-H5), 131.0 (C6'), 133.0 (C4'), 134.5 (SO_2Ph-C4), 135.3 (C2'), 140.2 (SO_2Ph-C1), 142.0 (C1'), 171.0 (CONH). HRMS (ESI, positive ion) $C_{25}H_{31}BN_2NaO_5S$ requires $[M+Na]^+$ 505.1930; Found 505.1931.



(-)-Pinanediol (*S*)-1-(2-(naphthalen-2-ylcarbonyl)benzamido)ethaneboronate 71.

71 is a pale yellow oil (52%). IR (nujol) υ/cm^{-1}: 3284 (amide NH), 1730 (ketone CO), 1640 (amide CO). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (3H, s, $CH_3$5a), 1.25 (3H, s, $CH_3$5b), 1.28 (3H, s, C*H*$_3$CHB), 1.35 (1H, d, *J* = 11.5 Hz, H8), 1.39 (3H, s, CH_3C3a), 1.82-1.87 (1H, br d, *J* = 15.6 Hz, H7*), 1.87-1.91 (1H, m, H6), 1.98 (1H, t, *J* = 5.7 Hz, H4), 2.12-2.19 (1H, m, H8*), 2.28-2.36 (1H, m, H7), 2.93-3.00 (1H, m, CHB), 4.27 (1H, dd, *J* = 8.2, 1.7 Hz, H7a), 6.14 (1H, s), 6.56 (1H, br s, CONH), 7.03-7.16 (3H, m), 7.19-7.22 (1H, m), 7.24-7.33 (5H, m), 7.42 (1H, d, *J* = 8.0 Hz). ^{13}C NMR (500 MHz, CDCl3) δ 16.3 (*C*H_3CB), 24.1 ($CH_3$5a), 26.4 (C8), 27.3 ($CH_3$5b), 29.8 (*C*H_3C3a), 36.2 (C7), 38.1 (C5), 39.8 (C6), 51.8 (C4), 73.4 (C7a), 84.8 (C3a), 126.4, 127.6, 128.0, 128.3, 128.4, 129.6, 129.7, 130.4, 130.5, 130.6, 133.6, 134.5, 141.8, 142.0, 143.4, 143.5, 171.6 (CONH). HRMS (ESI, positive ion) $C_{30}H_{32}BNNaO_4$ requires $[M+Na]^+$ 504.2317; Found 504.2318.



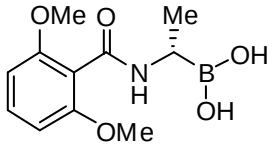
(-)-Pinanediol (*S*)-1-(2-(diphenylmethyl)benzamido)ethaneboronate 72.

72 is a pale yellow oil (49%). IR (nujol) υ/cm^{-1}: 3272 (amide NH), 1645 (amide CO). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.83 (3H, s, $CH_3$5a), 1.21 (3H, s, $CH_3$5b), 1.26 (3H, s, C*H*$_3$CHB), 1.35 (1H, d, *J* = 11.4 Hz, H8), 1.40 (3H, s, CH_3C3a), 1.82-1.87 (1H, br d, *J* = 15.6 Hz, H7*), 1.87-1.93 (1H, m, H6), 2.04 (1H, t, *J* = 5.4 Hz, H4), 2.07-2.12 (1H, m, H8*), 2.26-2.31 (1H, m, H7), 2.98-3.05 (1H, m, CHB), 4.34 (1H, d, *J* = 8.2 Hz, H7a), 7.03-7.20 (3H, m), 7.24-7.58 (6H, m), 7.65-7.89 (5H, m). ^{13}C NMR (500 MHz, CDCl3) δ 16.0 (*C*H_3CB), 24.2 ($CH_3$5a), 26.2 (C8), 27.3 ($CH_3$5b), 28.6 ($CHPh_2$), 29.6 (*C*H_3C3a), 36.5 (C7), 38.2 (C5), 39.6 (C6), 51.7 (C4), 73.8 (C7a), 86.3 (C3a), 127.5, 128.1, 128.7, 128.9, 129.6, 130.4, 130.9, 131.2, 139.5, 141.0, 171.2 (CONH). HRMS (ESI, positive ion) $C_{32}H_{36}BNNaO_3$ requires $[M+Na]^+$ 516.2680; Found 516.2688.

General procedure for the preparation of 10, 18-25, 28-30.

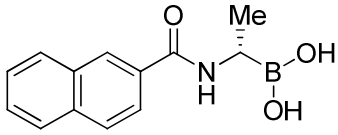
Aqueous potassium hydrogen fluoride (4.5 M, 3.70 mL, 16.5 mmol, 6 equiv.) was added to a solution of the above boronate (1.00 g, 2.8 mmol, 1 equiv.) in MeOH (10 mL) and the resulting suspension was stirred at room temperature for 1 h. It was then evaporated *in vacuo*

and the resulting residue dissolved in hot acetone. The insoluble salt was filtered and the filtrate concentrated *in vacuo*. Recrystallisation of the residue from Et_2O gave the trifluoroborate as a white solid. The latter was then dissolved in a mixture of MeCN and H_2O (1:1, 8ml) and chlorotrimethylsilane (1.10 mL, 8.4 mmol, 3 equiv.) was added. The resulting suspension was stirred at room temperature for overnight, after which the mixture was concentrated *in vacuo* and the product recrystallized from H_2O and MeCN.



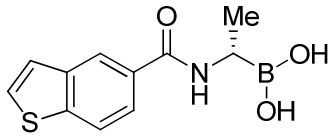
(*S*)-1-(2,6-Dimethoxybenzamido)ethaneboronic acid 10.

10 is a white solid (68%), mp 127-129°C. IR (nujol) υ/cm^{-1}: 2995-3410 (amide NH and boronic OH), 1633 (amide CO). ^{1}H NMR (500 MHz, CD_3OD) δ 1.22 (3H, d, *J* = 7.0 Hz, C*H*$_3$CB), 2.8.-2.90 (1H, m, CB), 3.86 (6H, s, OCH_3 x 2), 6.77 (2H, dd, *J* = 8.5, 2.1 Hz, H3' and H5'), 7.50 (1H, t, *J* = 8.5 Hz, H4'). ^{13}C NMR (500 MHz, CD_3OD) δ 14.6 (*C*H$_3$CHB), 41.4 (CHB), 55.0 (OCH_3 x 2), 105.4 (C3' and C5'), 133.3 (C4'), 135.1 (C2' and C6'), 160.0 (C1'), 172.3 (CONH). HRMS (ESI, negative ion) $C_{24}H_{25}BNO_3$ [M+2OMe-2OH-H]$^-$ requires 386.2144; Found 386.2144.



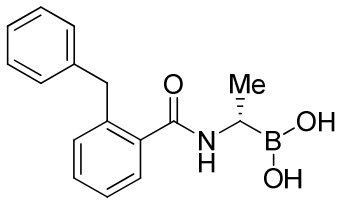
(*S*)-1-(Naphthalene-2-carboxamido)ethaneboronic acid 18.

18 is a white solid (82%), mp 183-185°C. IR (nujol) υ/cm^{-1}: 2971-3414 (amide NH and boronic OH), 1632 (amide CO). ^{1}H NMR (500 MHz, CD_3OD) δ 1.23 (3H, d, *J* = 7.0 Hz, CH_3), 2.85-2.83 (1H, m, CH), 7.71 (1H, t, *J* = 7.8 Hz), 7.76 (1H, t, *J* = 7.8 Hz), 7.93 (1H, s), 8.05-8.10 (2H, m), 8.13-8.18 (2H, m). ^{13}C NMR (500 MHz, CD_3OD) δ 14.5 (*C*H$_3$CHB), 41.0 (CHB), 127.6, 128.1, 128.8, 129.0, 130.0, 130.5, 130.9, 131.3, 140.1, 141.3, 171.0 (CONH). HRMS (ESI, positive ion) $C_{15}H_{18}BNNaO_3$ [M-2OH+2OMe+Na]$^+$ requires 294.1277; Found 294.1272.



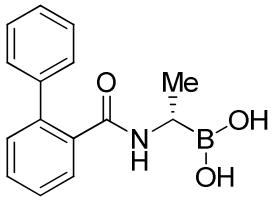
(*S*)-1-(1-Benzothiophene-5-carboxamido)ethaneboronic acid 19.

19 is a white solid (76%), mp 203-205°C. IR (nujol) υ/cm^{-1}: 3074-3416 (amide NH and boronic OH), 1637 (amide CO). ^{1}H NMR (500 MHz, CD_3OD) δ 1.22 (3H, d, *J* = 7.0 Hz, CH_3), 2.83-2.90 (1H, m, CH), 7.58 (1H, d, *J* = 5.3 Hz, H3'), 7.79 (1H, d, *J* = 5.3 Hz, H2'), 7.89 (1H, dd, *J* = 8.5, 1.7 Hz, H6'), 8.16 (1H, d, *J* = 8.5 Hz, H7'), 8.54 (1H, d, *J* = 1.7 Hz, H4'). ^{13}C NMR (500 MHz, CD_3OD) δ 14.5 (*C*H_3CHB), 41.6 (CHB), 122.3, 123.0, 123.7, 124.0, 124.1, 127.9, 139.0, 144.0, 170.8 (CONH). HRMS (ESI, positive ion) $C_{13}H_{16}BNNaO_3S$ [M-2OH+2OMe+Na]$^+$ requires 300.0836; Found 300.0837.



(*S*)-1-(2-Benzylbenzamido)ethaneboronic acid 20.

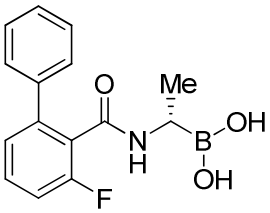
20 is a white solid (87%), mp 87-89°C. IR (nujol) υ/cm^{-1}: 3048-3419 (amide NH and boronic OH), 1639 (amide CO). ^{1}H NMR (500 MHz, CD_3CN) δ 1.12 (3H, d, *J* = 8.9 Hz, C*H*$_3$CB), 2.51 (2H, br s, $B(OH)_2$), 2.99-3.09 (1H, m, CB), 4.04-4.22 (2H, m, benzyl CH_2), 5.65 (1H, br s, NH), 7.06-7.29 (7H, m, benzyl-H, H3' and H5'), 7.42 (1H, t, *J* = 7.6 Hz, H4'), 7.51 (1H, d, *J* = 7.6 Hz, H2'). ^{13}C NMR (500 MHz, CD_3CN) δ 14.9 (*C*H_3CHB), 38.3 (benzyl CH_2), 48.8 (CHB), 125.7, 126.0, 128.4, 128.7, 129.1 (C2'), 130.7, 131.5 (C4'), 140.9 (C1') and 172.3 (CONH). HRMS (ESI, positive ion) $C_{18}H_{22}BNNaO_3$ [M-2OH+2OMe+Na]$^+$ requires 334.1590; Found 334.1591.



(*S*)-1-(2-Phenylbenzamido)ethaneboronic acid 21.

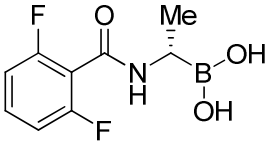
21 is a white solid (76%), mp 122-124°C. IR (nujol) υ/cm^{-1}: 3048-3416 (amide NH and boronic OH), 1634 (amide CO). ^{1}H NMR (500 MHz, CD_3CN) δ 0.93 (3H, d, *J* = 7.2 Hz, C*H*$_3$CB), 2.45 (2H, br s, $B(OH)_2$), 2.85-2.93 (1H, m, CB), 7.30-7.52 (7H, m, phenyl side chain-H, H2' and H5'), 7.65 (1H, t, *J* = 7.3 Hz, H3'), 7.72-7.78 (1H, m, H4'). ^{13}C NMR (500 MHz, CD_3CN) δ 14.4 (*C*H_3CHB), 41.6 (CHB), 127.5, 127.8, 128.6, 128.9, 129.1 (C4'),

130.6, 131.7 (C3'), 139.2 (C6'), 141.1 (C1') and 167.6 (CONH). HRMS (ESI, positive ion) $C_{17}H_{20}BNNaO_3$ $[M\text{-}2OH\text{+}2OMe\text{+}Na]^+$ requires 320.1428; Found 320.1432.



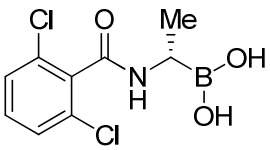
(*S*)-1-(2-Fluoro-6-phenylbenzamido)ethaneboronic acid 22.

22 is a white solid (68%), mp 120-122°C. IR (nujol) υ/cm^{-1}: 3047-3418 (amide NH and boronic OH), 1644 (amide CO). ^{1}H NMR (500 MHz, CD_3CN) δ 0.87 (3H, d, J = 7.0 Hz, CH_3CB), 2.78-2.95 (1H, m, CB), 3.43 (2H, br s, $B(OH)_2$), 7.18-7.48 (7H, m, phenyl side chain-H, H3' and H5'), 7.56-7.65 (1H, m, H4'), 8.23 (1H, br s, NH). ^{13}C NMR (500 MHz, CD_3CN) δ 14.4 (*C*H_3CHB), 41.0 (CHB), 124.4, 124.8, 125.9, 128.4, 132.8 (C4'), 138.1, 143.3 (C6'), 158.7 (C2'), 160.7 (C1') and 169.5 (CONH). HRMS (ESI, positive ion) $C_{17}H_{19}BFNNaO_3$ $[M\text{-}2OH\text{+}2OMe\text{+}Na]^+$ requires 338.1340; Found 338.1338.



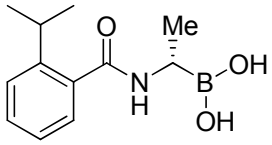
(*S*)-1-(2,6-Difluorobenzamido)ethaneboronic acid 23.

23 is a white solid (89%), mp 111–112°C. Elem. Anal.: calcd for $C_9H_{10}BF_2NO_3$ C, 47.21%; H, 4.40%; N, 6.12%; obtained C, 47.15%; H, 4.36%; N, 5.98%. IR (nujol) υ/cm^{-1}: 2971-3234 (amide NH and boronic OH), 1632 (amide CO). ^{1}H NMR (500 MHz, CD_3CN) δ 1.23 (3H, d, J = 7.4 Hz, CH_3CB), 3.15-3.24 (1H, m, CB), 4.25 (2H, br s, $B(OH)_2$), 7.08 (1H, d, J = 8.9 Hz, H3'), 7.10 (1H, d, J = 8.9 Hz, H5'), 7.56-7.64 (1H, m, H4'), 9.05 (1H, br s, NH). ^{13}C NMR (500 MHz, CD_3CN) δ 14.6 (*C*H_3CHB), 41.5 (CHB), 112.5 (C3' and C5'), 134.9 (C4'), 159.4 (C2' and C6'), 161.4 (C1'), 163.9 (CONH). ^{19}F NMR (376 MHz, CD_3CN) -112.7. HRMS (ESI, negative ion) $C_{11}H_{13}BF_2NO_3$ $[M\text{+}2OMe\text{–}2OH\text{-}H]^-$ requires 256.0957; Found 256.0953.



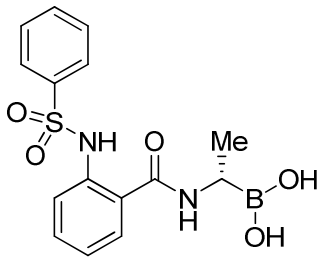
(*S*)-1-(2,6-Dichlorobenzamido)ethaneboronic acid 24.

24 is a white solid (84%), mp 125–127°C. IR (nujol) υ/cm^{-1}: 3108-3401 (amide NH and boronic OH), 1644 (amide CO). ^{1}H NMR (500 MHz, CD_3CN) δ 1.06 (3H, d, *J* = 7.1 Hz, C*H*$_3$CB), 2.95-3.04 (1H, m, CB), 6.35 (1H, br s, NH), 7.31 (1H, t, *J* = 8.2 Hz, H4'), 7.38 (2H, d, *J* = 8.2 Hz, H3' and H5'). ^{13}C NMR (500 MHz, CD_3CN) δ 15.9 (*C*H_3CHB), 40.8 (CHB), 128.0 (C3' and C5'), 130.2 (C4'), 131.8 (C2' and C6'), 137.8 (C1'), 164.0 (CONH). HRMS (ESI, positive ion) $C_{11}H_{14}BCl_2NNaO_3$ $[M-2OH+2OMe+Na]^+$ requires 312.0341; Found 312.0343.



(*S*)-1-(2-(Propan-2-yl)benzamido)ethaneboronic acid 25.

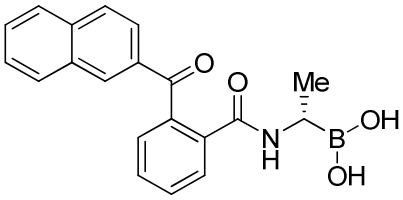
25 is a white solid (79%), mp 121-123°C. IR (nujol) υ/cm^{-1}: 3112-3420 (amide NH and boronic OH), 1637 (amide CO). ^{1}H NMR (500 MHz, CD_3CN) δ 1.18 (3H, d, *J* = 7.1 Hz, C*H*$_3$CB), 1.29 (6H, d, *J* = 7.4 Hz, isopropyl CH_3 x 2), 2.93-3.04 (1H, m, CB), 3.93-3.97 (1H, m, isopropyl CH), 7.29 (1H, t, *J* = 7.6 Hz, H3'), 7.51 (1H, t, *J* = 7.6 Hz, H4'), 7.58 (1H, d, *J* = 7.6 Hz, H5'), 7.61 (1H, d, *J* = 7.6 Hz, H2'), 9.64 (1H, br s, NH). ^{13}C NMR (500 MHz, CD_3CN) δ 14.4 (*C*H_3CHB), 23.6 (isopropyl CH_3), 30.0 (isopropyl CH), 42.6 (CHB), 125.8 (C3'), 125.9 (C6'), 126.5 (C4'), 129.0 (C2'), 132.8 (C5'), 148.9 (C1') and 175.3 (CONH). HRMS (ESI, positive ion) $C_{14}H_{22}BNNaO_3$ $[M-2OH+2OMe+Na]^+$ requires 286.1585; Found 286.1586.



(*S*)-1-(2-[(Phenylsulfonyl)amino]benzamido)ethaneboronic acid 28.

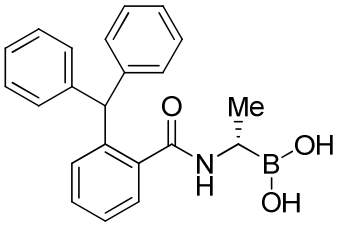
28 is a white solid (75%), mp 125-127°C. IR (nujol) υ/cm^{-1}: 3057-3369 (amide NH, boronic OH and sulphonamide NH), 1661 (amide CO) 1160 (sulphonamide SO). ^{1}H NMR (500 MHz, CD_3OD) δ 1.22 (3H, d, *J* = 7.0 Hz, CH_3), 2.83-2.90 (1H, m, CH), 7.00 (1H, t, *J* = 8.6 Hz, H5'), 7.28-7.41 (5H, m, SO_2Ph), 7.56 (1H, d, *J* = 8.6 Hz, H4'), 7.79 (1H, d, *J* = 8.6 Hz, H3'), 7.89 (1H, d, *J* = 8.6 Hz, H6'). ^{13}C NMR (500 MHz, CD_3OD) δ 14.4 (*C*H_3CHB), 41.5 (CHB),

121.0, 123.2, 126.7, 128.3, 131.0, 133.0, 134.5, 135.3, 140.2, 142.0, 171.0 (CONH). HRMS (ESI, positive ion) $C_{17}H_{20}BN_2O_5S$ $[M\text{-}2OH\text{+}2OMe\text{-}H]^-$ requires 375.1191; Found 375.1190.



(*S*)-1-(2-(Naphthalen-2-ylcarbonyl)benzamido)ethaneboronic acid 29.

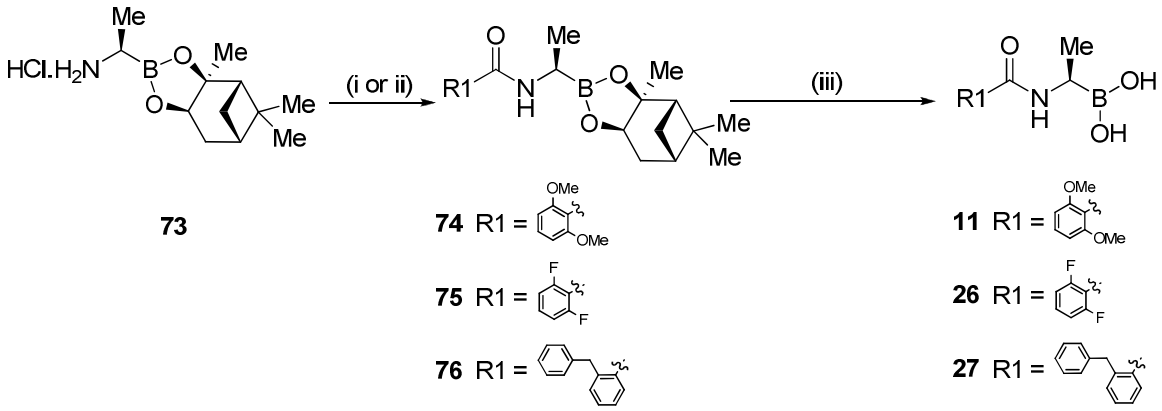
29 is a white solid (64%), mp 177-179°C. IR (nujol) υ/cm^{-1}: 3151-3401 (amide NH and boronic OH), 1726 (ketone CO), 1667 (amide CO). ^{1}H NMR (500 MHz, CD_3OD) δ 1.23 (3H, d, J = 7.0 Hz, CH_3), 2.83-2.90 (1H, m, CH), 6.14 (1H, s), 7.03-7.16 (3H, m), 7.19-7.22 (1H, m), 7.24-7.33 (5H, m), 7.42 (1H, d, J = 8.0 Hz). ^{13}C NMR (500 MHz, CD_3OD) δ 14.6 (*C*H_3CHB), 41.6 (CHB), 126.4, 127.6, 128.0, 128.3, 128.4, 129.6, 129.7, 130.4, 130.5, 130.6, 133.6, 134.5, 141.8, 142.0, 143.4, 143.5, 171.6 (CONH). HRMS (ESI, positive ion) $C_{15}H_{18}BNNaO_3$ $[M\text{-}2OH\text{+}2OMe\text{+}Na]^+$ requires 294.1272; Found 294.1272.



(*S*)-1-(2-(Diphenylmethyl)benzamido)ethaneboronate 30.

30 is a white solid (67%), mp 189-191°C. IR (nujol) υ/cm^{-1}: 3158-3421 (amide NH and boronic OH), 1635 (amide CO). ^{1}H NMR (500 MHz, CD_3OD) δ 1.23 (3H, d, J = 7.0 Hz, CH_3), 2.83-2.90 (1H, m, CH), 5.64 (1H, s, $CHPh_2$), 7.03-7.20 (3H, m), 7.24-7.58 (6H, m), 7.65-7.89 (5H, m). ^{13}C NMR (500 MHz, CD_3OD) δ 14.5 (*C*H_3CHB), 28.6 ($CHPh_2$), 41.3 (CHB), 127.5, 128.1, 128.7, 128.9, 129.6, 130.4, 130.9, 131.2, 139.5, 141.0, 171.2 (CONH). HRMS (ESI, positive ion) $C_{24}H_{26}BNNaO_3$ $[M\text{-}2OH\text{+}2OMe\text{+}Na]^+$ requires 410.1903; Found 410.1902.

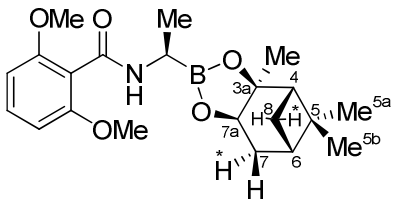
Scheme S6. Chemical synthesis of α-amido boronic acids **11, 15, 26**-**27**.



Reagents and conditions: (i) For compounds **74** and **75**; acid chlorides, DMAP, Et_3N, THF/ DMF, 0°C to RT; (ii) For compounds **76**; aryl acids, HATU, HOBt, *N*-methylmorpholine, THF/ DMF, 0°C to RT; (iii) KHF_2, MeOH, then chlorotrimethylsilane, MeCN/ H_2O.

General procedure for the preparation of 74 and 75.

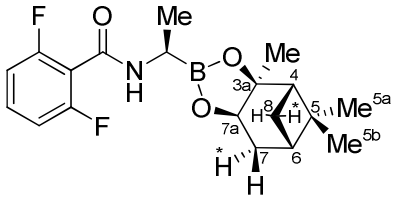
A solution of acid chloride (3.4 mmol, 1.1 equiv.) in anhydrous THF (2 mL) was added dropwise to a mixture of DMAP (75 mg, 0.6 mmol, 0.2 equiv.) and Et_3N (0.95 mL, 6.8 mmol, 2 equiv.) in anhydrous THF (15 mL) at 0 °C. After stirring for 30 min, **73**[16] (0.80 g, 3.1 mmol, 1 equiv.) in anhydrous THF/ DMF (3:5, 8 mL) was added and the resulting suspension was stirred at 0 °C for 30 min, then at room temperature for overnight. It was then evaporated *in vacuo*, resuspended in EtOAc and washed with H_2O and 5% $NaHCO_3$. The organic phase was evaporated *in vacuo* and purified by chromatography (EtOAc/ hexane 3:7).



(+)-Pinanediol (*R*)-1-(2,6-dimethoxybenzamido)ethaneboronate 74.

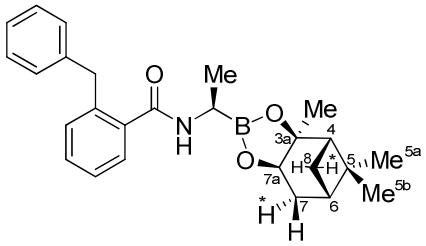
74 is a pale yellow oil (67%). IR (nujol) υ/cm^{-1}: 3282 (amide NH), 1647 (amide CO). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (3H, s, $CH_3$5a), 1.24 (1H, d, *J* = 10.5 Hz, H8), 1.27 (3H, s, $CH_3$5b), 1.37 (3H, s, C*H*$_3$CHB), 1.41 (3H, s, CH_3C3a), 1.82-1.86 (1H, m, H7*), 1.86-1.92 (1H, m, H6), 2.00 (1H, t, *J* = 5.8 Hz, H4), 2.11-2.19 (1H, m, H8*), 2.26-2.36 (1H, m, H7), 3.11-3.20 (1H, m, CHB), 3.80 (6H, s, OCH_3 x 2), 4.23-4.31 (1H, m, H7a), 6.54 (2H, d, *J* =

8.5 Hz, H3' and H5'), 6.73 (1H, br s, NH), 7.29 (1H, t, *J* = 8.5 Hz, H4'). ^{13}C NMR (500 MHz, CDCl3) δ 16.2 (*C*H$_3$CB), 24.1 (CH$_3$5a), 26.3 (C8), 27.0 (CH$_3$5b), 28.5 (*C*H$_3$C3a), 35.7 (C7), 38.4 (C5), 39.4 (C6), 51.7 (C4), 69.1 (OCH$_3$ x 2), 76.6 (C7a), 84.3 (C3a), 128.1 (C3' and C5'), 130.4 (C4'), 139.0 (C2' and C6'), 142.4 (C1'), 170.0 (CONH). HRMS (ESI, positive ion) $C_{21}H_{30}BNNaO_5$ requires $[M+Na]^+$ 410.2109; Found 410.2098.



(+)-Pinanediol (*R*)-1-(2,6-difluorobenzamido)ethaneboronate 75.

75 is a white solid (92%), mp 134-135°C. Anal. ($C_{19}H_{24}BF_2NO_3$) C, H, N. IR (nujol) υ/cm^{-1}: 3283 (amide NH), 1648 (amide CO). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (3H, s, CH$_3$5a), 1.27 (1H, d, *J* = 10.5 Hz, H8), 1.30 (3H, s, CH$_3$5b), 1.36 (3H, d, *J* = 7.1 Hz, C*H*$_3$CHB), 1.43 (3H, s, CH$_3$C3a), 1.89 (1H, br d, *J* = 15.5 Hz, H7*), 1.89-1.95 (1H, m, H6), 2.07 (1H, t, *J* = 5.3 Hz, H4), 2.20-2.26 (1H, m, H8*), 2.32-2.39 (1H, m, H7), 3.47-3.59 (1H, m, CHB), 4.36 (1H, dd, *J* = 8.9, 1.7 Hz, H7a), 6.29 (1H, br s, NH), 6.92 (1H, d, *J* = 8.1 Hz, H3'), 6.94 (1H, d, *J* = 8.1 Hz, H5'), 7.32-7.39 (1H, m, H4'). ^{13}C NMR (500 MHz, CDCl3) δ 16.6 (*C*H$_3$CB), 24.0 (CH$_3$5a), 26.3 (C8), 27.1 (CH$_3$5b), 28.6 (*C*H$_3$C3a), 33.1 (CB), 35.5 (C7), 38.2 (C5), 39.6 (C6), 51.4 (C4), 78.2 (C7a), 86.3 (C3a), 112.0 (C3' and C5'), 131.8 (C4'), 159.2 (C2' and C6'), 160.9 (C1'), 161.3 (CONH). ^{19}F NMR (376 MHz, $CDCl_3$) -111.6. HRMS (ESI, positive ion) $C_{19}H_{24}BF_2NNaO_3$ requires $[M+Na]^+$ 386.1713; Found 386.1710.



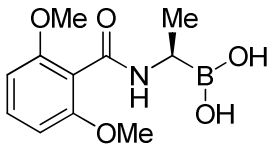
(+)-Pinanediol (*R*)-1-(2-benzylbenzamido)ethaneboronate 76.

To a solution of α-phenyl-o-toluic acid (0.80 g, 3.7 mmol, 1.2 equiv.), HATU (*O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate) (1.40 g, 3.7 mmol, 1.2 equiv.) and anhydrous HOBt (1-Hydroxybenzotriazole) (0.50 g, 3.7 mmol, 1.2 equiv.) in anhydrous DMF (10 mL) at 0 °C was added *N*-methylmorpholine (1.02 mL, 9.3 mmol, 3 equiv.). After stirring for 10 min, **73**[16] (0.80 g, 3.1 mmol, 1 equiv.) in anhydrous

THF/ DMF (3:5, 8 mL) was added and the resulting suspension was stirred at room temperature for overnight. The mixture was then evaporated *in vacuo*, resuspended in EtOAc and washed with 2% citric acid, sat. $NaHCO_3$, H_2O and brine. The organic phase was evaporated *in vacuo* and purified by chromatography (EtOAc/ hexane 1:4). This gave the above as a white solid (0.81 g, 63%), mp 155-157°C. IR (nujol) υ/cm^{-1}: 3271 (amide NH), 1643 (amide CO). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84 (3H, s, $CH_3$5a), 1.20 (3H, s, $CH_3$5b), 1.26 (1H, s, H8), 1.27 (3H, d, *J* = 7.8 Hz, C*H*$_3$CHB), 1.35 (3H, s, CH_3C3a), 1.79-1.84 (1H, br d, *J* = 14.3 Hz, H7*), 1.85-1.90 (1H, m, H6), 1.98 (1H, t, *J* = 5.5 Hz, H4), 2.09-2.18 (1H, m, H8*), 2.26-2.33 (1H, m, H7), 3.01-3.08 (1H, m, CHB), 4.19 (1H, d, *J* = 4.0 Hz, CH_2Ph), 4.22-4.26 (1H, dd, *J* = 8.7, 1.8 Hz, H7a), 6.93 (1H, br s, NH), 7.14-7.21 (5H, m, benzyl H), 7.24 (1H, d, *J* = 7.7 Hz, H5'), 7.25 (1H, t, *J* = 7.7 Hz, H3'), 7.35 (1H, t, *J* = 7.7 Hz, H4'), 7.42 (1H, d, *J* = 7.7 Hz, H2'). ^{13}C NMR (500 MHz, CDCl3) δ 16.5 (*C*H_3CB), 24.2 ($CH_3$5a), 26.5 (C8), 27.4 ($CH_3$5b), 28.9 (*C*H_3C3a), 36.1 (C7), 38.0 (C5), 38.8 (benzyl CH_2), 40.0 (C6), 52.0 (C4), 73.7 (C7a), 84.6 (C3a), 126.2 (benzyl C3 and C5), 126.3 (C5'), 128.1 (C2'), 128.5 (C3'), 129.0 (benzyl C4), 131.0 (C4'), 131.1 (benzyl C2 and C6), 132.3 (benzyl C1),139.8 (C6'), 140.6 (C1'), 170.7 (CONH). HRMS (ESI, positive ion) $C_{26}H_{32}BNNaO_3$ requires $[M+Na]^+$ 440.2367; Found 440.2370.

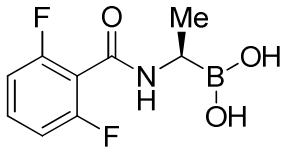
General procedure for the preparation of 11, 26-27.

Aqueous potassium hydrogen fluoride (4.5 M, 3.70 mL, 16.5 mmol, 6 equiv.) was added to a solution of the above boronate (1.00 g, 2.8 mmol, 1 equiv.) in MeOH (10 mL) and the resulting suspension was stirred at room temperature for 1 h. It was then evaporated *in vacuo* and the resulting residue dissolved in hot acetone. The insoluble salt was filtered and the filtrate concentrated *in vacuo*. Recrystallisation of the residue from Et_2O gave the trifluoroborate as a white solid. The latter was then dissolved in a mixture of MeCN and H_2O (1:1, 8ml) and chlorotrimethylsilane (1.10 mL, 8.4 mmol, 3 equiv.) was added. The resulting suspension was stirred at room temperature for overnight, after which the mixture was concentrated *in vacuo* and the product recrystallized from H_2O and MeCN.



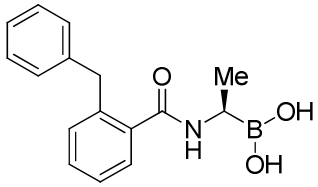
(*R*)-1-(2,6-Dimethoxybenzamido)ethaneboronic acid 11.

11 is a white solid (68%), mp 127-129°C. IR (nujol) υ/cm^{-1}: 2995-3410 (amide NH and boronic OH), 1633 (amide CO). ^{1}H NMR (500 MHz, CD_3OD) δ 1.22 (3H, d, *J* = 7.0 Hz, C*H*$_3$CB), 2.8.-2.90 (1H, m, CB), 3.86 (6H, s, OCH_3 x 2), 6.77 (2H, dd, *J* = 8.5, 2.1 Hz, H3' and H5'), 7.50 (1H, t, *J* = 8.5 Hz, H4'). ^{13}C NMR (500 MHz, CD_3OD) δ 14.6 (*C*H$_3$CHB), 41.4 (CHB), 55.0 (OCH_3 x 2), 105.4 (C3' and C5'), 133.3 (C4'), 135.1 (C2' and C6'), 160.0 (C1'), 172.3 (CONH). HRMS (ESI, negative ion) $C_{24}H_{25}BNO_3$ $[M+2OMe-2OH-H]^-$ requires 386.2144; Found 386.2143.



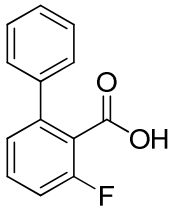
(*R*)-1-(2,6-Difluorobenzamido)ethaneboronic acid 26.

26 is a white solid (87%), mp 111–112°C. Elem. Anal.: calcd for $C_9H_{10}BF_2NO_3$ C, 47.21%; H, 4.40%; N, 6.12%; obtained C, 47.14%; H, 4.35%; N, 6.04%. IR (nujol) υ/cm^{-1}: 2971-3234 (NH and OH boronic acid), 1632 (Amide CO). ^{1}H NMR (500 MHz, CD_3CN) δ 1.23 (3H, d, *J* = 7.4 Hz, C*H*$_3$CB), 3.15-3.24 (1H, m, CB), 4.25 (2H, br s, $B(OH)_2$), 7.08 (1H, d, *J* = 8.9 Hz, H3'), 7.10 (1H, d, *J* = 8.9 Hz, H5'), 7.56-7.64 (1H, m, H4'), 9.05 (1H, br s, NH). ^{13}C NMR (500 MHz, CD_3CN) δ 14.6 (*C*H$_3$CHB), 41.5 (CHB), 112.5 (C3' and C5'), 134.9 (C4'), 159.4 (C2' and C6'), 161.4 (C1'), 163.9 (CONH). ^{19}F NMR (376 MHz, CD_3CN) -112.7. HRMS (ESI, negative ion) $C_{11}H_{13}BF_2NO_3$ $[M+2OMe–2OH-H]^-$ requires 256.0957; Found 256.0953.



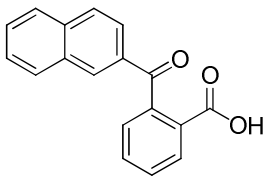
(*R*)-1-(2-Benzylbenzamido)ethaneboronic acid 27.

27 is a white solid (87%), mp 87-89°C. IR (nujol) υ/cm^{-1}: 3048-3419 (amide NH and boronic OH), 1639 (amide CO). ^{1}H NMR (500 MHz, CD_3CN) δ 1.12 (3H, d, *J* = 8.9 Hz, C*H*$_3$CB), 2.51 (2H, br s, $B(OH)_2$), 2.99-3.09 (1H, m, CB), 4.04-4.22 (2H, m, benzyl CH_2), 5.65 (1H, br s, NH), 7.06-7.29 (7H, m, benzyl-H, H3' and H5'), 7.42 (1H, t, *J* = 7.6 Hz, H4'), 7.51 (1H, d, *J* = 7.6 Hz, H2'). ^{13}C NMR (500 MHz, CD_3CN) δ 14.9 (*C*H$_3$CHB), 38.3 (benzyl CH_2), 48.8 (CHB), 125.7, 126.0, 128.4, 128.7, 129.1 (C2'), 130.7, 131.5 (C4'), 140.9 (C1') and 172.3 (CONH). HRMS (ESI, positive ion) $C_{18}H_{22}BNNaO_3$ $[M-2OH+2OMe+Na]^+$ requires 334.1590; Found 334.1593.



2-Fluoro-6-phenylbenzoic acid 77.

To a solution of biphenyl-2-carboxylic acid (1.05 g, 5.29 mmol, 1 equiv.) in anhydrous THF (40 mL) at -78^{o}C was added sec-BuLi (1.4M in cyclohexane, 8.40 mL, 11.6 mmol, 2.2 equiv.) dropwise over 30 mins. The mixture was then stirred at -78^{o}C for 3 h and *N*-fluorobenzenesulfonimide (5.00 g, 15.9 mmol, 3 equiv.) was added. The resulting yellow solution was allowed to stir at room temperature for overnight, after which, the mixture was poured into H_2O (25 mL/ 100 mL) and washed with Et_2O. The aqueous layer was acidified with 3M HCl aq and the resulting pale yellow precipitation was extracted with Et_2O, washed (H_2O, brine), dried ($MgSO_4$) and evaporated *in vacuo*. This gave the above as a pale yellow solid (0.69 g, 61%), mp 115-117°C. IR (nujol) υ/cm^{-1}: 2900-3024 (carboxalic acid OH), 1723 (carboxalic acid CO). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (1H, t, *J* = 8.4 Hz), 7.35 (1H, d, *J* = 8.4 Hz), 7.36-7.52 (6H, m), 11.62 (1H, br s, CO_2H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 114.8, 125.8, 127.4, 128.3, 128.7, 131.2, 131.8, 132.3, 131.9, 142.9, 160.9, 171.7. ^{19}F NMR (376 MHz, $CDCl_3$) -114.0. HRMS (ESI, negative ion) $C_{13}H_8FO_2$ $[M-H]^-$ requires 215.0514; Found 215.0507.



2-(Naphthalen-2-ylcarbonyl)benzoic acid 78.

To a suspension of phthalic anhydride (5.00 g, 33.8 mmol, 1 equiv.) in anhydrous DCM (30 mL) was added $AlCl_3$ (10.00 g, 74.3 mmol, 2.2 equiv.) and the mixture was stirred at room temperature for 30 mins. A solution of naphthalene (4.40 g, 33.8 mmol, 1 equiv.) in anhydrous DCM (10 mL) was then added dropwise, over 10 mins and the resulting deep red solution was allowed to stir at room temperature for overnight, after which, the mixture was poured into conc. HCl/ ice H_2O mixture (25 mL/ 100 mL). The organic layer was evaporated *in vacuo*, resuspended in DCM and extracted with sat. $NaHCO_3$. The aqueous layer was then acidified with 1M HCl aq. The resulting pale yellow precipitation was extracted with DCM, washed (H_2O, brine), dried ($MgSO_4$) and evaporated *in vacuo*. This gave the above as a pale

yellow solid (5.23 g, 56%), mp 120-122°C. IR (nujol) υ/cm^{-1}: 2900-3035 (carboxalic acid OH), 1712 (carboxalic acid CO), 1697 (ketone CO). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (1H, t, *J* = 7.8 Hz), 7.35 (1H, d, *J* = 7.8 Hz), 7.46-7.66 (4H, m), 7.77-8.05 (5H, m), 10.44 (1H, br s, CO_2H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 123.9, 124.5, 126.5, 127.8, 128.2, 128.5, 129.6, 129.8, 130.7, 131.2, 132.3, 131.7, 133.1, 133.6, 134.6, 135.6, 170.5. HRMS (ESI, positive ion) $C_{18}H_{12}NaO_3$ $[M+Na]^+$ requires 299.0679; Found 299.680.

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