67. Synthesis and *N*-Methyl-D-aspartate (NMDA) Antagonist Properties of the Enantiomers of α-Amino-5-(phosphonomethyl)[1,1′-biphenyl]-3-propanoic Acid. Use of a New Chiral Glycine Derivative

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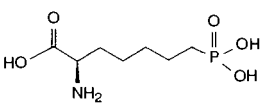
The enantiomers of the title compound, **7a** and *ent*-**7a**, and of substituted analogues are synthesized. The absolute configuration of **7a** is deduced from that of (*tert*-butyl 2-*tert*-butyl)-3-methyl-4-oxoimidazolidin-1-carboxylate (**15**) and from the *trans*-configuration of the intermediate **17a** which in turn is assigned on the basis of ^{1}H-NMR nuclear *Overhauser* effect (NOE) measurements. Instead of **15**, the 2-isopropyl-substituted analogue **21** can also be employed. Its preparation from glycine, methylamine, isobutyraldehyde, and $(Boc)_2O$, and the resolution through the bis-*O*,*O*′-(4-toluyl)tartrate salt **20** are described. In two functional tests (rat neocortical slice and frog hemisected spinal cord preparation) the (*S*)-enantiomer **7a** (SDZ EAB 515) is shown to be a very potent, selective competitive NMDA antagonist.

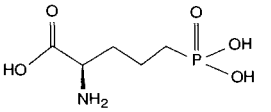
Introduction. – Extensive synthetic work was done in the field of competitive *N*-methyl-D-aspartate(NMDA)-receptor antagonists. By restricting the conformational flexibility of 2-amino-7-phosphonoheptanoic acid [1] (**1**) and 2-amino-5-phosphonopentanoic acid [2] (**2**), the compounds which were originally found to be antagonists, a number of stronger and selective competitive NMDA antagonists was discovered: 4-(3-phosphonopropyl)piperazine-2-carboxylic acid [3] (**3**), (*E*)-4-(3-phosphonopro-2-penyl)piperazine-2-carboxylic acid [4] (**6**) (*E*)-2-amino-4-methyl-5-phosphonopent-3-enoic acid [5] (**5**), and *cis*-4-(phosphonomethyl)piperidine-2-carboxylic acid [6] (**8**). So far, the (*R*)-enantiomers proved to be more active NMDA antagonists (**1**, **2** [7]; **3**, **6** [4]; **5** [8]). We present here syntheses of both enantiomers of the phenyl and biphenyl derivatives **4** and **7a** as well as of some substituted analogues **7c**, **e**, **g**. It is shown by biological *in vitro* tests that in the new series of biphenyl amino-phosphonocarboxylic acids **7**, the (*S*)-enantiomers are *ca.* 150 times more active as highly potent and selective competitive NMDA antagonists than the (*R*)-enantiomers.

Results and Discussion. – *Synthesis.* The benzylic bromides **13** used for the alkylation of glycine enolate derivatives were prepared in the following way (*Scheme 1*). Dimethyl [1,1′-biphenyl]-3,5-dicarboxylates **10a–f** were obtained in yields ranging from 63 to 76% by Pd-catalyzed cross coupling of dimethyl 5-bromobenzene-1,3-dicarboxylate (**9**) with

[1]) Part of the Ph. D. Thesis of D.B. (ETH Zürich, Dissertation No. 9527, 1991).



1 D-AP7



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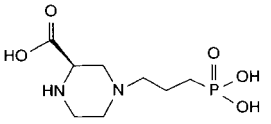
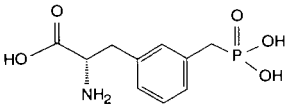
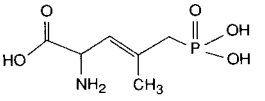


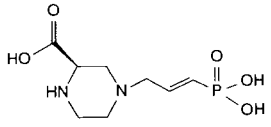
3 D-CPP



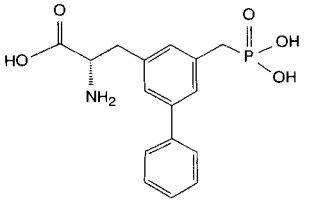
(*S*)-**4**



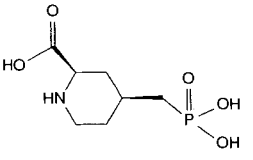
5 CGS37849



6 D-CPP-ene

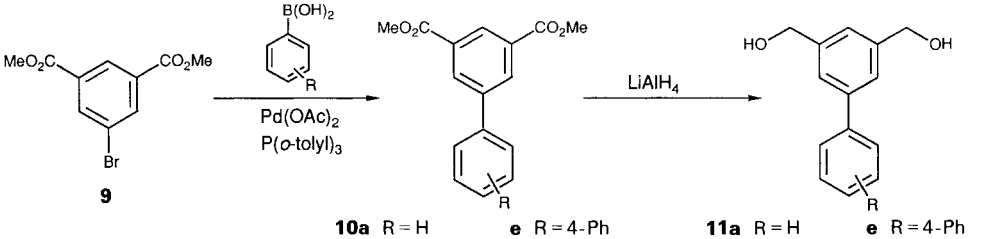


(*S*)-**7a** SDZ EAB 515



8 CGS19755

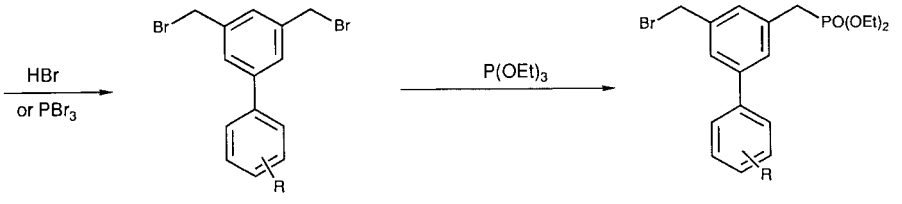
Scheme 1



9

10a R = H **e** R = 4-Ph
b R = 4-Cl **f** R = 3-NO_2
c R = 4-F **g** R = 3-NH_2
d R = 4-(*t*-Bu) **h** R = 3-NHAc

11a R = H **e** R = 4-Ph
b R = 4-Cl **g** R = 3-NH_2
c R = 4-F **h** R = 3-NHAc
d R = 4-(*t*-Bu)



12a R = H **d** R = 4-(*t*-Bu)
b R = 4-Cl **e** R = 4-Ph
c R = 4-F **h** R = 3-NHAc

13a R = H **d** R = 4-(*t*-Bu)
b R = 4-Cl **e** R = 4-Ph
c R = 4-F **h** R = 3-NHAc

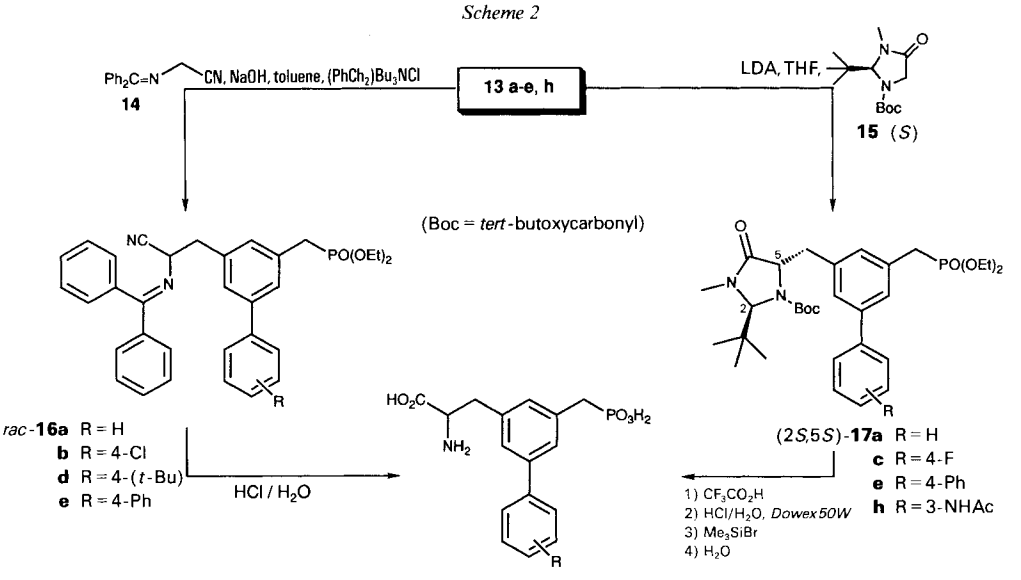
the corresponding benzeneboronic acids [9]. Sequential reduction of the NO_2 group in **10f** (H_2, PdC) and acetylation of the resulting aniline derivative **10g** gave the acetanilide **10h**. Reduction of the diesters **10a–g** with $LiAlH_4$ produced the diols **11a–g**. The acetamido-diol **11h** was obtained in an overall yield of 84% by triacetylation of **11g**, followed by selective hydrolysis of the ester groups (2 equiv. of NaOH, MeOH/H_2O, < 10°). Treatment of the corresponding diols with PBr_3 in toluene or with HBr in AcOH furnished the dibromides **12a–e, h** in good-to-excellent yields, and *Michaelis-Arbusov* reaction of the latter ones (1 equiv. of $P(OEt)_3$, xylene, 140°), followed by chromatography on silica gel, the diethyl bromo-phosphonates **13a–e, h**.

Racemic amino-phosphono-acids *rac*-**7a, b, d, e** were prepared by benzylation of the benzophenone imine **14** with the corresponding bromides **13a, b, d, e** under phase-transfer conditions (50% NaOH/toluene/$BnBu_3N^+Cl^-$), (→ *rac*-**16a, b, d, e**) and subsequent hydrolysis with 6M aq. HCl [10] (*Scheme 2*; overall yields 57, 59, 70, and 69% resp.).

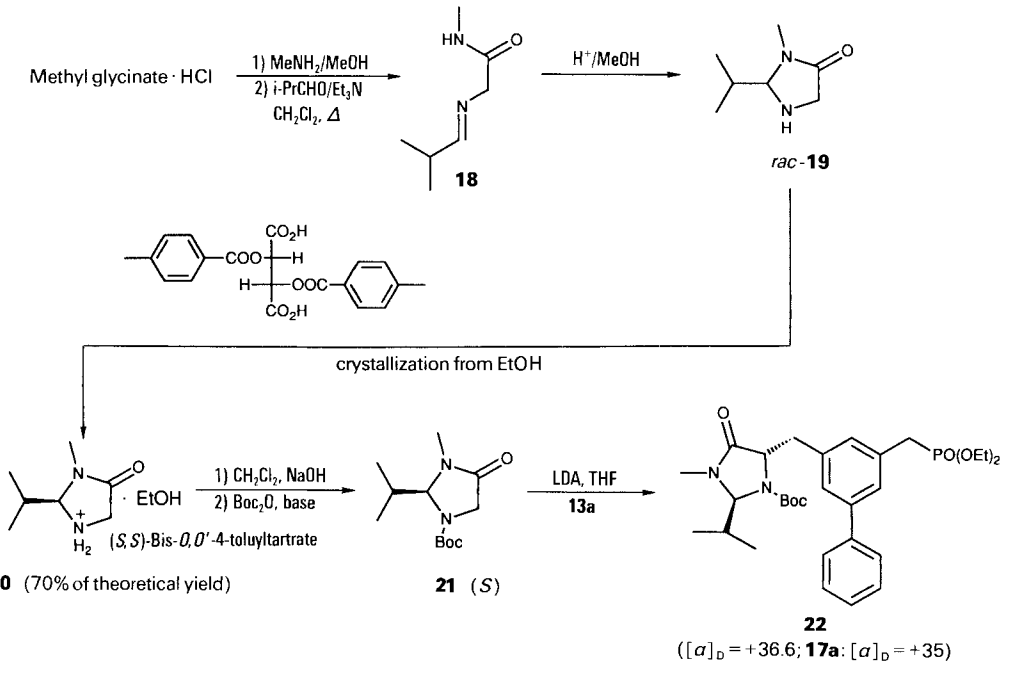
The enantiomerically pure amino-phosphono-acids **7** were prepared by employing the chiral glycine derivatives **15** and *ent*-**15** [11] (*Scheme 2*). Benzylation of the Li enolate of **15** by the diethyl bromo-phosphonates **13a–e, h** in THF at −65° led to the imidazolidinones **17a, c, e, h**. The sequence of Boc removal (CF_3CO_2H/CH_2Cl_2), hydrolysis to the diethylphosphono-amino acid (0.75M aq. HCl in the presence of *Dowex 50W* × *8*) [11], cleavage of the diethyl phosphonate with (bromo)trimethylsilane in CH_2Cl_2 [12], and crystallization from THF/H_2O gave the free amino diacids **7a, c, e, g** in good overall yields and in enantiomerically pure form.

Since there are occasional problems with large-scale supply of pivalaldehyde, an ingredient for the preparation of *tert*-butylimidazolidinone derivative **15**, we took this

Scheme 2



Scheme 3



occasion to test the availability and selectivity of enolate reactions of the corresponding, enantiomerically pure isopropylimidazolidinone derivative **21**[2]). As shown in *Scheme 3*, the glycine-derived imino-amide **18** was cyclized to give the unprotected imidazolidinone *rac*-**19**. Crystallization experiments with a number of readily available chiral acids quickly identified the bis-*O*,*O*′-(4-toluyl)tartrate **20** as a suitable diastereoisomeric salt for resolution. The enantiomerically pure base was obtained from the salt and acylated to give the dextrorotatory Boc derivative **21** when the (*S*,*S*)-tartrate was used for the enantiomer separation. When benzylated with bromide **13a**, **21** gave a 77% yield of the amino-acid derivative **22** which had the same sign and almost the same value of specific rotation as the corresponding derivative **17a**, obtained from **15**. Since both compounds have *trans*-configuration, we assign them the same absolute configuration (2*S*,5*S*), and thus the isopropylimidazolidinone derivative **21** ($[\alpha]_D = +1.2$ ($c = 1.3$, CH_2Cl_2)) obtained with the (*S*,*S*)-tartrate is (*S*)-configurated.

Absolute Configuration and Enantiomeric Purity of the Diacids. The sense of chirality and of optical rotation of reagent **15** was assigned to be (+)-(*R*) and (−)-(*S*) [11]. All alkylations of **15** furnished *trans*-products [11], and the compounds **17** are no exception: their signals of H–C(5) show a positive NOE effect upon irradiation with the frequency of the 2-(*tert*-butyl) protons. The parent compounds **17a** and *ent*-**17a** are each a single diastereoisomer, according to their 360-MHz NMR spectra measured at 120° in

[2]) Some 2-isopropyl-imidazolidinone enolates were tested previously in methylation reactions. The selectivities were clearly lower than with the corresponding *tert*-butyl analogs [13].

DMSO[3]), thus they must be pure (*S,S*)- and (*R,R*)-isomer, respectively. The enantiomeric purity of the free amino diacids (*R*)- and (*S*)-**7a** was determined to be 100% by thin layer chromatographic comparison on *Chiralplate®* (see *Exper. Part*).

Biological Tests and Structure-Activity Relationship. The NMDA antagonistic activity of the enantiomers of the title compound **7a** and of substituted analogues was determined by measuring the antagonism of NMDA-induced depolarisations in the rat neocortical slice preparation (CWP) [14] and in the frog hemisected spinal cord (FHS) [15] (see *Table*). Apparent pA_2 values for antagonism of NMDA-evoked depolarisations were independent of concentration (*i.e.* competitive antagonism) and with one exception (**7d**) were comparable in the two tests. The data show that insertion of a Ph ring in the middle of the chain of the AP7 molecule does not reduce the NMDA antagonistic activity of the racemates (compare pA_2 values of *rac*-**1** and *rac*-**4**) but reverses the enantioselectivity, that is, (*S*)-**4** is more active than (*R*)-**4**, which is in contrast to the results obtained so far for all NMDA antagonists the enantiomers of which were separated (AP5[5], AP7 [7], CPP [4], CPP-ene [4], and CGP-37849 [8]). In addition, the relative potency ratio between the active and the inactive enantiomer rises from a factor of 10 with AP7 to a factor of more than 40. Introduction of a biphenyl moiety in the chain of the AP7 molecule increases both effects: (*S*)-**7a** (SDZ EAB 515) is more than 40 times more active than D-AP7 and the 'reversed' selectivity factor of the enantiomers is *ca.* 150. The results from the two functional tests were essentially confirmed by a binding assay using ^{3}H-CGP39653 as a radioligand [16] (see *Table*).

Table. *Inhibition of the NMDA-Induced Depolarisation in the Rat Neocortical Slice Preparation* (CWP) [14] *and of the NMDA-Induced Depolarisation in the Frog Hemisected Spinal Cord* (FHS) [15]; *NMDA Receptor Affinities* (^{3}H-CGP39653 binding assay) [16]

		Apparent pA_2 values		[^{3}H]CGP39653 binding pK_i
		CWP	FHS	
rac-**1**	(DL-AP7)	4.88	5.5	
(*S*)-**1**	(L-AP7)	4.28	4.4	4.9
(*R*)-**1**	(D-AP7)	5.30	5.3	6.1
rac-**4**		4.94	5.3	
(*S*)-**4**		5.31		5.5
(*R*)-**4**		< 3.7		4.1
rac-**7a**		6.64	6.5	
(*S*)-**7a**	(SDZ EAB 515)	6.94	7.0	6.7
(*R*)-**7a**		4.77	5.0	4.8
rac-**7b**		6.76	6.5	
(*S*)-**7c**		6.94	7.0	
(*R*)-**7c**		4.90	5.0	
rac-**7d**		7.62	6.3	
(*S*)-**7e**		7.77	7.7	
(*S*)-**7g**		6.57	6.6	

Experimental Part

General. Tetrahydrofuran (THF) was purified by distillation from $LiAlH_4$. $(i\text{-}Pr)_2NH$ was distilled over CaH_2. All other commercially available chemicals were used as provided by the supplier without purification. TLC: silica gel *60 F-254* from *Merck*; *Chiralplate®* from *Macherey-Nagel*. Column chromatography (CC): silica gel *60* (230–400 mesh) from *Merck* at medium pressure. M.p.: *Reichert* hot stage; uncorrected. Optical rotations:

[3]) At lower temperatures, two slowly interconverting rotamers are observed.

Perkin-Elmer-241 polarimeter; cell length 10 cm. ^{1}H-NMR Spectra: *Varian-200-MHz* spectrometer, $CDCl_3$ solns., unless otherwise stated; δ in ppm with TMS as standard, coupling constants J in Hz.

Dimethyl [1,1'-Biphenyl]-3,5-dicarboxylate (**10a**). A mixture of dimethyl 5-bromobenzene-1,3-dicarboxylate [17] (**9**; 2.73 g, 10 mmol), benzeneboronic acid (1.34 g, 11 mmol), Et_3N (2.8 ml, 20 mmol), tris(2-tolyl)phosphine (125 mg, 0.4 mmol), $Pd(OAc)_2$ (45 mg, 0.4 mmol), and abs. DMF (25 ml) was stirred for 3.5 h at 100° under N_2. The mixture was evaporated, the residue treated with 10% aq. NH_3 soln. and extracted with AcOEt, the org. layer dried (Na_2SO_4) and evaporated, and the residue (2.0 g) crystallized from Et_2O/petroleum ether: 1.8 g (66%) of **10a**. M.p. 96–98° ([18]: m.p. 116–116.5°). ^{1}H-NMR: 3.95 (*s*, 6 H); 7.4–7.7 (*m*, 5 H); 8.45 (*d*, J = 1.9, 2 H); 8.65 (*dd*, J = 1.9, 1.9, 1 H).

Dimethyl 4'-Chloro[1,1'-biphenyl]-3,5-dicarboxylate (**10b**). As described for **10a**, with 1.9 g (7 mmol) of **9** and 1.2 g (7.7 mmol) of 4-chlorobenzeneboronic acid: 1.45 g (68%) of **10b**. M.p. 110–112° (Et_2O/petroleum ether). ^{1}H-NMR: 3.95 (*s*, 6 H); 7.43 (*d*, J = 8.5, 2 H); 7.57 (*d*, J = 8.5, 2 H); 8.40 (*d*, J = 1.7, 2 H); 8.64 (*dd*, J = 1.8, 1.8, 1 H).

Dimethyl 4'-Fluoro[1,1'-biphenyl]-3,5-dicarboxylate (**10c**). As described for **10a**, with 3.3 g (12 mmol) of **9** and 2.8 g (10 mmol) of 4-fluorobenzeneboronic acid: 1.8 g (62%) of **10c**. M.p. 98–102° (Et_2O/petroleum ether). ^{1}H-NMR: 3.95 (*s*, 6 H); 7.25 (*dd*, J = 9.5, 9.5, 2 H); 7.60 (*dd*, J = 9.5, 5.6, 2 H); 8.41 (*d*, J = 1.5, 2 H); 8.63 (*dd*, J = 1.6, 1.6, 1 H).

Dimethyl 4'-(1,1-Dimethylethyl)[1,1'-biphenyl]-3,5-dicarboxylate (**10d**). As described for **10a**, with 14.3 g (52 mmol) of **9** and 10.25 g (57.5 mmol) of 4-(1,1-dimethylethyl)benzeneboronic acid: 10.9 g (64%) of **10d**. M.p. 152–155° (Et_2O/petroleum ether). ^{1}H-NMR: 1.35 (*s*, 9 H); 3.95 (*s*, 6 H); 7.48 (*d*, J = 12.8, 2 H); 7.59 (*d*, J = 12.8, 2 H); 8.44 (*d*, J = 2.4, 2 H); 8.61 (*dd*, J = 2.4, 2.4, 1 H).

Dimethyl [1,1':4',1''-Terphenyl]-3,5-dicarboxylate (**10e**). As described for **10a**, with 14.05 g (51 mmol) of **7** and 11.2 g (56.5 mmol) of [1,1'-biphenyl]-4-boronic acid: 10.9 g (62%) of **10e**. M.p. 189–191° (cyclohexane). ^{1}H-NMR: 3.95 (*s*, 6 H); 7.38 (*d*, J = 7.0, 2 H); 7.44 (*d*, J = 7.0, 2 H); 7.6–7.77 (*m*, 5 H); 8.50 (*d*, J = 1.5, 2 H); 8.65 (*dd*, J = 1.5, 1.5, 1 H).

Dimethyl 3'-Nitro[1,1'-biphenyl]-3,5-dicarboxylate (**10f**). As described for **10a**, with 15.6 g (57.2 mmol) of **7** and 14.3 g (85.7 mmol) of 3-nitrobenzeneboronic acid: 13.4 g (74%) of **10f**. M.p. 147–149° (AcOEt/Et_2O). ^{1}H-NMR (360 MHz: 4.00 (*s*, 6 H); 7.68 (*dd*, J = 9.0, 9.0, 1 H); 8.00 (*d*, J = 9, 1, 1 H); 8.28 (*dd*, J = 9, 1.5, 1 H); 8.49 (*d*, J = 1.5, 2 H); 8.53 (*dd*, J = 1.6, 1.6, 1 H); 8.74 (*dd*, J = 1.8, 1.8, 1 H).

Dimethyl 3'-Amino[1,1'-biphenyl]-3,5-dicarboxylate (**10g**). A soln. of **10f** (22.1 g, 70 mmol) in 1.5 l MeOH was hydrogenated at r.t. 1 atm in the presence of 1.5 g of 5% Pd/C. The catalyst was filtered off and the solvent evaporated. The residue was crystallized from MeOH: 18.3 g (92%) of **10g**. M.p. 119–121°. ^{1}H-NMR (360 MHz): 3.80 (br. *s*, 2 H); 3.97 (*s*, 6 H); 6.73 (*dd*, J = 1.5, 1 H); 6.96 (*dd*, J = 1.8, 1.8, 1 H); 7.04 (*d*, J = 8, 1 H); 7.24 (*d*, J = 8, 1 H); 8.43 (*d*, J = 1.8, 2 H); 8.63 (*dd*, J = 1.8, 1.8, 1 H).

Dimethyl 3'-(Acetylamino)[1,1'-biphenyl]-3,5-dicarboxylate (**10h**). A soln. of **10g** (12.7 g, 44.5 mmol) in Py (90 ml) was treated with Ac_2O (8.4 ml, 88.8 mmol) and stirred for 30 min at 80°. The product was crystallized from the mixture by adding H_2O (*ca.* 200 ml): 14.2 g (98%) of **10h**. M.p. 197–199°. ^{1}H-NMR (360 MHz): 2.22 (*s*, 3 H); 3.97 (*s*, 3 H); 7.35–7.5 (*m*, 3 H); 7.60 (*d*, J = 8, 1 H); 7.74 (*d*, J = 1.8, 1 H); 8.41 (*d*, J = 1.8, 2 H); 8.65 (*dd*, J = 1.8, 1.8, 1 H).

5-(Hydroxymethyl)[1,1'-biphenyl]-3-methanol (**11a**). A soln. of **10a** (14.0 g, 52 mmol) in 200 ml of anh. THF was added with stirring to an ice-cooled suspension of $LiAlH_4$ (7.0 g, 185 mmol) in anh. THF (100 ml) and stirred under reflux for 4 h. The mixture was then cooled with ice, treated with AcOEt (100 ml) and 2M H_2SO_4 (100 ml) simultaneously, and extracted with AcOEt. The org. layer was washed with sat. aq. $KHCO_3$ soln., dried (Na_2SO_4), and evaporated. The residue was crystallized from AcOEt/Et_2O/petroleum ether: 10.6 g (96%) of **11a**. M.p. 98–101°. ^{1}H-NMR ((D_6)DMSO): 4.55 (*d*, J = 6, 4 H); 5.23 (*t*, J = 6, 2 H); 7.28 (*s*, 1 H); 7.33–7.52 (*m*, 5 H); 7.65 (*d*, J = 8, 2 H).

4'-Chloro-5-(hydroxymethyl)[1,1'-biphenyl]-3-methanol (**11b**). As described for **11a**, with 11.9 g (39 mmol) of **10b**: 9.0 g (93%) of **11b**. M.p. 139–143°. ^{1}H-NMR (80 MHz (D_6)DMSO): 4.60 (*d*, J = 6, 4 H); 4.95 (*t*, J = 6, 2 H); 7.3 (*s*, 1 H); 7.4–7.85 (*m*, 6 H).

4'-Fluoro-5-(hydroxymethyl)[1,1'-biphenyl]-3-methanol (**11c**). As described for **11a**, with 15.3 g (53 mmol) of **10c**: 10.5 g (88%) of **11c**. M.p. 91–94°. ^{1}H-NMR ((D_6)DMSO): 4.55 (*d*, J = 6, 4 H); 5.24 (*t*, J = 6, 2 H); 7.28 (*s*, 1 H); 7.28 (*dd*, J = 9.5, 9.5, 2 H); 7.42 (*d*, J = 1.5, 2 H); 7.68 (*dd*, J = 9.5, 5.6, 2 H).

4'-(1,1-Dimethylethyl)-5-(hydroxymethyl)[1,1'-biphenyl]-3-methanol (**11d**). As described for **11a**, with 2.0 g (6.1 mmol) of **10d**: 1.3 g (79%) of **11d**. M.p. 110–113°. ^{1}H-NMR: 1.35 (*s*, 9 H); 1.90 (*s*, 2 H); 4.72 (*s*, 4 H); 7.32 (*s*, 1 H); 7.41–7.56 (*m*, 6 H).

5-(Hydroxymethyl)[1,1':4',1''-terphenyl]-3-methanol (**11e**). As described for **11a**, with 2.0 g (5.75 mmol) of **10e**: 1.5 g (90%) of **11e**. M.p. 174–177°. ^{1}H-NMR ((D_6)DMSO): 4.57 (*d*, J = 6, 4 H); 5.22 (*t*, J = 6, 2 H); 7.30 (*s*, 1 H); 7.39 (*d*, J = 7, 1 H); 7.47 (*d*, J = 7, 2 H); 7.52 (*s*, 2 H); 7.73 (*d*, J = 7, 2 H); 7.76 (*s*, 4 H).

3'-Amino-5-(hydroxymethyl)[1,1'-biphenyl]-3-methanol (**11g**). As described for **11a**, with 14.25 g (50 mmol) of **10g**: 9.85 g (86%) of **11g**. M.p. 112–114°. ^{1}H-NMR ((D$_6$)DMSO): 3.21 (*s*, 2 H); 4.55 (*d*, *J* = 6, 4 H); 5.07 (*t*, *J* = 6, 2 H); 6.55 (*dd*, *J* = 8, 1.5, 1 H); 6.77 (*d*, *J* = 8, 1 H); 6.86 (*dd*, *J* = 1.8, 1.8, 1 H); 7.09 (*dd*, *J* = 8, 8, 1 H); 7.23 (*d*, *J* = 1.5, 1 H); 7.38 (*d*, *J* = 1.5, 2 H).

N-{*3',5'-Bis(hydroxymethyl)[1,1'-biphenyl]-3-yl*}*acetamide* (**11h**). A soln. of **11g** (19.4 g, 84.7 mmol) in abs. Py (100 ml) was treated with Ac_2O (32.1 ml, 338 mmol) and stirred for 30 min at 80°. The product was crystallized from the mixture by adding H_2O (*ca.* 450 ml): 29.4 g (98%) of triacetylated **11g**. M.p. 106–108°. To the soln. of this product in MeOH (340 ml) was added, at 10°, within 5 min, 1M NaOH (170 ml). The soln. was stirred at 5° for 30 min. After standing overnight at –20°, colourless crystals of **11h** were separated: 19.2 g, 86%. M.p. 166–168°. ^{1}H-NMR (360 MHz, (D$_6$)DMSO): 2.06 (*s*, 3 H); 4.56 (*d*, *J* = 6, 4 H); 5.28 (*t*, *J* = 6, 2 H); 7.28 (*s*, 1 H); 7.30 (*d*, *J* = 8, 1 H); 7.38 (*dd*, *J* = 8, 8, 1 H); 7.42 (*s*, 2 H); 7.58 (*d*, *J* = 8, 1 H); 7.89 (*s*, 1 H); 10.05 (*s*, 1 H).

3,5-Bis(bromomethyl)-1,1'-biphenyl (**12a**). A soln. of **11a** (12.0 g, 56 mmol) in toluene (140 ml) was treated at 80° with a soln. of PBr_3 (10.0 ml, 106 mmol) in toluene (40 ml). After 1 h at 80°, the mixture was poured on ice. The org. layer was washed with sat. aq. $KHCO_3$ soln., dried ($NaSO_4$), and evaporated. The residue was crystallized from toluene/petroleum ether: 15.9 g (83%) of **12a**. M.p. 157–159°. ^{1}H-NMR: 4.52 (*s*, 4 H); 7.39 (*s*, 1 H); 7.40–7.50 (*m*, 3 H); 7.52–7.60 (*m*, 4 H).

3,5-Bis(bromomethyl)-4'-chloro-1,1'-biphenyl (**12b**). As described for **12a**, with 2.0 g (8.0 mmol) of **11b**: 2.6 g (87%) of **12b**. M.p. 120–124°. ^{1}H-NMR: 4.50 (*s*, 4 H); 7.37–7.41 (*m*, 2 H); 7.42 (*s*, 1 H); 7.46–7.53 (*m*, 4 H).

3,5-Bis(bromomethyl)-4'-fluoro-1,1'-biphenyl (**12c**). As described for **12a**, with 10.7 g (46.0 mmol) of **11c**: 14.85 g (90%) of **12c**. M.p. 90–95°. ^{1}H-NMR: 4.50 (*s*, 4 H); 7.11 (*dd*, *J* = 8, 8, 2 H); 7.39 (*s*, 1 H); 7.44–7.60 (*m*, 4 H).

3,5-Bis(bromomethyl)-4'-(1,1-dimethylethyl)-1,1'-biphenyl (**12d**). As described for **12a**, with 2.0 g (7.4 mmol) of **11d**: 2.6 g (89%) of **12d**. M.p. 110–115°. ^{1}H-NMR: 1.34 (*s*, 9 H); 4.50 (*s*, 4 H); 7.36 (*s*, 1 H); 7.41–7.57 (*m*, 6 H).

3,5-Bis (bromomethyl)-1,1':4',1''-terphenyl (**12e**). As described for **12a**, with 2.0 g (6.9 mmol) of **11e**: 2.2 g (77%) of **12e**. M.p. 178–184°. ^{1}H-NMR: 4.51 (*s*, 4 H); 7.30–7.52 (*m*, 4 H); 7.59 (*d*, *J* = 7, 3 H); 7.66 (*s*, 5 H).

N-{*3',5'-Bis(bromomethyl)[1,1'-biphenyl]-3-yl*}*acetamide* (**12h**). To a soln. of **11h** (7.2 g, 26.5 mmol) in $CHCl_3$ (135 ml) was added at reflux temp. within 10 min a soln. of PBr_3 (5.0 ml, 53 mmol) in $CHCl_3$ (135 ml). After 1 h, 2M aq. $KHCO_3$ soln. (210 ml) was added dropwise under stirring at 10°. The org. phase was separated, concentrated to *ca.* 100 ml, and kept overnight at –20°. The crystals were washed with cold $CHCl_3$: 13.2 g (94%) of **12h**. M.p. 152–154°. ^{1}H-NMR (360 MHz): 2.20 (*s*, 3 H); 4.52 (*s*, 4 H); 7.31 (*d*, *J* = 7, 1 H); 7.37 (*d*, *J* = 7, 1 H); 7.40 (*s*, 1 H); 7.49 (*d*, *J* = 7, 1 H); 7.51 (*s*, 2 H); 7.77 (*s*, 1 H).

Diethyl {*5-(Bromomethyl)[1,1'-biphenyl]-3-yl*}*methylphosphonate* (**13a**). A soln. of **12a** (3.0 g, 8.8 mmol) in xylene (30 ml) was treated with triethyl phosphite (1.7 ml, 9.7 mmol) and stirred under reflux for 90 min. The mixture was evaporated and the residue (3.8 g) purified by chromatography (silica gel, AcOEt). The fractions containing the product of R_f 0.30 (TLC, AcOEt) yielded **13a** (1.65 g, 47%). M.p. 82–84° (Et_2O). ^{1}H-NMR: 1.24 (*t*, *J* = 7, 6 H); 3.18 (*d*, *J* = 21, 2 H); 4.03 (*dq*, *J* = 7, 6, 4 H); 4.51 (*s*, 2 H); 7.27–7.51 (*m*, 6 H); 7.53–7.60 (*m*, 2 H).

Diethyl {*5-(Bromomethyl)-4'-chloro[1,1'-biphenyl]-3-yl*}*methylphosphonate* (**13b**). As described for **13a**, with 5.9 g (15.75 mmol) of **12b**: 3.35 g (49%) of **13b**. M.p. 96–97°. ^{1}H-NMR: 1.23 (*t*, *J* = 7, 6 H); 3.18 (*d*, *J* = 21, 2 H); 4.02 (*dq*, *J* = 7, 6, 4 H); 4.50 (*s*, 2 H); 7.30 (*s*, 1 H); 7.38 (*d*, *J* = 9, 2 H); 7.41–7.46 (*m*, 2 H); 7.48 (*d*, *J* = 9, 2 H).

Diethyl {*5-(Bromomethyl)-4'-fluoro[1,1'-biphenyl]-3-yl*}*methylphosphonate* (**13c**). As described for **13a**, with 14.65 g (41 mmol) of **12c**: 8.2 g (48%) of **13c**. Oil. ^{1}H-NMR: 1.23 (*t*, *J* = 7, 6 H); 3.18 (*d*, *J* = 21, 2 H); 4.02 (*dq*, *J* = 7, 6, 4 H); 4.50 (*s*, 2 H); 7.10 (*dd*, *J* = 8, 8, 2 H); 7.28 (*s*, 1 H); 7.35–7.58 (*m*, 4 H).

Diethyl {*5-(Bromomethyl)-4'-(1,1-dimethylethyl)[1,1'-biphenyl]-3-yl*}*methylphosphonate* (**13d**). As described for **13a**, with 9.1 g (23 mmol) of **12d**: 3.2 g (32%) of **13d**. ^{1}H-NMR: 1.26 (*t*, *J* = 7, 6 H); 1.34 (*s*, 9 H); 3.20 (*d*, *J* = 21, 2 H); 4.03 (*dq*, *J* = 7, 6, 4 H); 4.51 (*s*, 2 H); 7.28 (*s*, 1 H); 7.41–7.54 (*m*, 6 H).

Diethyl {*5-(Bromomethyl)[1,1':4',1''-terphenyl]-3-yl*}*methylphosphonate* (**13e**). As described for **13a**, with 26.0 g (62.5 mmol) of **12e**: 10.0 g (34%) of **13e**. ^{1}H-NMR: 1.26 (*t*, *J* = 7, 6 H); 3.20 (*d*, *J* = 21, 2 H); 4.03 (*dq*, *J* = 7, 6, 4 H); 4.52 (*s*, 2 H); 7.10 (*dd*, *J* = 8, 8, 2 H); 7.29–7.58 (*m*, 6 H); 7.62 (*s*, 1 H); 7.66 (*s*, 5 H).

Diethyl {*5-(Bromomethyl)-3'-(acetamido)[1,1'-biphenyl]-3-yl*}*methylphosphonate* (**13h**). As described for **13a**, with 2.6 g (6.5 mmol) of **12h**: 1.3 g (43%) of **13h**. M.p. 121–123° (CH_2Cl_2/Et_2O). ^{1}H-NMR (360 MHz): 1.26 (*t*, *J* = 7, 6 H); 2.19 (*s*, 3 H); 3.19 (*d*, *J* = 21, 2 H); 4.06 (*dq*, *J* = 7, 6, 4 H); 4.50 (*s*, 2 H); 7.25–7.38 (*m*, 3 H); 7.45 (*d*, *J* = 7, 2 H); 7.53 (*d*, *J* = 7, 1 H); 7.68 (*s*, 1 H); 8.73 (*s*, 1 H).

(RS)-α-Amino-3-(phosphonomethyl)benzenepropanoic Acid [19] (*rac*-**4**). As described for *rac*-**7a**, with 7.77 g (35.3 mmol) of **14** and 9.1 g (35.3 mmol) of diethyl [3-(bromomethyl)benzyl]phosphonate [19]: 1.5 g (16% overall) of *rac*-**4**. M.p. 271–275° (dec.). Anal. calc. for $C_{10}H_{14}NO_5P \cdot 0.39\ H_2O$ (266.136): C 45.1, H 5.6, N 5.3, O 32.4, P 11.6; found: C 45.8, H 5.6, N 5.4, P 10.9.

(RS)-α-Amino-5-(phosphonomethyl)[1,1'-biphenyl]-3-propanoic Acid (*rac*-**7a**). To a mixture of [(diphenylmethylidene)amino]acetonitrile [10] (**14**; 8.1 g, 36.8 mmol) and 0.8 g of benzyl(tributyl)ammonium chloride in 40 ml toluene was added at 0° sequentially the soln. of NaOH (3.5 g) in H_2O (7.0 ml) and the soln. of **13a** (10.0 g, 25.2 mmol) in toluene (30 ml). The mixture was stirred 24 h at r.t. and then partitioned between H_2O and toluene. The org. phase was dried (Na_2SO_4) and evaporated. The oily residue (17.2 g) was purified by chromatography (silica gel, AcOEt/cyclohexane 1:1). The fractions containing the product of R_f 0.28 (TLC, AcOEt) gave **16a** (12.3 g, 91%) as a yellow oil. A soln. of the residue in conc. HCl soln. (45 ml) and H_2O (15 ml) was stirred under reflux for 14 h. The mixture was extracted with toluene/Et_2O 1:1 and the aq. phase evaporated. A soln. of the residue in H_2O/THF 1:1 was treated at 0° with propene oxide to yield *rac*-**7a** (4.4 g, 52% overall). M.p. 263–267° (dec.). Anal. calc. for $C_{16}H_{18}NO_5P$ (335.30): C 57.3, H 5.4, N 4.2, P 9.2; found: C 56.8, H 5.7, N 4.0, P 9.2.

(RS)-α-Amino-4'-chloro-5-(phosphonomethyl)[1,1'-biphenyl]-3-propanoic Acid (*rac*-**7b**). As described for *rac*-**7a**, with 3.7 g (16.8 mmol) of **14** and 4.9 g (11.3 mmol) of **13b**: 2.2 g (52% overall) of *rac*-**7b**. M.p. 275–280° (dec.). Anal. calc. for $C_{16}H_{17}ClNO_5P \cdot 0.15\ H_2O$ (372.44): C 51.6, H 4.7, Cl 9.5, N 3.8, O 22.1, P 8.3; found: C 51.4, H 4.8, Cl 9.5, N 3.9, O 21.7, P 7.8.

(RS)-α-Amino-4'-(1,1'-dimethylethyl)-5-(phosphonomethyl)[1,1'-biphenyl]-3-propanoic Acid (*rac*-**7d**). As described for *rac*-**7a**, with 2.4 g (11 mmol) of **14** and 3.35 g (7.9 mmol) of **13d**: 2.1 g (68% overall) of *rac*-**7d**. M.p. 330° (dec.). Anal. calc. for $C_{20}H_{26}NO_5P$ (391.42): C 61.4, H 6.7, N 3.6, O 20.4, P 7.9; found: C 61.2, H 6.8, N 3.4, O 19.9, P 7.7.

(RS)-α-Amino-5-(phosphonomethyl)[1,1':4',1''-terphenyl]-3-propanoic Acid (*rac*-**7e**). As described for *rac*-**7a**, with 2.8 g (12.7 mmol) of **14** and 4.0 g (9.0 mmol) of **13e**: 2.2 g (59% overall) of *rac*-**7e**. M.p. 295° (dec.). Anal. calc. for $C_{22}H_{22}NO_5P \cdot 0.1\ H_2O$ (413.41): C 63.9, H 5.8, N 3.4, O 19.3, P 7.5; found: C 63.9, H 5.7, N 3.3, O 19.3, P 6.9.

(2S)-α-Amino-3-(phosphonomethyl)benzenepropanoic Acid ((*S*)-**4**). As described for **17a**, with 1.4 g (5.4 mmol) of (*S*)-1,1-dimethylethyl 2-(1,1-dimethylethyl)-3-methyl-4-oxoimidazolidine-1-carboxylate [11] (**15**) and 1.60 g (5 mmol) of diethyl [3-(bromomethyl)benzyl]phosphonate [19]: 1.72 g (69%) of the alkylated **15**, which after deprotection and hydrolysis as described for (*S*)-**7a**, gave (*S*)-**4** (0.47 g, 53% overall). M.p. 240–245° (dec.). $[\alpha]_D^{20} = -3.7$ (*c* = 1.6M HCl). ^{1}H-NMR (D_2O): 3.00–3.12 (*m*, 1 H); 3.01 (*d*, *J* = 20.6, 2 H); 3.28 (*dd*, *J* = 14.6, 5, 1 H); 4.15 (*dd*, *J* = 8, 5, 1 H); 7.09–7.33 (*m*, 4 H). Anal. calc. for $C_{10}H_{14}NO_5P \cdot 0.5\ H_2O$ (268.206): C 45.8, H 5.6, N 5.2, O 32.8, P 11.5; found: C 45.9, H 5.6, N 5.3, O 32.9, P 10.5.

(2R)-α-Amino-3-(phosphonomethyl)benzenepropanoic Acid ((*R*)-**4**). As described for **17a**, with 4.85 g (19 mmol) of *ent*-**15** (*R*) and 5.65 g (17.6 mmol) of diethyl [3-(bromomethyl)benzyl]phosphonate [19]: 7.78 g (89%) of the alkylated *ent*-**15**. Deprotection and hydrolysis as described for (*S*)-**7a** gave (*R*)-**4** (2.55 g, 56% overall). M.p. 245–250° (dec.). $[\alpha]_D^{20} = +3.8$ (*c* = 1.6M HCl). ^{1}H-NMR (D_2O): as for (*S*)-**4**. Anal. calc. for $C_{10}H_{14}NO_5P \cdot 0.25\ H_2O$ (263.70): C 45.6, H 5.5, N 5.3, O 31.9, P 11.7; found: C 45.8, H 5.8, N 5.2, O 32.0, P 11.2.

1,1-Dimethylethyl (2S,5S)-5-{{5-[(Diethoxyphosphoryl)methyl][1,1'-biphenyl]-3-yl}methyl}-2-(1,1-dimethyl-ethyl)-3-methyl-4-oxoimidazolidine-1-carboxylate (**17a**). To a stirred soln. of $(i\text{-}Pr)_2NH$ (1.42 ml, 10 mmol) in 13 ml of THF were added at *ca.* −70° over 10 min 10 mmol of BuLi (1.6M soln. in hexan). After stirring the resulting soln. at −70° for 30 min, a soln. of **15** (2.5 g, 10 mmol) in 6 ml of THF was added and stirring continued for 20 min. Then a soln. of **13a** (3.6 g, 9 mmol) in THF (6 ml) was added and stirring continued at −70°. After 2 h, the mixture was poured into 50 ml of sat. aq. NH_4Cl soln. and extracted with Et_2O. The org. layer was dried (Na_2SO_4) and evaporated. The oily residue (5.6 g) was purified by chromatography (silica gel, AcOE). The fractions containing the product of R_f 0.21 (TLC, AcOE) gave **17a** (4.2 g, 81%). Oil. $[\alpha]_D^{20} = +35$ (*c* = 1, EtOH). ^{1}H-NMR (360 MHz, (D_6)DMSO, 120°): 0.91 (*s*, 9 H); 1.20 (*t*, *J* = 7, 3 H); 1.21 (*t*, *J* = 7, 3 H); 1.39 (*s*, 9 H); 2.76 (*s*, 3 H); 3.13 (*d*, *J* = 21, 2 H); 3.19 (*dd*, *J* = 15, 2, 1 H); 3.62 (*dd*, *J* = 15, 6, 1 H); 3.92–4.03 (*m*, 4 H); 4.22 (br. *s*, 1 H); 4.75 (*s*, 1 H); 7.00 (*d*, *J* = 2, 1 H); 7.20 (*d*, *J* = 2, 1 H); 7.26–7.34 (*m*, 1 H); 7.35–7.44 (*m*, 3 H); 7.52 (*d*, *J* = 7, 2 H).

From 2.5 g (10 mmol) of *ent*-**15** [11] and 3.65 g (9 mmol) of **13a**, 4.15 g (79%) of *ent*-**17a** ((2*R*,5*R*)) was obtained. $[\alpha]_D^{20} = -38$ (*c* = 1, EtOH). ^{1}H-NMR (360 MHz, (D_6)DMSO, 120°): as for **17a**.

(αS)-α-Amino-5-(phosphonomethyl)[1,1'-biphenyl]-3-propanoic Acid ((*S*)-**7a**). A soln. of **17a** (25.0 g, 43.7 mmol) in CH_2Cl_2 (150 ml) was treated with CF_3COOH (47 ml). After 15 h stirring at r.t., the mixture was evaporated. The residue was partitioned between sat. aq. $KHCO_3$ soln. and AcOEt and the org. phase dried (Na_2SO_4) and evaporated. The residue (20.1 g) was dissolved in 0.75M aq. HCl (200 ml) and, after addition of *Dowex 50W* × *4* (50–100 mesh, 70 g), the mixture heated under reflux for 44 h. The resin was washed in a column sequentially with H_2O, EtOH (200 ml), and H_2O (500 ml), before the amino acid was eluted with 10% aq. NH_3 soln. (400 ml). The NH_3 eluates were concentrated and freeze-dried. The residue (18.8 g) was dissolved in CH_2Cl_2 (200 ml) and treated with Me_3SiBr (40 ml). After 16 h at r.t., the mixture was evaporated. A soln. of the residue in THF/H_2O 1:1 (275 ml) was treated at 0° with propene oxide (30 ml) and stirred at 0° for 5 h. The precipitate was

filtered off, washed with THF/H_2O 1:1, and dried: (*S*)-**7a** (8.4 g, 57% overall). White crystals. TLC (*Chiralplate®* MeCN/H_2O/MeOH 4:2:1): R_f 0.40; pure. M.p. 268–272° (dec.). $[\alpha]_D^{20} = 0 \pm 0.5$; $[\alpha]_{365}^{20} = -20.3$ (c = 1.6M HCl). ^{1}H-NMR (360 MHz, NaOD): 3.21–3.32 (*m*, 1 H); 3.23 (*d*, J = 19.5, 2 H); 3.40 (*dd*, J = 13.5, 5, 1 H); 4.44 (*dd*, J = 6, 6, 1 H); 7.24 (*s*, 1 H); 7.32–7.38 (*m*, 1 H); 7.40–7.48 (*m*, 3 H); 7.53 (*s*, 1 H); 7.63 (*d*, J = 7, 2 H). ^{13}C-NMR (90 MHz, NaOD): 35.4 (*d*, J = 130); 37.08 (*s*); 55.15 (*s*); 127.03 (*d*, J = 3); 128.09 (*s*); 128.77 (*s*); 129.08 (*d*, J = 6); 130.90 (*d*, J = 6); 135.7 (*d*, J = 7); 136.3 (*d*, J = 2.5); 141.6 (*s*); 143.3 (*d*, J = 2.5); 171.5 (*s*). Anal. calc. for $C_{16}H_{18}NO_5P \cdot 0.2\ H_2O$ (338.90): C 56.7, H 5.5, N 4.1, P 9.1; found: C 56.6, H 5.5, N 4.3, P 8.4.

From 3.7 g (6.5 mmol) of *ent*-**17a**, 1.4 g (67% overall) of (*R*)-**7a** were obtained. TLC (*Chiralplate®*, MeCN/H_2O/MeOH 4:2:1): R_f 0.29. M.p. 274–276° (dec.). $[\alpha]_D^{20} = 0 \pm 0.5$; $[\alpha]_{365}^{20} = +19.2$ (c = 1.6M HCl). Anal. calc. for $C_{16}H_{18}NO_5P \cdot 0.2\ H_2O$ (338.90): C 56.7, H 5.5, N 4.1, P 9.1; found: C 56.8, H 5.7, N 4.1, P 8.6.

(αS)-α-Amino-4′-fluoro-5-(phosphonomethyl)[1,1′-biphenyl]-3-propanoic Acid ((*S*-**7c**). As described for **17a** and for **7a**, with 3.6 g (14.0 mmol) of **15** and 5.5 g (13.0 mmol) of **13c**: 1.2 g (26% overall) of (*S*)-**7c**. TLC (*Chiralplate®*, MeCN/H_2O/MeOH 4:2:1): R_f 0.47. M.p. 269–272° (dec.). $[\alpha]_D^{20} = 0 \pm 0.5$; $[\alpha]_{365}^{20} = +15.9$ (c = 1.6M HCl). Anal. calc. for $C_{16}H_{17}FNO_5P$ (353.29): C 54.4, H 4.9, F 5.4, N 4.0, P 8.8; found: C 54.6, H 4.9, N 4.0, P 8.7.

From 3.3 g (12.9 mmol) of *ent*-**15** and 5.0 g (12.0 mmol) of **13c**, 0.8 g (20% overall) of (*R*)-**7c** were obtained. TLC (*Chiralplate®*, MeCN/H_2O/MeOH 4:2:1): R_f 0.35. M.p. 268–272° (dec.). $[\alpha]_D^{20} = 0 \pm 0.5$; $[\alpha]_{365}^{20} = -13.0$ (c = 1.6M HCl). Anal. calc. for $C_{16}H_{17}FNO_5P$ (353.29): C 54.4, H 4.9, F 5.4, N 4.0, P 8.8; found: C 54.3, H 5.1, N 3.9, P 8.1.

(αS)-α-Amino-5-(phosphonomethyl)[1,1′:4′,1″-terphenyl]-3-propanoic Acid ((*S*)-**7e**). As described for **17a** and for **7a**, with 2.6 g (10.1 mmol) of **15** and 4.4 g (9.3 mmol) of **13e**: 1.8 g (47% overall) of (*S*)-**7e**. M.p. 270° (dec.). $[\alpha]_D^{20} = +3.2$ (c = 1.1M NaOH). Anal. calc. for $C_{22}H_{22}NO_5P$ (411.35): C 54.4, H 4.9, F 5.4, N 4.0, P 8.8; found: C 54.6, H 4.9, N 4.0, P 8.7.

(αS)-α,3′-Diamino-5-(phosphonomethyl)[1,1′-biphenyl]-3-propanoic Acid ((*S*)-**7g**). As described for **17a** and for **7a**, with 14.1 g (55.0 mmol) of **15** and 18.7 g (41.1 mmol) of **13h**: 3.6 g (25% overall) of (*S*)-**7g**. M.p. > 310°. $[\alpha]_D^{20} = -3.3$ (c = 1.6M HCl). Anal. calc. for $C_{16}H_{19}N_2O_5P$ (350.32): C 54.9, H 5.5, N 8.0, O 22.8, P 8.8; found: C 54.7, H 5.4, N 7.9, P 9.0.

rac-*3-Methyl-2-(1-methylethyl)imidazolidin-4-one* (*rac*-**19**). Following the procedure published for the analogous 2-(1,1-dimethylethyl) derivative [11], 62.8 g (0.5 mol) of glycine hydrochloride, 8M $MeNH_2$ in MeOH, and isobutyraldehyde were used to prepare 25 g (35%) of *rac*-**19** slightly yellow oil. B.p. 70–72°/2·10^{-5} Torr. ^{1}H-NMR (200 MHz): 0.79 (*d*, J = 6.8, 3 H, Me_2CH); 0.99 (*d*, J = 6.9, Me_2CH); 2.00 (br. *s*, NH); 2.01 (*m*, Me_2CH); 2.79 (*s*, MeN); 3.47 (*s*, CH_2(5)); 4.38 (*m*, H–C(2)).

(2S)-3-Methyl-2-(1-methylethyl)-4-oxoimidazolidinium Hydrogen (S,S)-Bis-O,O′-(4-toluyl)tartrate·EtOH (**20**). (+)-Bis-*O,O′*-(4-toluyl)-D-tartaric acid (30.9 g, 80 mmol) was dissolved in 60 ml of boiling EtOH. Then a soln. of *rac*-**19** (11.4 g, 80 mmol) in 20 ml of EtOH was added with stirring. The resulting hot orange soln. was allowed to cool slowly to +4° in a *Dewar* cylinder. After 17 h, the crystals formed were filtered off and washed with cold EtOH: **20** (20.4 g, 89%), $[\alpha]_D$ = +90.2 (c = 0.94, EtOH). After recrystallization from 40 ml of EtOH, 16.4 g (71%) of **20** were obtained. Colorless powder. M.p. 143–145° (dec.). $[\alpha]_D$ = +88.3 (c = 0.91, EtOH). IR (KBr): 3420*m* (br.), 2970*w* (br.), 2630*w* (br.), 2520*w* (br.), 1720*s* (br.), 1630*m*, 1610*s*, 1575*m*, 1510*w*, 1470*w*, 1435*w*, 1410*m*, 1380*w*, 1330*w* (br.), 1270*s*, 1210*w*, 1180*m*, 1130*m*, 1120*m*, 1110*s*, 1040*w*, 1020*w*. ^{1}H-NMR (200 MHz, (D_6)DMSO): 0.68 (*d*, J = 6.6, 3 H, Me_2CH); 0.88 (*d*, J = 6.7, 3H, Me_2CH); 1.06 (*t*, CH_3CH_2OH); 1.97 (*m*, Me_2CH); 2.39 (*s*, 2 MeC_6H_4CO); 2.67 (*s*, MeN); 3.26 (*A* of *AB*, J = 15.9, 1H, CH_2(5)); 3.44 (*q*, CH_3CH_2OH); 4.36 (br., H–C(2)); 5.78 (*s*, H–C(2′), H–C(3′) of tartrate); 6.40 (br., NH, OH, 2 COOH); 7.38 (*d*, J = 7.5, 4 arom. H); 7.90 (*d*, J = 7.2, 4 arom. H). Anal. calc. for $C_{29}H_{38}N_2O_{10}$ (574.63): C 60.62, H 6.67, N 4.88; found: C 59.68, H 6.43, N 5.02.

1,1-Dimethylethyl (2S)-3-Methyl-2-(1-methylethyl)-4-oxoimidazolidin-1-carboxylate (**21**). As described for the analogous 1,1-dimethylethyl derivative [11], a suspension of **20** (14.37 g, 25 mmol) was washed in 80 ml of CH_2Cl_2 with 40 ml of 2N NaOH. After drying ($MgSO_4$) and evaporation, the remaining oil was treated under cooling (ice) with a soln. of bis(1,1-dimethylethyl) dicarbonate (32 mmol) and 293 mg of 4-(dimethylamino)-pyridine in 45 ml of acetone. The soln. was stirred overnight at r.t. and then mixed with 3.4 ml of Et_3N. After stirring for another 2 h, H_2O (3 ml) was added and stirring continued for another 2 h. The soln. was concentrated and diluted with 150 ml of Et_2O. The extract was washed twice with 1N HCl and with sat. $NaHCO_3$ soln., dried, and evaporated: 2.25 g (37%) of yellow oil. CC (hexane/AcOEt 1:1) gave 1.85 g (31%) of pure **21**. Colorless oil. TLC (hexane/AcOEt 1:1): R_f 0.27. $[\alpha]_D$ = +1.23 (c = 1.3, CH_2Cl_2). IR ($CHCl_3$): 3020*w*, 3000*m*, 2980*m*, 2930*m*, 2880*w*, 1700*s*, 1600*w*, 1475*m*, 1455*m*, 1440*m*, 1410*s*, 1385*s*, 1370*s*, 1355*m*, 1330*m*, 1305*m*, 1210*m*, 1165*s*, 1125*m*, 1110*m*, 1090*w*, 1010*w*. ^{1}H-NMR (200 MHz): 0.87 (*d*, J = 7.8, 3 H, Me_2CH); 0.97 (*d*, J = 7.8, 3 H, Me_2CH); 1.46 (*s*, *t*-Bu); 2.27 (br. *m*, Me_2CH); 2.88 (*s*, *Me*N); 3.72 (*A* of *AB*, J = 17.6, 1 H, CH_2(5)); 4.08 (*B* of *AB*, J = 17.6, 1 H, CH_2(5)); 5.06 (br., H–C(2)). ^{13}C-NMR (100 MHz): 15.81, 17.13, 27.96, 28.30, 32.21, 49.83, 78.75, 81.05, 154.01, 168,95. MS

(among others): 243 (11), 199 (53), 187 (7), 169 (49), 143 (76), 99 (72), 86 (36), 71 (41), 57 (100), 41 (87), 29 (59). Anal. calc. for $C_{12}H_{22}N_2O_3$ (242.32): C 59.48, H 9.15, N 11.56; found: C 59.55, H 9.27, N 11.23.

1,1-Dimethylethyl (2S,5S)-5-{5-[(Diethoxyphosphoryl)methyl][1,1'-biphenyl]-3-methyl}-2-(1-methylethyl)-4-oxoimidazolidine-1-carboxylate (**22**). A soln. of 0.74 ml (0.53 g, 5.25 mmol) of $(i\text{-Pr})_2NH$ in 25 ml of THF was cooled to −78°, and 3.28 ml (5.25 mmol) of BuLi (*ca.* 1.5M in hexane) were added dropwise. The resulting colorless soln. was stirred at −60° for 30 min. A soln. of 1.21 g (5 mmol) of **21** in 20 ml of THF was added *via* cannula. The formed deep yellow enolate soln. was stirred for 20 min at −60°, then cooled to −65° and treated with a soln. of 1.83 g (4.6 mmol) of **13a** in 5 ml of THF. The soln. was stirred at −60° for 2 h and hydrolyzed with sat. aq. NH_4Cl soln. The aq. phase was extracted with Et_2O and the extract dried (Na_2SO_4) and evaporated: 2.82 g of a very viscous yellow oil. TLC (hexane/i-PrOH 4:1): R_f 0.15, 0.29. ^{1}H-NMR (300 MHz): at r.t., rotamers; at 60° only 1 diastereoisomer (> 98% ds). Purification by CC ($AcOEt/CH_2Cl_2$ 3:1 and hexane/i-PrOH 4:1) afforded 1.97 g (77%) of **22** (R_f 0.29) as a pale yellow, very viscous oil, and 0.36 g of a doubly alkylated non-identified side product (R_f 0.15). **22**: $[\alpha]_D = +36.6$ ($c = 1.18$, EtOH; *cf.* $[\alpha]_D = +35$ for **17a**). IR ($CHCl_3$): 3020*w*, 3000*m*, 2980*m*, 2930*w*, 2900*w*, 2880*w*, 2460*w*, 1750*w*, 1695*s*, 1600*w*, 1575*w*, 1470*w*, 1455*m*, 1440*w*, 1415*m*, 1395*m*, 1385*s*, 1370*m*, 1340*m*, 1295*w*, 1250*m* (br.), 1165*m*, 1135*m*, 1095*w*, 1055*m*, 1030*m*. ^{1}H-NMR (400 MHz; 60°): 0.79 (*d*, $J = 6.9$, 3 H, Me_2CH); 0.93 (*d*, $J = 7.4$, 3 H, Me_2CH); 1.25 (*t*, $J = 7.1$, 1 CH_3CH_2O); 1.27 (*t*, $J = 7.1$, 1 CH_3CH_2O); 1.46 (br. *s*, *t*-Bu); 2.38 (br., Me_2CH); 2.67 (*s*, *Me*N); 3.13 (*d*, $J = 21.7$, CH_2P); 3.62 (br., H–C(5)); 3.96–4.09 (*m*, 2 CH_3CH_2O); 4.34 (br. *s*, CH_2–C(5)); 7.00 (*d*, $J = 1.9$, H–C(2)); 7.26–7.57 (*m*, 8 arom. H). ^{13}C-NMR (100 MHz): 14.82, 16.42, 18.58, 20.56, 28.38, 29.47, 30.34, 32.95, 34.32, 35.85, 60.17, 62.24, 78.70, 80.83, 127.11, 128.64, 130.26, 131.75, 136.40, 140.65, 152.43, 170.08. MS (among others): 515 (42), 485 (9), 457 (30), 415 (100), 387 (11), 369 (9). 318 (41), 290 (10), 262 (9), 207 (11), 181 (32), 165 (16), 84 (6), 57 (73), 41 (25). Anal. calc. for $C_{30}H_{43}N_2O_6P$ (558.66): C 64.50, H 7.76, N 5.01; found: C 64.48, H 8.01, N 4.86.

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