151. Syntheses of Biphenyl Analogues of AP7, a New Class of Competitive *N*-Methyl-D-aspartate (NMDA) Receptor Antagonists

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(24.VII.95)

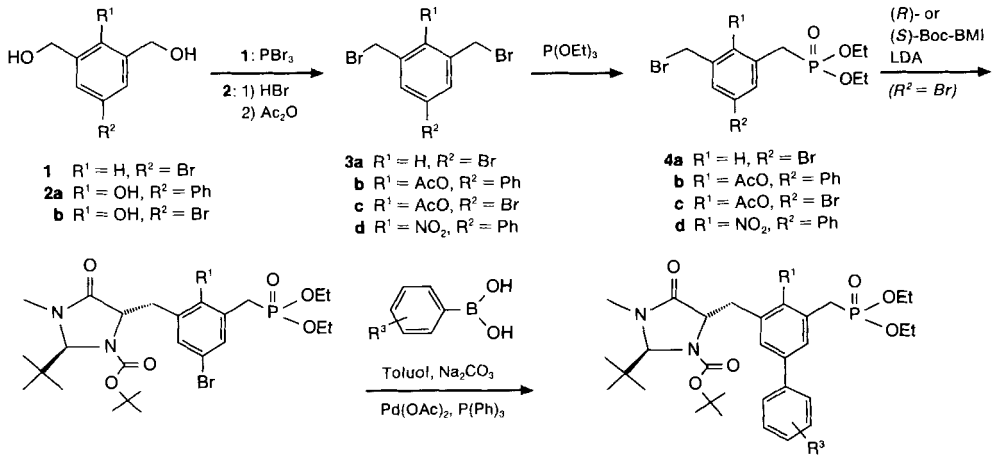
Syntheses of a series of enantiomerically pure, substituted analogues **7b–t** of SDZ EAB 515 (**7a**) were described (*Schemes 1* and *2*). Affinities for the NMDA receptor were measured ([^{3}H]CGP-39653 binding assay) and competitive NMDA antagonistic potencies determined in a functional test (rat neocortical slice preparation). Structure-activity relationships show that attachment of an OH group at position 4 of the chain-inserted benzene ring of the biphenyl moiety and/or expansion of the angle between the planes of the two benzene rings by *ortho*-substituents increase *in vitro* activities into the low nanomolar range.

1. Introduction. – By restricting the conformational flexibility of (2*R*)-2-amino-7-phosphonoheptanoic acid (D-AP7) [1], the 'prototype' of a competitive (NMDA) *N*-methyl-D-aspartate antagonist, more active and selective representatives were found, *e.g.* (*R*)-4-(3-phosphonopropyl)piperazine-2-carboxylic acid (D-CPP) [2] or (*R,E*)-4-(3-phosphonoprop-2-enyl)piperazine-2-carboxylic acid (D-CPP-ene) [2] (see *Table*). Insertion of a benzene ring in the middle of the AP7 chain does not reduce the NMDA antagonistic activity but inverses enantioselectivity from (*R*) to (*S*), whereas the addition of a second benzene ring (see SDZ EAB 515, **7a**) further increases both potency and enantioselectivity [3]. We describe here the preparation of a series of enantiomerically pure, substituted analogues of SDZ EAB 515 (**7a**). It is shown by biological *in vitro* tests that derivatives with an OH group at position 4 of the chain-inserted benzene ring of the biphenyl moiety and/or a Cl substituent in the *ortho*-position of the additional benzene ring (compounds **7f**, **h**, **n**, **p**, **q**) are competitive NMDA antagonists with potencies in binding as well as functional assays in the low nanomolar range.

2. Results and Discussion. – *Synthesis.* Due to strategic and logistic considerations, our recently published synthetic pathway to **7a** [3] was not ideally suitable for preparing derivatives with substituents at the additional 'lower' benzene ring. Therefore, we developed an alternative synthesis in which the biphenyl moiety in molecules of type **7** was built up in a later step of the synthesis.

Thus, as outlined in *Scheme 1*, the benzyl bromides and **4a–c** were used for the diastereoselective alkylation of the Li enolate of (*R*)- or (*S*)-1,1-dimethylethyl 2-(1,1-dimethylethyl)-3-methyl-4-oxoimidazolidine-1-carboxylate ((*R*)- or (*S*)-Boc-BMI) [4] in THF at −65° to give **5a** and **5b**, respectively. Similarly, benzyl bromides **4b** and **4d** yielded directly the target intermediates **6p** and **6t**, respectively. The bromides **4a–d** were prepared by treating the dibromides **3a–c**[1]) with 1 equiv. of triethyl phosphite in xylene at 140° (*Michaelis-Arbuzov* reaction), followed by chromatography of the reaction mixture on

Scheme 1



1 R^1 = H, R^2 = Br
2a R^1 = OH, R^2 = Ph
b R^1 = OH, R^2 = Br

3a R^1 = H, R^2 = Br
b R^1 = AcO, R^2 = Ph
c R^1 = AcO, R^2 = Br
d R^1 = NO_2, R^2 = Ph

4a R^1 = H, R^2 = Br
b R^1 = AcO, R^2 = Ph
c R^1 = AcO, R^2 = Br
d R^1 = NO_2, R^2 = Ph

(*R,R*)- or (*S,S*)-**5a** R^1 = H
(*R,R*)- or (*S,S*)-**5b** R^1 = AcO

R^1 = *H*:	(*S,S*)-**6a** R^3 = H	(*R,R*)- or (*S,S*)-**6f** R^3 = 2′-Cl
	(*S,S*)-**6b** R^3 = 4′-Cl	(*S,S*)-**6g** R^3 = 2′-F
	(*S,S*)-**6c** R^3 = 4′-MeO	(*S,S*)-**6h** R^3 = 2′,4′-Cl_2
	(*S,S*)-**6d** R^3 = 3′-NO_2	(*R,R*)- or (*S,S*)-**6i** R^3 = 4′-BzO
	(*S,S*)-**6e** R^3 = 2′-Me	(*R,R*)- or (*S,S*)-**6k** R^3 = 4′-OH
R^1 = *AcO*:	(*S,S*)-**6l** R^3 = 2′-F	(*R,R*)- or (*S,S*)-**6p** R^3 = H[a])
	(*S,S*)-**6m** R^3 = 4′-Cl	(*R,R*)- or (*S,S*)-**6q** R^3 = 2′-Cl
	(*S,S*)-**6n** R^3 = 4′-Me	(*S,S*)-**6r** R^3 = 2′,4′-Cl_2
	(*S,S*)-**6o** R^3 = 2′-Me	(*S,S*)-**6s** R^3 = 4′-Ph
R^1 = NO_2:	(*S,S*)-**6t** R^3 = H[b])	

[a]) Directly from **4b**. [b]) Directly from **4d**.

silica gel. The key step, *i.e.*, the Pd-catalyzed cross coupling [6] of the highly functionalized bromobenzene derivatives **5a** and **5b** with a series of substituted benzeneboronic acids, gave **6a–i**, **l–o**, **q–s** with good yields.

Transesterification of the diethyl phosphonate moiety of **6a–h**, **k** to the *O,O*-bis(trimethylsilyl) phosphonate moiety accompanied by Boc removal (Me_3SiBr/MeCN), hydrolysis (0.375M aqueous H_2SO_4 in the presence of *Dowex 50W* × *8* [4]), and crystallization from THF/2M aqueous HCl led to amino diacids **7a–i** (R^1 = H) in good overall yields (*Scheme 2*). Similarly, **7t** (R^1 = NO_2) was obtained from **6t**, and **7s** (R^1 = MeO) from **6p** (R^1 = AcO), after treatment of the latter with pyrrolidine [7] followed by MeI. The hydroxy-substituted enantiomers **7k–r** (R^1 = OH) were synthesized directly by treating the AcO-substituted intermediates **6l–s** in 0.375M aqueous H_2SO_4 in the presence of *Dowex 50W* × *8*[2]).

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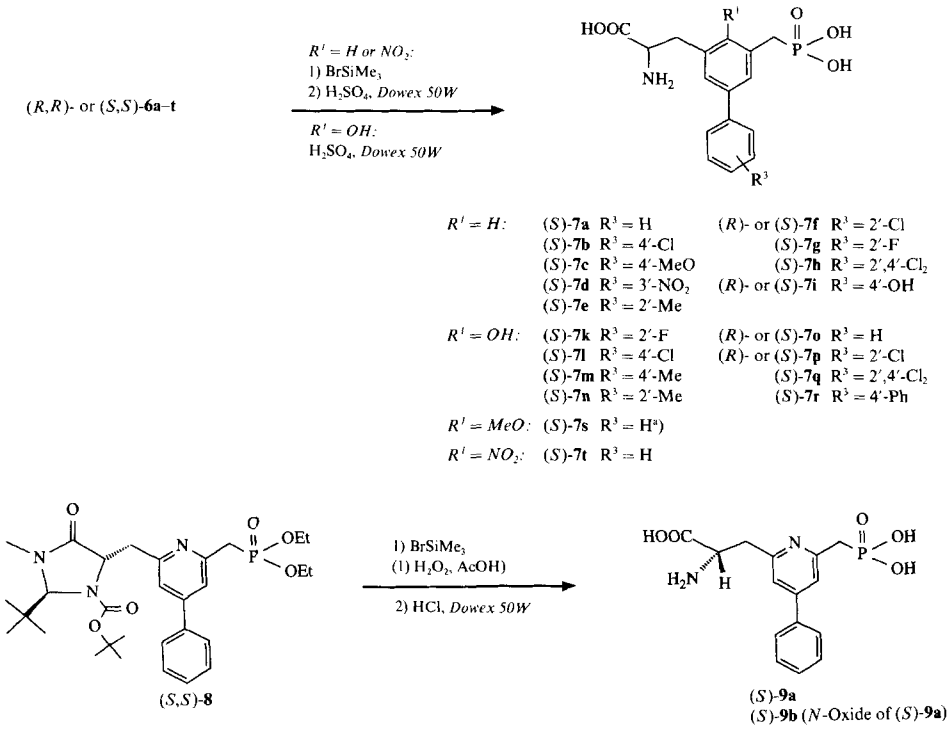
[1]) The dibromides **3a–c**, in turn, were synthesized from **1** and **2**, and **3d** from 5-bromo-1,3-dimethylbenzene by Pd-catalyzed cross coupling with benzeneboronic acid, nitration (→3,5-dimethyl-4-nitro(1,1′-biphenyl) [5]), and side-chain bromination with *N*-bromosuccinimide in CCl_4 (see *Exper. Part*).

[2]) Cleavage of dialkyl phosphonates under such mild conditions is very unusual. We suppose an anchimeric effect, with the O-atom of the phenol resp. of the *N*-oxide acting as an internal nucleophile at the neighboring P=O group leading to strained five-membered cyclic phosphonates as intermediates, which are easily hydrolyzed.

Scheme 2



[a]) From (*S,S*)-**6p**, see *Exper. Part.*

The pyridine derivatives (*S*)-**9a** and (*S*)-**9b** were synthesized in an analogous manner starting from the known 2,6-bis(bromomethyl)-4-phenylpyridine [8] *via* (*S,S*)-**8** or its *N*-oxide (see *Exper. Part*)[2])[3]).

The free amino diacids **7** and **9** proved to be enantiomerically pure (ee > 98%) by analysis on *Chiraplate*® TLC (see *Exper. Part*) and on capillary electrophoresis.

Biological Tests and Structure-Activity Relationship. The substituted analogues of SDZ EAB 515 were tested in a rat neocortical slice preparation (CWP) [9] by measuring the inhibition of NMDA-induced depolarization. The results of this functional test were essentially confirmed by a binding assay using [^{3}H]CGP39653 as a radioligand [10]. As seen in the *Table*, compounds with an OH group attached at position 4 in the chain-inserted benzene ring show a 6- to 10-fold increase in *in vitro* activity (compare **7a** with **7o** or **7h** with **7q**). Methylation of the phenolic OH (see (*S*)-**7s**) destroys this positive effect; replacement of the OH by a NO_2 group (see (*S*)-**7t**) or a *N*-oxide (see (*S*)-**9b**) decreases activity.

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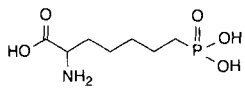
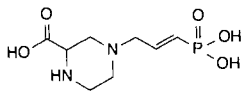
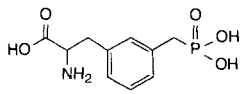
[3]) In the case of the *N*-oxide of (*S,S*)-**8**, the phosphonate moiety was completely hydrolyzed under the reaction conditions used to prepare the pyridine oxide (35% H_2O_2/AcOH, 70°).

Table. *Inhibition of the NMDA-Induced Depolarization in the Rat Neocortical Slice Preparation* (CWP) [9]; *NMDA Receptor Affinities* (^{3}H-CGP39653 binding assay) [10]

		NMDA Antagonistic activity (CWP, apparent pA_2 values)		Enantio-selectivity (selectivity factor)	^{3}H-CGP39653 Binding, pK_i
		(*S*)	(*R*)		
AP7		4.3 (0.1)	5.3 (1)	10	(*R*): 6.15
(*R*): SDZ EAA 494 (D-CCP-ene)		5.5 (1.6)	6.7 (25)	15	(*R*): 6.7
		5.3 (1)	< 3.7 (< 0.025)	> 40	(*S*): 5.45
(*S*): SDZ EAB 515	**7a** R^1 = H, R^3 = H	6.94 (44)	4.77 (0.29)	150	(*S*): 6.67
	7b R^1 = H, R^3 = 4′-Cl	6.76			(*S*): 7.1
	7c R^1 = H, R^3 = 4′-MeO	7.16			
	7d R^1 = H, R^3 = 3′-NO_2	6.95			
	7e R^1 = H, R^3 = 2′-Me	7.16			(*S*): 7.2
(*S*): SDZ 220–581	**7f** R^1 = H, R^3 = 2′-Cl	7.8 (315)	5.9 (4)	80	(*S*): 7.7
	7g R^1 = H, R^3 = 2′-F	7.12			
	7h R^1 = H, R^3 = 2′,4′-Cl_2	7.86			
	7i R^1 = H, R^3 = 4′-OH	7.33 (105)	5.4 (1.2)	85	(*S*): 7.3
	7o R^1 = OH, R^3 = H	7.7 (250)	6.4 (12.5)	20	(*S*): 7.3
	7l R^1 = OH, R^3 = 4′-Cl	7.94			(*S*): 7.7
	7n R^1 = OH, R^3 = 2′-Me	8.07			(*S*): 7.8
	7p R^1 = OH, R^3 = 2′-Cl	8.65 (2200)	7.6 (200)	11	(*S*): 8.35
	7k R^1 = OH, R^3 = 2′-F	7.85			
	7q R^1 = OH, R^3 = 2′,4′-Cl_2	8.75			(*S*): 8.45
	7r R^1 = OH, R^3 = 4′-Ph	8.43			
	7t R^1 = NO_2, R^3 = H	6.0			
	7s R^1 = MeO, R^3 = H	5.9			
	9a	5.9			
	9b	5.4			

The angle between the planes of the two benzene rings proved to be another important requirement for high binding affinity of these compounds. We assume that expansion of this angle by repulsive interaction between *ortho*-substituents enhances an interaction between the biphenyl moiety and a hydrophobic pocket of the NMDA receptor. The somewhat weaker effect of an *ortho*-Me group compared to that of an *ortho*-Cl substituent (compare **7f** with **7e** resp. **7p** with **7n**) must be due to different electronic influence to the aromatic ring. The most potent competitive NMDA antagonistic compounds of this series result by the combination of these two factors. Thus **7q** is *ca.* 65-fold more active than the unsubstituted compound SDZ EAB 515 (**7a**) and 2800-fold more potent than the original lead compound D-AP7.

Our data show that, without exception, the (*S*)-enantiomers are more active than the corresponding (*R*)-enantiomers, with selectivity factors between the enantiomers as high as 150. This contrasts with the situation found with most of the known competitive NMDA antagonists. The absolute (*S*)-configuration corresponds to that of natural α-amino acids (*e.g.* L-phenylalanine). This renders this class of compound as potential substrates for the L-carrier transport system of large amino acids of the endothelial blood-brain barrier. The *in vivo* pharmacology of this new class of potent competitive NMDA antagonists will be published elsewhere.

Experimental Part

General. See [3a]. For TLC on *Chiralplate®* from *Macherey-Nagel*, the amino acid was dissolved in 2M NH_3 and detected with a 0.1% ninhydrin soln. in EtOH.

3,5-Bis(bromomethyl)(1,1'-biphenyl)-4-yl Acetate (**3b**). As described for **3c** with 4-phenylphenol (10.0 g, 58.7 mmol): **2a** (11.1 g, 82%) with m.p. 104–109° ([12]: m.p. 113–114).

Treatment of **2a** with HBr and Ac_2O gave **3b** (9.1 g, 54% overall). M.p. 123–125°. ^{1}H-NMR: 2.50 (*s*, 3 H); 4.45 (*s*, 4 H); 7.3–7.5 (*m*, 3 H); 7.5–7.65 (*m*, 4 H).

4-Bromo-2,6-bis(bromomethyl)phenyl Acetate (**3c**). To a soln. of 4-bromophenol (124.1 g, 0.717 mol) and KOH (48.3 g, 0.86 mol) in H_2O (120 ml) was added dropwise with stirring at 50° within 40 min, a 37% aq. CH_2O soln. (168 ml). After 36 h stirring at 50°, the mixture was poured on ice/2M H_2SO_4 (pH 2) and stirred at r.t. After 30 min, the crystals were filtered off, washed with H_2O, then suspended in 20% $NaHSO_3$ soln. (450 ml) and AcOEt (400 ml), and stirred for 1.5 h. The crystals were filtered off and washed with H_2O and AcOEt: 79.2 g (48%) of **2b**, m.p. 164–168°.

A soln. of **2b** (20.0 g, 86 mmol) and 48% aq. HBr soln. (95 ml) in AcOH (80 ml) was stirred for 1 h at 80°. The mixture was poured on ice-water, and the crystals were filtered off and dried. A soln. of this crystalline product (30 g) in Ac_2O (24 ml), AcOH (350 ml), and conc. H_2SO_4 (0.5 ml) was stirred for 3 h at 60° under Ar. The mixture was poured on ice-water, and the crystals were filtered off: 29.2 g (85%) of **3c**. M.p. 150–153° ([13]: m.p. 159–160°). ^{1}H-NMR: 2.42 (*s*, 3 H); 4.30 (*s*, 4 H); 7.52 (*s*, 2 H).

3,5-Bis(bromomethyl)-4-nitro(1,1'-biphenyl) (**3d**). A suspension of 3,5-dimethyl-4-nitro(1,1'-biphenyl) [5] (5.7 g, 25 mmol), NBS (16.3 g, 91 mmol), α,α'-azo-bis[isobutyronitrile] (150 mg), and abs. CCl_4 (160 ml) was irradiated with 2 spot lamps (2 × 150 W) and stirred under reflux for 17 h. The mixture was filtered and the filtrate evaporated. The residue (11.4 g) was dissolved in Et_2O (20 ml) and filtered. The filtrate was purified by CC (silica gel, hexane fraction/Et_2O 9:1): **3d** (2.2 g, 23%) with R_f 0.25 (TLC, cyclohexane/AcOEt 9:1) and m.p. 129–131° (Et_2O/petroleum ether) and the monobrominated intermediate with R_f 0.33 (TLC, cyclohexane/AcOEt 9:1) and m.p. 50–51° (Et_2O/petroleum ether). ^{1}H-NMR of **3d**: 4.55 (*s*, 4 H); 7.40–7.63 (*m*, 5 H); 7.69 (*s*, 2 H).

Diethyl{[3-Bromo-5-(bromomethyl)phenyl]methyl}phosphonate (**4a**). A soln. of 5-bromobenzene-1,3-dimethanol (**1**) [11] (14.3 g, 66 mmol) in toluene (220 ml) was treated at 80° with a soln. of PBr_3 (11.5 ml, 122 mmol) in toluene (30 ml). After 2 h at 80°, the mixture was poured on ice. The org. layer was washed with sat. aq. $KHCO_3$ soln. dried (Na_2SO_4), and evaporated: **3a** (21.55 g).

A soln. of **3a** (21.55 g) in xylene (220 ml) was treated with $P(OEt)_3$ (12.1 ml, 69.5 mmol) and stirred under reflux for 2 h. The mixture was evaporated and the residue (28 g) purified by CC (silica gel, AcOEt): **4a** (11.7 g, 47%). R_f 0.34 (TLC, AcOEt). M.p. 61–63°. ^{1}H-NMR: 1.24 (*t*, *J* = 7, 6 H); 3.07 (*d*, *J* = 22, 2 H); 4.02 (*dq*, *J* = 7, 6, 4 H); 4.37 (*s*, 2 H); 7.24 (*s*, 1 H); 7.38 (*m*, 2 H).

Diethyl{[4-(Acetyloxy)-5-(bromomethyl)(1,1'-biphenyl)-3-yl]methyl}phosphonate (**4b**). As described for **4c**, with 20.6 g (51.7 mmol) of **3b**: 11.6 g (49%) of **4b**. R_f 0.35 (TLC, AcOEt). ^{1}H-NMR: 1.25 (*t*, *J* = 7, 6 H); 2.42 (*s*, 3 H); 3.10 (*d*, *J* = 22, 2 H); 3.95–4.15 (*m*, 4 H); 4.41 (*s*, 2 H); 7.30–7.48 (*m*, 3 H); 7.55 (*m*, 3 H); 7.62 (*d*, *J* = 2, 1 H).

Diethyl{[2-(Acetyloxy)-5-bromo-3-(bromomethyl)phenyl]methyl}phosphonate (**4c**). A soln. of **3c** (15.3 g, 38.2 mmol) in xylene (130 ml) was treated with $P(OEt)_3$ (7.3 ml, 45 mmol) and stirred under reflux for 2 h. The mixture was evaporated and the residue purified by CC (silica gel, AcOEt/cyclohexane 1:1). The fractions containing the product of R_f 0.30 (TLC, AcOEt) yielded **4c** (7.4 g, 42%). M.p. 112–115° (Et_2O/petroleum ether). ^{1}H-NMR: 1.23 (*t*, *J* = 7, 6 H); 2.40 (*s*, 3 H); 3.00 (*d*, *J* = 22, 2 H); 3.94–4.10 (*m*, 4 H); 4.27 (*s*, 2 H); 7.45 (*d*, *J* = 2, 1 H); 7.52 (*d*, *J* = 2, 1 H).

Diethyl {[5-(Bromomethyl)-4-nitro(1,1'-biphenyl)-3-yl]methyl}phosphonate (**4d**). As described for **4c**, with **3d** (2.6 g, 67.5 mmol): 0.9 g (30%) of **4d**. R_f 0.45 (TLC, AcOEt). ^{1}H-NMR: 1.25 (*t*, *J* = 7, 6 H); 3.38 (*d*, *J* = 22, 2 H); 3.95–4.13 (*m*, 4 H); 4.48 (*s*, 2 H); 7.32–7.51 (*m*, 3 H); 7.51–7.65 (*m*, 3 H); 7.68 (*d*, *J* = 2, 1 H).

1,1-Dimethylethyl (2S,5S)-5-{{3-Bromo-5-[(diethoxyphosphoryl)methyl]phenyl}methyl}-2-(1,1-dimethylethyl)-3-methyl-4-oxoimidazolidine-1-carboxylate ((*S,S*)-**5a**). To a stirred soln. of (i-Pr)$_2$NH (0.74 ml, 5.4 mmol) in abs. THF (8 ml) was added at −70° over 10 min 1.6M BuLi in hexane (5.4 mmol). After 20 min stirring at −70°, a soln. of (*S*)-1,1-dimethylethyl 2-(1,1-dimethylethyl)-3-methyl-4-oxoimidazolidine-1-carboxylate ((*S*)-Boc-BMI) [4] (1.4 g, 5.4 mmol) in abs. THF (4 ml) was added and stirring continued for 20 min. Then a soln. of **4a** (2.0 g, 5 mmol) in THF (4 ml) was added and stirring continued at −70°. After 1 h, the mixture was warmed up to r.t. and then poured into sat. aq. NH_4Cl soln. (50 ml) and extracted with AcOEt. The org. layer was washed with sat. NaCl soln., dried ($NaSO_4$), and evaporated. The oily residue (3.1 g) was purified by CC (120 g of silica gel, AcOEt): (*S,S*)-**5a** (2.0 g, 69%). Oil. R_f 0.30 (TLC, AcOEt). $[\alpha]_D^{20} = +22.3$ (*c* = 1, EtOH). ^{1}H-NMR (360 MHz): 0.93 (*s*, 9 H); 1.26 (*t*, *J* = 7, 3 H); 1.28 (*t*, *J* = 7, 3 H); 1.50 (*s*, 9 H); 2.88 (*s*, 3 H); 3.02 (*d*, *J* = 21, 2 H); 3.19 (*d*, *J* = 14, 1 H); 3.75 (br. *s*, 1 H); 3.97–4.08 (*m*, 4 H); 4.29 (br. *s*, 1 H); 4.62 (*s*, 1 H); 7.00 (*d*, *J* = 2, 1 H); 7.20 (*d*, *J* = 2, 1 H); 7.31 (*d*, *J* = 2, 1 H).

1,1-Dimethylethyl (2R,5R)-5-{{3-Bromo-5-[(diethoxyphosphoryl)methyl]phenyl}methyl}-2-(1,1-dimethylethyl)-3-methyl-4-oxoimidazolidine-1-carboxylate ((*R,R*)-**5a**). As described for (*S,S*)-**5**, with (*R*)-Boc-BMI [4] (13.8 g, 53.8 mmol) and **4a** (20.0 g, 50 mmol): 27.3 (95%) of (*R,R*)-**5a**. $[\alpha]_D^{20} = -23.6$ (*c* = 1, EtOH). ^{1}H-NMR: as for (*S,S*)-**5a**.

1,1-Dimethylethyl (2S,5S)-5-{{2-(Acetyloxy)-5-bromo-3-[(diethoxyphosphoryl)methyl]phenyl}methyl}-2-(1,1-dimethylethyl)-3-methyl-4-oxoimidazolidine-1-carboxylate ((*S,S*)-**5b**). As described for (*S,S*)-**5a**, with (*S*)-Boc-BMI (1.23 g, 4.8 mmol) and **4c** (2.0 g, 4.4 mmol): (*S,S*)-**5b** (2.1 g, 75%). R_f 0.18 (TLC, AcOEt). ^{1}H-NMR: 0.92 (*s*, 9 H); 1.22 (*t*, *J* = 7, 6 H); 1.35 (*s*, 9 H); 2.35 (*s*, 3 H); 2.90 (*s*, 3 H); 2.96 (*d*, *J* = 21, 2 H); 3.25 (*m*, 2 H); 3.92–4.10 (*m*, 4 H); 4.21 (br. *s*, 1 H); 4.85 (*s*, 1 H); 7.15 (*d*, *J* = 2, 1 H); 7.40 (*d*, *J* = 2, 1 H).

1,1-Dimethylethyl (2R,5R)-5-{{2-(Acetyloxy)-5-bromo-3-[(diethoxyphosphoryl)methyl]phenyl}methyl}-2-(1,1-dimethylethyl)-3-methyl-4-oxoimidazolidine-1-carboxylate ((*R,R*)-**5b**). As described for (*S,S*)-**5a**, with (*R*)-Boc-BMI (3.1 g, 12.1 mmol) and **4c** (5.0 g, 10.9 mmol): (*R,R*)-**5b** (5.2 g, 75%). R_f 0.19 (TLC, AcOEt). ^{1}H-NMR: as for (*S,S*)-**5b**.

1,1-Dimethyl (2S,5S)-5-{{5-[(Diethoxyphosphoryl)methyl](1,1'-biphenyl)-3-yl}methyl}-2-(1,1-dimethylethyl)-3-methyl-4-oxoimidazolidine-1-carboxylate ((*S,S*)-**6a**). As described for (*S,S*)-**6f**, with (*S,S*)-**5a** (3.1 g, 5.4 mmol) and benzeneboronic acid (0.75 g, 6.1 mmol): 2.65 g (86%) of (*S,S*)-**6a**. R_f 0.20 (TLC, AcOEt). $[\alpha]_D^{20} = +37$ (*c* = 1, EtOH; [3]: $[\alpha]_D^{20} = +35$ (*c* = 1, EtOH)). ^{1}H-NMR: identical to that described in [3].

(*S,S*)-**6b**, (*S,S*)-**6c**, (*S,S*)-**6d**, and (*S,S*)-**6e** were prepared as described for (*S,S*)-**6f**.

1,1-Dimethylethyl (2S,5S)-5-{{2'-Chloro-5-[(diethoxyphosphoryl)methyl](1,1'-biphenyl)-3-yl}methyl}-2-(1,1-dimethylethyl)-3-methyl-4-oxoimidazolidine-1-carboxylate ((*S,S*)-**6f**). A soln. of (*S,S*)-**5a** (3.1 g, 5.4 mmol), 2-chlorobenzeneboronic acid (0.95 g, 6.1 mmol), 2M aq. Na_2CO_3 (6.5 ml) and EtOH (1.3 ml) in toluene (65 ml) was degassed in an ultrasonic bath and flushed with Ar before PPh_3 (180 mg, 0.7 mmol) and $Pd(OAc)_2$ (40 mg, 0.18 mmol) were added. The mixture was stirred for 6 h at 100° under Ar. The org. layers were dried (Na_2SO_4) and evaporated. The oily residue (3.7 g) was purified by CC (silica gel, AcOEt): 2.65 g (81%) of **6f**. Oil R_f 0.29 (TLC, AcOEt). $[\alpha]_D^{20} = +31.3$ (*c* = 1, EtOH). ^{1}H-NMR (360 MHz, (D$_6$)DMSO, 120°): 0.91 (*s*, 9 H); 1.20 (*t*, *J* = 7, 6 H); 1.36 (*s*, 9 H); 2.73 (*s*, 3 H); 3.12 (*d*, *J* = 21, 2 H); 3.10 (*dd*, *J* = 15, 2, 1 H); 3.65 (*dd*, *J* = 15, 6, 1 H); 3.90–4.04 (*m*, 4 H); 4.23 (br. *s*, 1 H); 4.72 (*s*, 1 H); 6.96 (*d*, *J* = 2, 1 H); 7.02 (*d*, *J* = 2, 1 H); 7.18 (*d*, *J* = 2, 1 H); 7.26 (*m*, 1 H); 7.35 (*m*, 2 H); 7.48 (*m*, 1 H).

1,1-Dimethylethyl (2R,5R)-5-{{2'-Chloro-5-[(diethoxyphosphoryl)methyl](1,1'-biphenyl)-3-yl}methyl}-2-(1,1-dimethylethyl)-3-methyl-4-oxoimidazolidine-1-carboxylate ((*R,R*)-**6f**). As described for (*S,S*)-**6f** with (*R,R*)-**5a** (7.50 g, 13 mmol) and 2-chlorobenzeneboronic acid (2.3 g, 14.7 mmol): 5.0 g (63%) of (*R,R*)-**6f**. ^{1}H-NMR: as for (*S,S*)-**6f**.

(*S,S*)-**6g**, and (*S,S*)-**6h** were prepared as described for (*S,S*)-**6f**.

1,1-Dimethylethyl (2S,5S)-5-{{5-[(Diethoxyphosphoryl)methyl]-4'-hydroxy(1,1'-biphenyl)-3-yl}methyl}-2-(1,1-dimethylethyl)-3-methyl-4-oxoimidazolidine-1-carboxylate ((*S,S*)-**6k**). As described for (*S,S*)-**6f**, with (*S,S*)-**5a** (23.0 g, 40.0 mmol) and 4-(benzyloxy)benzeneboronic acid (10.0 g, 44 mmol): (*S,S*)-**6i**. R_f 0.26 (TLC, AcOEt).

A soln. of (*S,S*)-**6i** (26.5 g) in EtOH (400 ml) was hydrogenated at r.t. in the presence of 5% Pd/C. the catalyst was filtered off and the solvent evaporated. The residue (23.7 g) was crystallized from Et_2O/petroleum ether: 20.1 g (85%) of (*S,S*)-**6k**. M.p. 156–160°. $[\alpha]_D^{20} = +41.8$ (*c* = 0.225, EtOH).

1,1-Dimethylethyl (2R,5R)-5-{{5-[(Diethoxyphosphoryl)methyl]-4'-hydroxy(1,1'-biphenyl)-3-yl}methyl}-2-(1,1-dimethylethyl)-3-methyl-4-oxoimidazolidine-1-carboxylate ((*R,R*)-**6k**). As described for (*S,S*)-**6k**, with

(*R,R*)-**5a** (6.2 g, 10.7 mmol) and 4-(benzyloxy)benzeneboronic acid (7.7 g, 11.8 mmol) (*R,R*)-**6i**. A sample of (*R,R*)-**6i** (5.3 g, 7.8 mmol) was hydrogenated as described for (*S,S*)-**6i**: 3.3 g (72%) of (*R,R*)-**6k**. M.p. 154–156°. $[\alpha]_D^{20} = -43.5$ ($c = 1$, EtOH).

(*S,S*)-**6l**, (*S,S*)-**6m**, (*S,S*)-**6n**, and (*S,S*)-**6o** were prepared as described for (*S,S*)-**6f**.

*1,1-Dimethylethyl (2*S*,5*S*)-5-{{4-(Acetyloxy)-5-[(diethoxyphosphoryl)methyl](1,1'-biphenyl)-3-yl}methyl}-2-(1,1-dimethylethyl)-3-methyl-4-oxoimidazolidine-1-carboxylate* ((*S,S*)-**6p**). As described for (*S,S*)-**5a**, with (*S*)-Boc-BMI (11.1 g, 43.3 mmol) and **4b** (17.7 g, 38.9 mmol): 18.7 g (76%) of (*S,S*)-**6p**. ^{1}H-NMR: 0.94 (*s*, 9 H); 1.22 (*t*, $J = 7$, 6 H); 1.30 (*s*, 9 H); 2.38 (*s*, 3 H); 2.88 (*s*, 3 H); 3.10 (*d*, $J = 21$, 2 H); 3.35 (*m*, 2 H); 3.93–4.08 (*m*, 4 H); 4.30 (br. *s*, 1 H); 4.90 (*s*, 1 H); 7.15 (*d*, $J = 2$, 1 H); 7.40 (*d*, $J = 2$, 1 H).

*1,1-Dimethyl (2*R*,5*R*)-5-{{4-(Acetyloxy)-5-[(diethoxyphosphoryl)methyl](1,1'-biphenyl)-3-yl}methyl}-2-(1,1-dimethylethyl)-3-methyl-4-oxoimidazolidine-1-carboxylate* ((*R,R*)-**6p**). As described for (*S,S*)-**5a**, with (*R*)-Boc-BMI (2.45 g, 9.55 mmol) and **4b** (4.0 g, 8.8 mmol): 4.1 g (76%) of (*R,R*)-**6p**. ^{1}H-NMR as for (*S,S*)-**6p**.

(*R,R*)- and (*S,S*)-**6q**, (*S,S*)-**6r**, and (*S,S*)-**6s** were prepared as described for (*S,S*)-**6f**.

*1,1-Dimethylethyl (2*S*,5*S*)-5-{{5-[(Diethoxyphosphoryl)methyl]-4-nitro(1,1'-biphenyl)-3-yl}methyl}-2-(1,1-dimethylethyl)-3-methyl-4-oxoimidazolidine-1-carboxylate* ((*S,S*)-**6t**). As described for (*S,S*)-**5a** with (*S*)-Boc-BMI (210 mg, 0.82 mmol) and **4d** (340 mg, 0.77 mmol): 250 mg (53%) of (*S,S*)-**6t**. ^{1}H-NMR: 0.94 (*s*, 9 H); 1.20 (*t*, $J = 7$, 6 H); 1.28 (*s*, 9 H); 2.92 (*s*, 3 H); 3.31 (*dd*, $J = 22$, 6, 2 H); 3.48 (*d*, $J = 6$, 1 H); 3.53–3.70 (*m*, 1 H); 3.92–4.11 (*m*, 4 H); 4.31 (br. *s*, 1 H); 4.98 (*s*, 1 H); 7.20 (*d*, $J = 2$, 1 H); 7.30–7.58 (*m*, 6 H).

*(*S*)-α-Amino-5-(phosphonomethyl)(1,1'-biphenyl)-3-propanoic Acid* ((*S*)-**7a**). Deprotection and hydrolysis of (*S,S*)-**6a** as described for (*S*)-**7f** gave (*S*)-**7a**, identical (m.p., TLC, $[\alpha]_D$, $[\alpha]_{365}$, ^{1}H-NMR) to the product obtained in [3].

*(*S*)-α-Amino-4'-chloro-5-(phosphonomethyl)(1,1'-biphenyl)-3-propanoic Acid* ((*S*)-**7b**). As described for (*S,S*)-**6f**, with (*S,S*)-**5a** (2.0 g, 3.4 mmol) and 4-chlorobenzeneboronic acid (570 mg, 3.7 mmol): (*S,S*)-**6b**. Deprotection and hydrolysis as described for (*S*)-**7f** gave (*S*)-**7b** (0.55 g, 44% overall). M.p. 260–270° (dec.). $[\alpha]_D^{20} = 0 \pm 0.5$; $[\alpha]_{365}^{20} = +19.6$ ($c = 1$, 6M HCl). Anal. calc. for $C_{16}H_{17}ClNO_5P \cdot 0.3\ H_2O$ (375.15): C 51.23, H 4.73, Cl 9.45, N 3.73, O 22.68, P 8.26; found: C 51.40, H 5.10, Cl 9.30, N 3.80, O 22.60, P 7.80.

*(*S*)-α-Amino-4'-methoxy-5-(phosphonomethyl)(1,1'-biphenyl)-3-propanoic Acid* ((*S*)-**7c**). As described for (*S,S*)-**6f**, with (*S,S*)-**5a** (2.9, 5.0 mmol) and 4-methoxybenzeneboronic acid (1.2 g, 7.9 mmol): (*S,S*)-**6c**. A sample was deprotected and hydrolyzed as described for (*S*)-**7f**: (*S*)-**7c**. M.p. 272–274°. $[\alpha]_D^{20} = 0 \pm 0.5$; $[\alpha]_{436}^{20} = +5.7$ ($c = 1$, 6M HCl). Anal. calc. for $C_{17}H_{20}NO_6P \cdot 0.2\ H_2O$ (365.32): C 55.37, H 5.57, N 3.80, O 26.86, P 8.40; found: C 55.30, H 5.70, N 3.90, P 8.50.

*(*S*)-α-Amino-3'-nitro-5-(phosphonomethyl)(1,1'-biphenyl)-3-propanoic Acid* ((*S*)-**7d**). As described for (*S,S*)-**6f**, with (*S,S*)-**5a** (8.3 g, 14.4 mmol) and 3-nitrobenzeneboronic acid (3.6 g, 21.5 mmol): (*S,S*)-**6d**. A sample was deprotected and hydrolyzed as described for (*S*)-**7f**: (*S*)-**7d**. M.p. 210° (dec.). $[\alpha]_D^{20} = +1.6$ ($c = 1$, 6M HCl). Anal. calc. for $C_{16}H_{17}N_2O_7P$ (380.290): C 50.53, H 4.51, N 7.37, O 29.45, P 8.14; found: C 50.30, H 4.70, N 7.40, P 7.60.

*(*S*)-α-Amino-2'-methyl-5-(phosphonomethyl)(1,1'-biphenyl)-3-propanoic Acid* ((*S*)-**7e**). As described for (*S,S*)-**6f**, with (*S,S*)-**5a** (6.0 g, 10.4 mmol) and 2-methylbenzeneboronic acid (2.1 g, 15.4 mmol): (*S,S*)-**6e** (5.4 g, 88%) with R_f 0.20 (TLC, AcOEt). Deprotection and hydrolysis as described for (*S*)-**7f** gave (*S*)-**7e** (1.65 g, 51% overall). M.p. 260–265° (dec.). $[\alpha]_D^{20} = +3.0$ ($c = 1$, 6M HCl). Anal. calc. for $C_{17}H_{20}NO_5P \cdot 0.2\ H_2O$ (352.93): C 57.86, H 5.83, N 3.97, O 23.57, P 8.78; found: C 57.90, H 5.90, N 4.10, P 8.50.

*(*S*)-α-Amino-2'-chloro-5-(phosphonomethyl)(1,1'-biphenyl)-3-propanoic Acid* ((*S*)-**7f**). A soln. of (*S,S*)-**6f** (7.0 g, 11.5 mmol) in MeCN (32 ml) was treated with Me_3SiBr (10 ml). After 24 h stirring at r.t., the mixture was evaporated. A soln. of the residue in xylene (19 ml) was added to 0.375M aq. H_2SO_4 (50 ml) at 70° and stirring continued for 4 h. The aq. phase was separated, and after addition of *Dowex 50W X4* (50–100 mesh, 14 g), the mixture was heated under reflux for 144 h. The resin was washed in a column sequentially with H_2O, EtOH (28 ml), and H_2O (32 ml) before the amino acid was eluted with aq. 10% NH_3 soln. (100 ml). The residue of the NH_3 eluates were solved in 2M aq. HCl (6 ml) and THF (2 ml) at 60° (pH 2), and stirring was continued at r.t. The crystals were filtered off and dried: (*S*)-**7f** (2.55 g, 62% overall). R_f 0.35 (*Chiralplate*® ammonium salt, MeCN/H_2O/MeOH 4:2:1). M.p. 280–288° (dec.). $[\alpha]_D^{20} = -6.0$ ($c = 1.6$M HCl). ^{1}H-NMR (NaOD): 3.00 (*m*, 1 H); 3.01 (*d*, $J = 21$, 2 H); 3.32 (*dd*, $J = 13.5$, 1 H); 3.93 (*dd*, $J = 7.5$, 1 H); 7.20 (*s*, 2 H); 7.22–7.35 (*m*, 1 H); 7.33 (*s*, 1 H); 7.50 (*m*, 1 H). Anal. calc. for $C_{16}H_{17}ClNO_5P$ (369.74): C 51.98, H 4.63, Cl 9.59, N 3.79, O 21.64, P 8.38; found: C 52.01, H 4.67, Cl 9.90, N 3.80, O 21.89, P 8.10.

*(*R*)-α-Amino-2'-chloro-5-(phosphonomethyl)(1,1'-biphenyl)-3-propanoic Acid* ((*R*)-**7f**). As described for (*S*)-**7f**, with (*R,R*)-**6f** (5.0 g, 8.2 mmol): 2.45 g (77% overall) of the amorphous monoammonium salt of (*R*)-**7f**. R_f 0.31 (*Chiralplate*®, MeCN/H_2O/MeOH 4:2:1). Anal. calc. for $C_{16}H_{20}ClN_2O_5P \cdot 0.55\ NH_4OH$ (389.02): C 49.40, H 5.12, Cl 9.11, N 5.58, O 22.83, P 7.96; found: C 49.45, H 5.30, Cl 9.20, N 5.70, O 22.90, P 8.30.

A sample was converted to the free amino acid (*R*)-**7f**. M.p. 270–280° (dec.). $[\alpha]_D^{20} = +6.3$ ($c = 1$, 6M HCl).

(S)-α-Amino-2'-fluoro-5-(phosphonomethyl)(1,1'-biphenyl)-3-propanoic Acid ((*S*)-**7g**). As described for (*S,S*)-**6f**, with (*S,S*)-**5a** (8.6 g, 14.9 mmol) and 2-fluorobenzeneboronic acid (2.8 g, 20.0 mmol): (*S,S*)-**6g** (7.27 g, 82%) with R_f 0.15 (TLC, AcOEt). Deprotection and hydrolysis as described for (*S*)-**7f** gave (*S*)-**7g** (2.9 g, 66% overall). M.p. 272–276° (dec.). $[\alpha]_D^{20} = +1.1$ ($c = 1$, 6M HCl). Anal. calc. for $C_{16}H_{17}FNO_5P \cdot 0.2\ H_2O$ (356.89): C 53.85, H 4.91, F 5.32, N 3.92, P 8.68; found: C 53.80, H 4.90, N 3.80, P 8.70.

(S)-α-Amino-2',4'-dichloro-5-(phosphonomethyl)(1,1'-biphenyl)-3-propanoic Acid ((*S*)-**7h**). As described for (*S,S*)-**6f**, with (*S,S*)-**5a** (8.0 g, 13.9 mmol) and 2,4-dichlorobenzeneboronic acid (3.9 g, 20.0 mmol): (*S,S*)-**6h** (8.6 g, 96%) with R_f 0.19 (TLC, AcOEt). Deprotection and hydrolysis as described for (*S*)-**7f** gave (*S*)-**7h** (2.7 g, 48% overall). M.p. 272–277° (dec.). $[\alpha]_D^{20} = -6.0$ ($c = 1$, 6M HCl). Anal. calc. for $C_{16}H_{16}Cl_2NO_5P \cdot 0.1\ H_2O$ (405.99): C 47.34, H 4.02, Cl 17.46, N 3.45, O 20.10, P 7.63: found: C 47.30, H 4.10, Cl 17.60, N 3.40, P 7.60.

(S)-α-Amino-4'-hydroxy-5-(phosphonomethyl)(1,1'-biphenyl)-3-propanoic Acid ((*S*)-**7i**). As described for (*S*)-**7f**, with (*S,S*)-**6k** (18.9 g, 32 mmol): 7.0 g (62% overall) of (*S*)-**7i**. R_f 0.45 (*Chiralplate®*, ammonium salt, MeCN/H_2O/MeOH 4:2:1). M.p. 275–285° (dec.). $[\alpha]_D^{20} = 0 \pm 0.5$; $[\alpha]_{436}^{20} = +4.2$ ($c = 1.055$, 6M HCl). Anal. calc. for $C_{16}H_{20}NO_7P \cdot 1.1\ H_2O$ (371.29): C 51.76, H 5.49, N 3.77, O 30.64, P 8.34; found: C 51.60, H 5.40, N 4.00, O 30.20, P 7.80.

(R)-α-Amino-4'-hydroxy-5-(phosphonomethyl)(1,1'-biphenyl)-3-propanoic Acid ((*R*)-**7i**). As described for (*S*)-7i, with (*R,R*)-**6k** (9.7 g, 16.5 mmol): 2.4 g (42% overall) of (*R*)-**7i**. R_f 0.40 (*Chiralplate®*, ammonium salt, MeCN/H_2O/MeOH 4:2:1). M.p. 280–290° (dec.). $[\alpha]_D^{20} = 0 \pm 0.5$; $[\alpha]_{436}^{20} = -4.4$ ($c = 1$, 6M HCl). Anal. calc. for $C_{16}H_{20}NO_7P \cdot 0.1\ H_2O$ (353.46): C 54.37, H 5.20, N 3.96, P 8.76; found: C 54.40, H 5.20, N 3.90, P 8.80.

(S)-α-Amino-2'-fluoro-4-hydroxy-5-(phosphonomethyl)(1,1'-biphenyl)-3-propanoic Acid ((*S*)-**7k**). As described for (*S,S*)-**6f**, with (*S,S*)-**5b** (10.0 g, 15.8 mmol) and 2-fluorobenzeneboronic acid (2.8 g, 20 mmol): 5.3 g (51%) of (*S,S*)-**6l**. Hydrolysis as described for (*S*)-**7p** gave (*S*)-**7k** (1.15 g, 39%). M.p. 248–252° (dec.). $[\alpha]_D^{20} = +5.6$ ($c = 1$, 6M HCl). Anal. calc. for $C_{16}H_{17}ClNO_6P \cdot 0.2\ H_2O$/THF 1:1 (386.41): C 52.10, H 4.93, F 4.92, N 3.62, P 8.02; found: C 51.80, H 5.10, F 4.70, N 3.70, P 8.20.

(S)-α-Amino-4'-chloro-4-hydroxy-5-(phosphonomethyl)(1,1'-biphenyl)-3-propanoic Acid ((*S*)-**7l**). As described for (*S,S*)-**6f**, with (*S,S*)-**5b** (2.5 g, 3.9 mmol) and 4-chlorobenzeneboronic acid (0.66 g, 4.2 mmol): 2.35 g (90%) of (*S,S*)-**6m**. Hydrolysis of (*S,S*)-**6m** (4.66 g, 7.0 mmol) as described for (*S*)-**7p** gave (*S*)-**7l** (2.3 g, 86%). M.p. 253–260° (dec.). $[\alpha]_D^{20} = +6.0$ ($c = 1$, 6M HCl). Anal. calc. for $C_{16}H_{17}ClNO_6P$ (385.74): C 49.82, H 4.44, Cl 9.19, N 3.63, P 8.03; found: C 49.90, H 4.70, Cl 9.10, N 3.60, P 7.50.

(S)-α-Amino-4-hydroxy-4'-methyl-5-(phosphonomethyl)(1,1'-biphenyl)-3-propanoic Acid ((*S*)-**7m**). As described for (*S,S*)-**6f**, with (*S,S*)-**5b** (2.5 g, 3.9 mmol) and 4-methylbenzeneboronic acid (0.6 g, 4.2 mmol): 2.15 g (85%) of (*S,S*)-**6n**. Hydrolysis of (*S,S*)-**6n** (2.0 g, 3.1 mmol) as described for (*S*)-**7p** gave (*S*)-**7m** (0.95 g, 84%). M.p. 265–275° (dec.). $[\alpha]_D^{20} = +7.4$ ($c = 0.5$, 6M HCl). Anal. calc. for $C_{17}H_{20}NO_6P \cdot 0.2\ H_2O$ (368.95): C 55.35, H 5.57, N 3.80, P 8.40; found: C 55.41, H 5.75, N 3.95, P 8.40.

(S)-α-Amino-4-hydroxy-2'-methyl-5-(phosphonomethyl)(1,1'-biphenyl)-3-propanoic Acid ((*S*)-**7n**). As described for (*S,S*)-**6f**, with (*S,S*)-**5b** (10.0 g, 15.8 mmol) and 2-methylbenzeneboronic acid (3.6 g, 26 mmol): 7.15 g (70%) of (*S,S*)-**6o**. Hydrolysis as described for (*S*)-**7p** gave (*S*)-**7n** (2.9 g, 72%). M.p. 255–260° (dec.). $[\alpha]_D^{20} = +3.7$ ($c = 1$, 6M HCl). Anal. calc. for $C_{17}H_{20}NO_6P \cdot 0.15\ H_2O$ (368.02): C 55.40, H 5.56, N 3.81, P 8.42; found: C 55.60, H 5.70, N 3.80, P 8.40.

(S)-α-Amino-4-hydroxy-5-(phosphonomethyl)(1,1'-biphenyl)-3-propanoic Acid ((*S*)-**7o**). Hydrolysis of (*S,S*)-**6p** (18.5 g, 29 mmol) as described for (*S*)-**7p** gave (*S*)-**7o** (7.45 g, 73%). R_f 0.60 (*Chiralplate®*, ammonium salt, MeCN/H_2O/MeOH 4:2:1). M.p. 255–260° (dec.). $[\alpha]_D^{20} = +5.1$ ($c = 1$, 6M HCl). Anal. calc. for $C_{16}H_{18}NO_6P$ (351.30): C 54.70, H 5.16, N 3.99, P 8.82; found: C 54.60, H 5.20, N 3.80, P 8.70.

(R)-α-Amino-4-hydroxy-5-(phosphonomethyl)(1,1'-biphenyl)-3-propanoic Acid ((*R*)-**7o**). Hydrolysis of (*R,R*)-**6p** (2.8 g, 4.4 mmol) as described for (*S*)-**7p** gave (*R*)-**7o** (0.7 g, 45%). R_f 0.51 (*Chiralplate®*, ammonium salt, MeCN/H_2O/MeOH 4:2:1). M.p. 255–260° (dec.). $[\alpha]_D^{20} = -4.8$ ($c = 1$, 6M HCl). Anal. calc. for $C_{16}H_{18}NO_6P \cdot 0.7\ H_2O$ (363.91): C 52.81, H 5.37, N 3.85, O 29.46, P 8.51; found: C 52.90, H 5.30, N 4.20, O 30.20, P 7.90.

(S)-α-Amino-2'-chloro-4-hydroxy-5-(phosphonomethyl)(1,1'-biphenyl)-3-propanoic Acid ((*S*)-**7p**). As described for (*S,S*)-**6f**, with (*S,S*)-**5b** (10.0 g, 15.8 mmol) and 2-chlorobenzeneboronic acid (4.0 g, 25.5 mmol): 10.0 g (95%) of (*S,S*)-**6q** with R_f 0.19 (TLC, AcOEt). The residue was dissolved in 0.375M aq. H_2SO_4 (105 ml) and EtOH (21 ml) and, after addition of *Dowex 50W X4* (50–100 mesh, 33 g) the mixture heated under reflux for 7 days. The resin was washed in a column sequentially with H_2O (100 ml), EtOH (100 ml), and H_2O (200 ml) before the amino acid was eluted with aq. 10% NH_3 soln. (120 ml). The NH_3 eluates were concentrated and freeze-dried. The residue (5.1 g) was dissolved in H_2O (30 ml) and the pH adjusted to 2 with 4M HCl: (*S*)-**7p** (3.6 g, 62% overall). R_f 0.62

(*Chiralplate*®, ammonium salt, MeCN/H_2O/MeOH 4:2:1). M.p. 253–258° (dec.). $[\alpha]_D^{20} = -4.2$ ($c = 1$, 6M HCl). Anal. calc. for $C_{16}H_{17}ClNO_6P \cdot 0.05\ NH_4Cl$ (388.42): C 49.48, H 4.46, Cl 9.58, N 3.79, P 7.97; found: C 49.66, H 4.40, Cl 9.70, N 3.80, P 7.70.

(R)-α-Amino-2'-chloro-4-hydroxy-5-(phosphonomethyl)(1,1'-biphenyl)-3-propanoic Acid ((*R*)-**7p**). As described for (*S,S*)-**6f** with (*R,R*)-**5b** (3.1 g, 4.8 mmol) and 2-chlorobenzeneboronic acid (1.14 g, 7.2 mmol): 2.3 g (72%) of (*R,R*)-**6q**. Hydrolysis as described for (*S*)-**7p** gave (*R*)-**7p** (0.75 g, 56%). R_f 0.54 (*Chiralplate*®, ammonium salt, MeCN/H_2O/MeOH 4:2:1). M.p. 254–259° (dec.). $[\alpha]_D^{20} = +3.8$ ($c = 1$, 6M HCl). Anal. calc. for $C_{16}H_{17}ClNO_6P$ (385.74): C 49.82, H 4.44, Cl 9.19, N 3.63, P 8.03; found: C 50.00, H 4.60, Cl 9.20, N 3.60, P 7.50.

(S)-α-Amino-2',4'-dichloro-4-hydroxy-5-(phosphonomethyl)(1,1'-biphenyl)-3-propanoic Acid ((*S*)-**7q**). As described for (*S,S*)-**6f**, with (*S,S*)-**5b** (8.0 g, 12.6 mmol) and 2,4-dichlorobenzeneboronic acid (4.0 g, 20.9 mmol): 7.5 g (85%) of (*S,S*)-**6r**. Hydrolysis as described for (*S*)-**7p** gave (*S*)-**7q** (3.5 g, 78%). M.p. 250–259° (dec.). $[\alpha]_D^{20} = +2.9$ ($c = 1$, 6M HCl). Anal. calc. for $C_{16}H_{16}Cl_2NO_6P \cdot 0.35\ H_2O$ (426.49): C 45.06, H 3.95, Cl 16.63, N 3.28, P 7.26; found: C 45.40, H 3.90, Cl 16.60, N 3.30, P 6.90.

(S)-α-Amino-4-hydroxy-5-(phosphonomethyl)(1,1':4',1''-terphenyl)-3-propanoic Acid ((*S*)-**7r**). As described for (*S,S*)-**6f**, with (*S,S*)-**5b** (1.0 g, 1.6 mmol) and 4-phenylbenzeneboronic acid (0.6 g, 3 mmol): 0.8 g (70%) of (*S,S*)-**6s**. Hydrolysis of (*S,S*)-**6s** (1.1 g, 1.6 mmol) as described for (*S*)-**7p** gave (*S*)-**7r** (0.55 g, 81%). Dec. at 270°. $[\alpha]_D^{20} = +1.1$ ($c = 1$, 6M HCl). Anal. calc. for $C_{22}H_{22}NO_6P \cdot 0.15\ H_2O/NH_3$ 1:1 (432.65): C 61.08, H 5.30, N 3.72, P 7.16; found: C 61.00, H 5.20, N 3.70, P 6.60.

(S)-α-Amino-4-methoxy-5-(phosphonomethyl)(1,1'-biphenyl)-3-propanoic Acid ((*S*)-**7s**). A soln. of (*S,S*)-**6p** (1.0 g, 1.6 mmol), pyrrolidine (0.5 ml), and THF (10 ml) was stirred for 2 h at r.t. The mixture was evaporated to give the phenol derivative (0.8 g, 85%) with m.p. 98–103°. A mixture of this intermediate with MeI (0.8 ml), K_2CO_3 (0.4 g), and aceton (25 ml) was stirred for 16 h at 50°. The mixture was filtered and the filtrate evaporated. Deprotection and hydrolysis as described for (*S*)-**7f** gave (*S*)-**7s** (0.25 g, 50% overall). M.p. 220–225°. $[\alpha]_D^{20} = +6.2$ ($c = 1$, 6M HCl). Anal. calc. for $C_{17}H_{20}NO_6P \cdot 0.4\ H_2O$ (372.53): C 54.81, H 5.63, N 3.76, O 27.49; P 8.31; found: C 54.90, H 5.75, N 3.90, O 28.20, P 7.90.

(S)-α-Amino-4-nitro-5-(phosphonomethyl)(1,1'-biphenyl)-3-propanoic Acid ((*S*)-**7t**). As described for (*S*)-**7f**, with 270 mg (0.44 mmol) of (*S,S*)-**6t**: 95 mg (57% overall) of (*S*)-**7t**. M.p. > 300°. $[\alpha]_D^{20} = +36$ ($c = 0.1$, 6M HCl). FAB-MS: 381 (37), 234 (18), 210 (9) (among others).

1,1-Dimethylethyl (2S,5S)-5-{{6-[(Diethoxyphosphoryl)methyl]-4-phenylpyridin-2-yl}methyl}-2-(1,1-dimethylethyl)-3-methyl-4-oxoimidazolidine-1-carboxylate ((*S,S*)-**8**). *Michaelis-Arbuzov* reaction as described for **4c**, with 2,6-bis(bromomethyl)-4-phenylpyridine [8] (1.0 g, 2.9 mmol) gave 0.55 g (47%) of *diethyl {[6-(bromomethyl)-4-phenylpyridin-2-yl]methyl}phosphonate*. R_f 0.19 (TLC, AcOEt). ^{1}H-NMR: 1.25 (*t*, $J = 7$, 6 H); 3.35 (*d*, $J = 21$, 2 H); 4.00–4.18 (*m*, 4 H); 4.56 (*s*, 2 H); 7.36–7.53 (*m*, 5 H); 7.53–7.66 (*m*, 2 H).

Alkylation of (*S*)-Boc-BMI (3.2 g, 12.6 mmol) with {[6-(bromomethyl)-4-phenylpyridin-2-yl]methyl}phosphonate (4.2 g, 10.5 mmol) as described for (*S,S*)-**5a** gave 4.6 g (76%) of (*S,S*)-**8**. ^{1}H-NMR: 0.92 (*s*, 9 H); 1.23 (*t*, $J = 7$, 6 H); 1.20 (*s*, 9 H); 2.98 (*s*, 3 H); 3.30 (*dd*, $J = 22$, 4, 2 H); 3.48 (*d*, $J = 12$, 1 H); 3.90–4.12 (*m*, 4 + 1 H); 4.310 (br. *s*, 1 H); 4.80 (*s*, 1 H); 7.18 (*s*, 1 H); 7.30–7.46 (*m*, 4 H); 7.46–7.60 (*m*, 2 H).

(S)-α-Amino-4-phenyl-6-(phosphonomethyl)pyridine-2-propanoic Acid ((*S*)-**9a**). As described for (*S*)-**7f** with 3.4 g (5.2 mmol) of (*S,S*)-**8**: 0.7 g (40% overall) of (*S*)-**9a**. M.p. 263° (dec.). $[\alpha]_D^{20} = +27$ ($c = 0.1$, 6M HCl). Anal. calc. for $C_{15}H_{17}N_2O_5P \cdot 0.4\ H_2O$ (343.49): C 52.49, H 5.22, N 8.16, O 25.10, P 9.02; found: C 52.60, H 5.10, N 8.25, O 24.70, P 8.50.

(S)-α-Amino-4-phenyl-6-(phosphonomethyl)-2-pyridinepropanoic Acid 1-Oxide ((*S*)-**9b**). A soln. of (*S,S*)-**8** (2.1 g, 3.6 mmol) in AcOH (10 ml) was treated with 35% H_2O_2 soln. (0.6 ml) and stirred at 70° for 6 h. The mixture was poured on ice-water, and the crystals were filtered off and dried, 1.5 g (78%) of *1,1-dimethylethyl (2S,5S)-2-(1,1-dimethylethyl)-3-methyl-4-oxo-5-{[4-phenyl-6-(phosphonomethyl)pyridin-2-yl]methyl}imidazolidine-1-carboxylate 1'-oxide*. Hydrolysis of 0.8 g (1.5 mmol) of this crystalline product as described for (*S*)-**7p** gave (*S*)-**9b** (0.3 g, 57% overall). TLC (*Chiralplate*®, ammonium salt, MeCN/H_2O/MeOH 4:2:1): R_f 0.77; pure. M.p. 270° (dec.). $[\alpha]_D^{20} = 0 \pm 0.5$ ($c = 1$, 6M HCl). Anal. calc. for $C_{15}H_{17}N_2O_6P$ (352.28): C 51.14, H 4.86, N 7.95, P 8.79; found: C 50.80, H 5.00, N 7.90, P 8.60.

We thank Mrs. *T. Zardin, Sandoz*, Basel, for NMR studies and Mr. *G. Yowell* for the analytical determination of enantiomeric purities by capillary electrophoresis.

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