An Alternative Synthesis of the Enantiomerically Pure Competitive NMDA Antagonists SDZ 220-581 and SDZ EAB 515

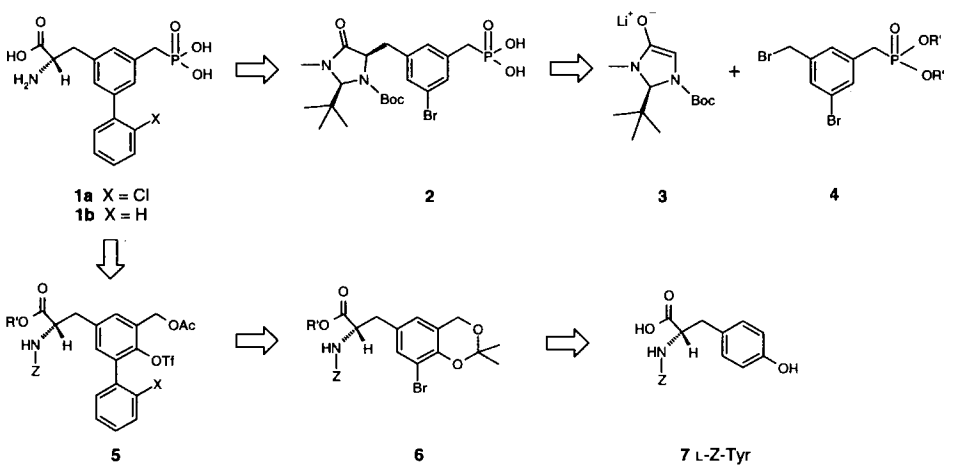
by **Werner Müller***, **Markus Bänziger**, and **Peter Kipfer**

Novartis Pharma AG, CH-4002 Basel

An alternative synthesis of enantiomerically pure SDZ 220-881 (**1a**) and SDZ EAB 515 (**1b**) starting from L-Z-tyrosine is described.

Introduction. – Biphenyl analogues of AP7 ((2*R*)-2-amino-7-phosphonoheptanoic acid) such as SDZ 220-581 (**1a**) and SDZ EAB 515 (**1b**) are selective competitive NMDA antagonists with high affinities for the NMDA recognition site *in vitro* [1][2] and with corresponding *in vivo* activities in various animal models [3]. Recently [1], we published a synthesis of enantiomerically pure SDZ EAB 515 (**1b**) and its substituted analogues by employing the chiral glycine derivative **3** (*Scheme 1*) [4]. We describe here an alternative synthesis of such compounds by starting from the readily available L-Z-tyrosine.

Scheme 1

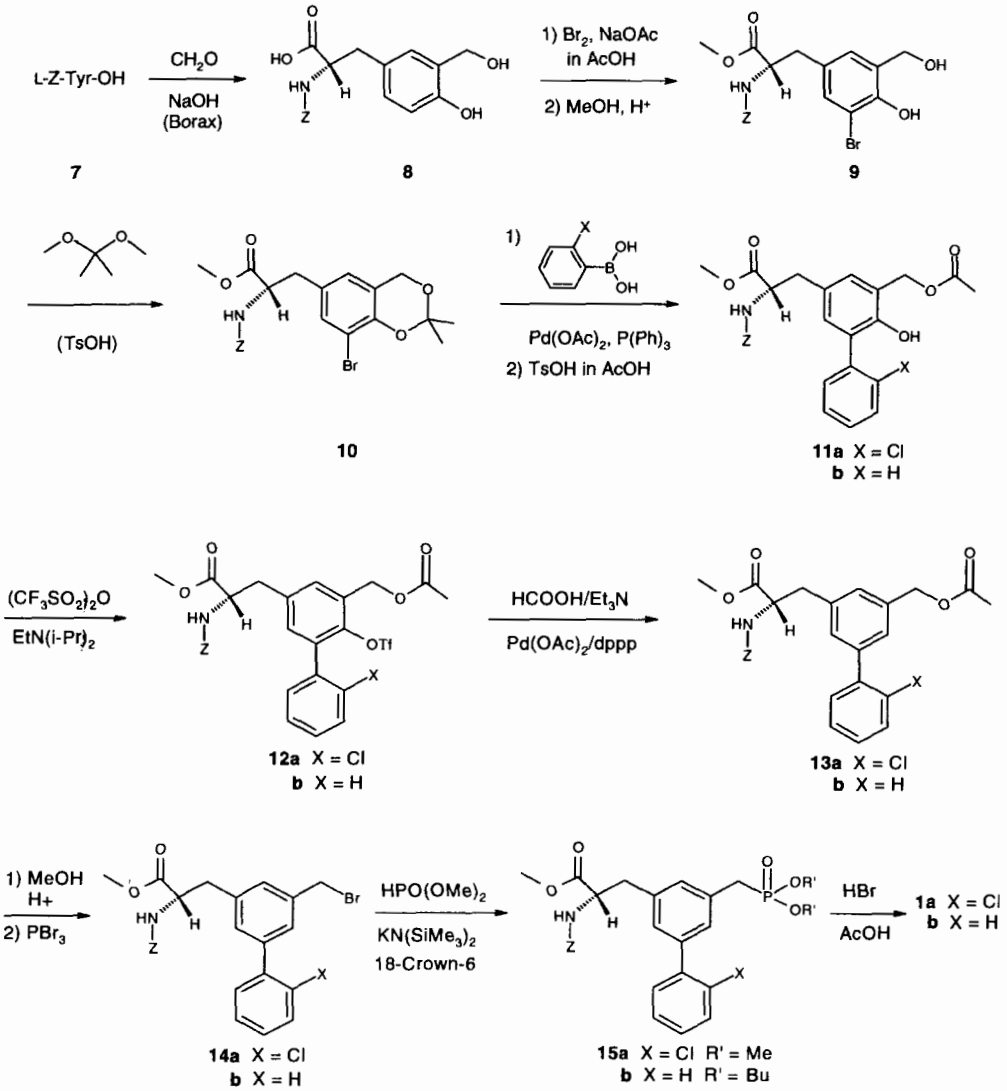


Results and Discussion. – Compounds of type **1** are 3,5-disubstituted L-phenylalanines (*Scheme 1*). Retrosynthetic analysis towards introduction of the CH_2OH and Br substituents at C(3) and C(5) of the phenylalanine by electrophilic substitution reactions leads to L-tyrosine as possible starting material. In fact, the phenolic OH group in the L-tyrosine molecule activates the *ortho*-positions in the Ph ring and directs the CH_2OH and the Br substituent into the desired positions. As outlined in *Scheme 2*, hydroxymethylation of

L-Z-tyrosine with a mixture of formaline, NaOH, and borax as a complex builder at 40° for 4 days, followed by bromination in AcOH and then esterification gave the crystalline intermediate **9** in 68% yield over three steps.

The cyclic dimethyl-ketal group of diol **9** proved to be a suitable protecting group for the conditions of standard *Suzuki* cross coupling. Reaction of the crystalline bromo derivative **10** with, *e.g.*, 2-chlorobenzeneboronic acid in the presence of catalytic amounts of $Pd(OAc)_2$ and PPh_3, followed by simultaneous cleavage of the acetal protecting group and selective acetylation of the benzylic alcohol function, gave **11a** with a yield of 33% over three steps.

Scheme 2



To remove the directing phenolic functional group, we used the method of Pd^0-catalyzed deoxygenation of phenol triflate [5]. Thus, phenols **11a** and **11b** were treated with $(CF_3SO_2)_2O$ and $EtN(i\text{-}Pr)_2$ in dry CH_2Cl_2 at $-50°$ and the corresponding trifluoromethanesulfonates **12a** and **12b** reduced with triethylammonium formate and 1,3-bis(diphenylphosphino)propane (dppp). This bidentate phosphine ligand has been described to be especially useful for sterically hindered phenols [6]. Transesterification ($MeOH/H^+$) followed by treatment of the resulting benzyl alcohol with BBr_3 led to bromides **14a** and **14b** in good overall yields (37 and 71%, resp., over three steps).

The phosphonates **15a** and **15b** were prepared by treating the corresponding bromides **14a** and **14b** with dimethyl and dibutyl phosphite, respectively, in toluene with potassium bis(trimethylsilyl)amide as base and 18-crown-6 at 0° (*Michaelis-Becker* reaction), followed by chromatography of the reaction mixture over silica gel. Hydrolysis (aq. HBr in AcOH) and crystallization from THF/aq. HCl led to amino diacids **1a** and **1b**, respectively, in good yields. The free amino diacids (*S*)-**1** proved to be identical to the product obtained by the former synthetic pathway [1] and enantiomerically pure by analysis on *Chiralplate*^{R} TLC (see *Exper. Part*) and on capillary electrophoresis.

Experimental Part

General. $EtN(i\text{-}Pr)_2$ was dried over molecular sieves (4 Å). All other commercially available chemicals were used as provided by the supplier without purification. TLC: silica gel *60 F-254* from *Merck*; *Chiralplate*^{R} from *Macherey-Nagel* (amino acid dissolved in 2M NH_3 and detected with a 0.1% soln. of ninhydrin in EtOH). Column chromatography: silica gel *60* (230–400 mesh) from *Merck* at medium pressure. M.p.: *Reichert* hot stage; uncorrected. Optical rotations: *Perkin-Elmer 241* polarimeter; cell length 10 cm. ^{1}H-NMR Spectra: *Varian Gemini-200*, 200 MHz spectrometer, $CDCl_3$ solns., unless otherwise stated; δ in ppm with TMS as standard, coupling constants J in Hz. The enantiomeric purity (% ee) were determinated by capillary electrophoresis (UV detector, area under the curve).

*N-(Benzyloxycarbonyl)-3-(hydroxymethyl)-*L*-tyrosine* (**8**) [7]. A mixture of *N-(benzyloxycarbonyl)-*L*-tyrosine* (**7**; 25.0 g, 79 mmol), $Na_2B_4O_7 \cdot 10\,H_2O$ (65 g), formaline (37% aq. CH_2O soln.; 25 ml, 330 mmol), 1M aq. NaOH (156 ml, 156 mmol), and H_2O (450 ml) was stirred for 120 h at 40°. The pH of the mixture was adjusted to 2 with 10% HCl and extracted with AcO(i-Pr). The org. layer was dried (Na_2SO_4) and evaporated to give **8** (26.7 g) as an oil, which was used without further purification for the next reaction. ^{1}H-NMR: 2.75 (*m*, 1 H); 2.95 (*m*, 1 H); 3.4 (br. *s*, 1 H); 4.1 (*m*, 1 H); 4.43 (*s*, 2 H); 4.95 (*s*, 2 H); 6.7 (*d*, J = 7, 1 H); 6.95 (*d*, J = 7, 1 H); 7.2 (*s*, 1 H); 7.3 (*s*, 5 H); 7.6 (*d*, J = 7, 1 H); 9.2 (*s*, 1 H); 12.6 (br. *s*, 1 H).

*N-(Benzyloxycarbonyl)-3-bromo-5-(hydroxymethyl)-*L*-tyrosine Methyl Ester* (**9**). To a soln. of **8** (26.6 g, max. 79 mmol) and NaOAc (6.65 g, 81 mmol) in AcOH (300 ml), Br_2 (4.05 ml, 79 mmol) was added dropwise with stirring at 10° within 5 min. After stirring at 15° for 30 min, the mixture was evaporated. The residue was partitioned between ice/H_2O and AcO(i-Pr). The org. phase was dried (Na_2SO_4) and evaporated. A soln. of this residue (37.2 g) and TsOH (0.7 g) in 280 ml of MeOH was stirred under reflux for 3 h. The mixture was evaporated. The residue treated with 10% aq. $KHCO_3$ soln. and extracted with AcO(i-Pr). The org. layer was dried (Na_2SO_4), evaporated, and the residue (33 g) was crystallized from cyclohexane/AcOEt 2:1 to afford **9** (23.5 g, 68% over 3 steps). M.p. 97–100°. ^{1}H-NMR ((D_6)DMSO): 2.1 (*s*, 2 H); 2.75 (*m*, 1 H); 2.92 (*m*, 1 H); 3.62 (*s*, 3 H); 4.18 (*m*, 1 H); 4.52 (*s*, 2 H); 5.0 (*s*, 2 H); 7.3 (*m*, 7 H); 7.8 (*d*, J = 14, 1 H). Anal. calc. for $C_{19}H_{20}BrNO_6$ (438.27): C 52.07, H 4.58, Br 18.23, N 3.20; found: C 52.30, H 4.60, Br 17.70, N 3.30.

*(S)-Methyl 2-[(Benzyloxycarbonyl)amino]-3-(8-bromo-2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)propanoate* (**10**). A soln. of **9** (16.3 g, 37.2 mmol), aceton dimethyl acetal (9.4 ml, 76.7 mmol), and TsOH (0.4 g) in 200 ml of THF was stirred at 55° for 4.5 h. The mixture was evaporated, the residue treated with 10% aq. $KHCO_3$ soln. and extracted with AcO(i-Pr). The org. layer was dried (Na_2SO_4), evaporated, and the residue (17.4 g) was crystallized from cyclohexane/AcOEt 3:1 to afford 15.9 g (89%) of **10**. M.p. 87–90°. ^{1}H-NMR ((D_6)DMSO): 1.5 (*s*, 6 H); 2.8 (*m*, 1 H); 2.95 (*m*, 1 H); 3.65 (*s*, 3 H); 4.25 (*m*, 1 H); 4.78 (*s*, 2 H); 5.0 (*m*, 2 H); 6.95 (*s*, 1 H); 7.35 (*m*, 6 H); 7.85 (*d*, J = 14, 1 H). Anal. calc. for $C_{22}H_{24}BrNO_6$ (478.34): C 55.24, H 5.06, Br 16.70, N 2.93, O 20.07; found: C 55.12, H 4.97, Br 16.80, N 3.11, O 19.90.

(S)-Methyl 3-[5-(Acetoxymethyl)-2'-chloro-6-hydroxy-1,1'-biphenyl-3-yl]-2-[(benzyloxycarbonyl)amino]-propanoate (**11a**). A soln. of **10** (12.0 g, 25.0 mmol), 2-chlorobenzeneboronic acid (4.7 g, 30.0 mmol), 2M aq. Na_2CO_3 soln. (29 ml), and EtOH (4 ml) in toluene (360 ml) was degassed in an ultrasonic bath and flushed with Ar before $Pd(OAc)_2$ (0.3 g) and PPh_3 (0.7 g) were added. The mixture was stirred at reflux under Ar for 2 h. After addition of charcoal, the mixture was filtered and the filtrate extracted with AcO(i-Pr). The org. layer was dried (Na_2SO_4) and evaporated. A soln. of this residue (15.2 g) and TsOH (0.17 g) in 80 ml of AcOH was stirred at 70° for 3 h. The mixture was evaporated, the residue treated with 10% aq. $KHCO_3$ soln., and extracted with AcO(i-Pr). The org. layer was dried (Na_2SO_4) and evaporated to give **11a** (4.2 g, 33% over 3 steps). Oil. ^{1}H-NMR ((D_6)DMSO): 2.1 (*s*, 3 H); 2.8 (*m*, 1 H); 2.98 (*m*, 1 H); 3.65 (*s*, 3 H); 4.25 (*m*, 1 H); 5.0 (*s*, 2 H); 5.1 (*s*, 2 H); 6.95 (*s*, 1 H); 7.16 (*s*, 1 H); 7.35 (*m*, 8 H); 7.52 (*m*, 1 H); 7.82 (*d*, *J* = 14, 1 H); 8.65 (*s*, 1 H).

(S)-Methyl 3-[5-(Acetoxymethyl)-6-hydroxy-1,1'-biphenyl-3-yl]-2-[(benzyloxycarbonyl)amino]propanoate (**11b**). As described for **11a** with 3.7 g (7.7 mmol) of **10** and 1.1 g (9.0 mmol) of benzeneboronic acid: 1.7 g (46%) of **11b**. ^{1}H-NMR ((D_6)DMSO): 2.05 (*s*, 3 H); 2.84 (*m*, 1 H); 3.0 (*m*, 1 H); 3.65 (*s*, 3 H); 4.25 (*m*, 1 H); 5.0 (*s*, 2 H); 5.1 (*s*, 2 H); 7.15 (*s*, 2 H); 7.3–7.54 (*m*, 9 H); 7.85 (*d*, *J* = 14, 1 H); 8.6 (*s*, 1 H).

(S)-Methyl 3-{5-(Acetoxymethyl)-2'-chloro-6-[(trifluoromethyl)sulfonyl]-1,1'-biphenyl-3-yl}-2-[(benzyloxycarbonyl)amino]propanoate (**12a**). To a stirred soln. of **11a** (5.4 g, 10.5 mmol) in $EtN(i\text{-}Pr)_2$ (2.2 ml, 13 mmol) and abs. CH_2Cl_2 (55 ml), $(CF_3SO_2)_2O$ (2.15 ml, 13 mmol) was added dropwise at *ca.* −65° over 5 min. Stirring was continued at *ca.* −55° for 1 h. After addition of ice/sat. aq. $KHCO_3$ soln., the mixture was extracted with AcO(i-Pr). The org. layer was dried (Na_2SO_4) and evaporated. A soln. of this residue (7.7 g) in cyclohexane/AcOEt 2:1 was purified by adding silica gel and charcoal. The filtrate was evaporated to give **12a** (6.9 g). Oil. ^{1}H-NMR ((D_6)DMSO): 2.0 (*s*, 3 H); 2.92 (*m*, 1 H); 3.18 (*m*, 1 H); 3.62 (*s*, 3 H); 4.35 (*m*, 1 H); 4.92 (*s*, 2 H); 5.1 (*s*, 2 H); 7.2–7.55 (*m*, 9 H); 7.6 (*s*, 2 H); 7.9 (*d*, *J* = 14, 1 H).

(S)-Methyl 3-{5-(Acetoxymethyl)-6-[(trifluoromethyl)sulfonyl]-1,1'-biphenyl-3-yl}-2-[(benzyloxycarbonyl)-amino]propanoate (**12b**). As described for **12a** with 1.7 g (3.5 mmol) of **5b** and $(CF_3SO_2)_2O$ (0.7 ml, 4.2 mmol): 2.2 g of **12b**. Oil. ^{1}H-NMR ((D_6)DMSO): 2.1 (*s*, 3 H); 2.95 (*m*, 1 H); 3.15 (*m*, 1 H); 3.65 (*s*, 3 H); 4.4 (*m*, 1 H); 4.95 (*s*, 2 H); 5.15 (*s*, 2 H); 7.3 (*s*, 5 H); 7.55 (*s*, 4 H); 7.5 (*s*, 2 H); 7.9 (*d*, *J* = 14, 1 H).

(S)-Methyl 3-[5-(Acetoxymethyl)-2'-chloro-1,1'-biphenyl-3-yl]-2-[(benzyloxycarbonyl)amino]propanoate (**13a**). A stirred mixture of **12a** (48.3 g, 75 mmol), LiCl (3.1 g), Et_3N (200 ml, 1.48 mol), and DMF (500 ml) was flushed with Ar and cooled below 15° before HCOOH (56 ml, 1.48 mol) was added dropwise. After addition of $Pd(OAc)_2$ (1.7 g, 7.5 mmol) and 1,3-bis(diphenylphosphino)propane (3.1 g, 7.5 mmol), stirring was continued at *ca.* 60° under Ar. After 4 h, the soln. was evaporated and the residue partitioned between H_2O and AcO(i-Pr). The org. layer was washed with 10% aq. NH_4Cl soln. and 10% aq. $KHCO_3$ soln., dried (Na_2SO_4), and evaporated to give **13a** (41.9 g). Oil. ^{1}H-NMR: 2.1 (*s*, 3 H); 3.18 (*d*, 2 H); 3.72 (*s*, 3 H); 4.7 (*m*, 1 H); 5.1 (*s*, 4 H); 5.3 (*m*, 1 H); 7.14 (*d*, *J* = 14, 2 H); 7.2–7.5 (*m*, 10 H).

(S)-Methyl 3-[5-(Acetoxymethyl)-1,1'-biphenyl-3-yl]-2-[(benzyloxycarbonyl)amino]propanoate (**13b**). As described for **13a** with 1.6 g (2.6 mmol) of **12b**, LiCl (130 mg), Et_3N (8.0 ml, 57 mmol), DMF (22 ml), HCOOH (2.2 ml, 57 mmol), $Pd(OAc)_2$ (0.44 g), and 1,3-bis(diphenylphosphino)propane (0.78 g): 1.4 g of **13b**. Oil. ^{1}H-NMR: 2.1 (*s*, 3 H); 3.2 (*m*, 2 H); 3.75 (*s*, 3 H); 4.7 (*m*, 1 H); 5.1 (*s*, 4 H); 5.25 (*m*, 1 H); 7.2–7.6 (*m*, 13 H).

(S)-Methyl 2-[(Benzyloxycarbonyl)amino]-3-[5-(bromomethyl)-2'-chloro-1,1'-biphenyl-3-yl]propanoate (**14a**). A soln. of **13a** (41.9 g) in MeOH (350 ml) and conc. HCl (4.0 ml) was stirred at *ca.* 65°. After 2 h, the mixture was cooled with ice, $KHCO_3$ (8 g) was added, and the resulting soln. evaporated. The residue was partitioned between H_2O and AcO(i-Pr). The org. phase was dried (Na_2SO_4) and evaporated. The oily residue (38 g) was purified by chromatography on silica gel, using cyclohexane/AcOEt 2:1. The fractions containing the product with R_f 0.56 (TLC, cyclohexane/AcOEt 1:1) were evaporated to give an oil. To a soln. of this residue (19.2 g) in 200 ml of toluene, PBr_3 (1.4 ml) was added dropwise below −10° over 10 min. Stirring was continued at r.t. After 2 h, 10% aq. $KHCO_3$ soln. was added to the mixture. The org. phase was dried (Na_2SO_4) and evaporated to give **14a** (14.5 g, 37% over 3 steps). M.p. 50–53°. ^{1}H-NMR: 3.18 (*m*, 2 H); 3.75 (*s*, 3 H); 4.48 (*s*, 2 H); 4.7 (*m*, 1 H); 5.1 (*s*, 2 H); 5.3 (*d*, *J* = 10, 1 H); 7.15 (*s*, 2 H); 7.38–7.55 (*m*, 10 H).

(S)-Methyl 2-[(Benzyloxycarbonyl)amino]-3-[5-(bromomethyl)-1,1'-biphenyl-3-yl]propanoate (**14b**). As described for **14a** with 1.4 g of **13b**, 4M aq. HCl (3.8 ml), MeOH (12 ml), and PBr_3 (0.25 ml): 0.9 g (71% over 3 steps) of **14b**. Oil. ^{1}H-NMR: 3.2 (*m*, 2 H); 3.75 (*s*, 3 H); 4.5 (*s*, 2 H); 4.7 (*m*, 1 H); 5.1 (*s*, 2 H); 5.3 (*m*, 1 H); 7.3 (*s*, 2 H); 7.3–7.6 (*m*, 11 H).

(S)-Methyl 2-[(Benzyloxycarbonyl)amino]-3-{2'-chloro-5-[(dimethoxyphosphinoyl)methyl]-1,1'-biphenyl-3-yl}propanoate (**15a**). A soln. of $HPO(OMe)_2$ (1.75 ml, 19.0 mmol) in abs. toluene (35 ml) was treated at r.t. with $KN(SiMe_3)_2$ (23.6 ml of 15% soln. in toluene; 15.6 mmol). Stirring was continued at r.t. After 20 min, the mixture was cooled to 0° and treated with a soln. of **14a** (3.35 g, 6.5 mmol) and 18-crown-6 (0.14 g) in toluene (30 ml). The

mixture was stirred at 0° for 1 h and hydrolyzed with sat. aq. NH_4Cl soln. The aq. phase was extracted with toluene. The org. layer was dried (Na_2SO_4) and evaporated. The oily residue (3.9 g) was purified by chromatography (silica gel, AcOEt/cyclohexane 1:1). The fractions containing the product of R_f 0.34 (TLC, AcOEt) yielded **15a** (2.8 g, 78%). ^{1}H-NMR: 3.15 (*d*, *J* = 21, 2 H); 3.18 (*m*, 2 H); 3.65 (*dd*, *J* = 8, 4, 6 H); 3.75 (*s*, 3 H); 4.7 (*m*, 1 H); 5.1 (*s*, 2 H); 5.33 (*d*, *J* = 10, 1 H); 7.3 (*s*, 5 H); 7.32 (*m*, 6 H); 7.45 (*m*, 1 H).

(S)-Methyl 2-[(Benzyloxycarbonyl)amino]-3-{5-[(dimethoxyphosphinoyl)methyl]-1,1'-biphenyl-3-yl}propanoate (**15b**). As described for **15a** with $HPO(OBu)_2$ (1.35 ml, 6.9 mmol) in abs. toluene (4 ml), $KN(SiMe_3)_2$ (11.8 ml of 15% soln. in toluene, 7.8 mmol), 18-crown-6 (70 mg), and **14b** (0.96 g, 2.0 mmol) in abs. toluene (2 ml): 0.3 g (25%) of **15b**. R_f 0.36 (TLC, AcOEt/cyclohexane 1:1). ^{1}H-NMR: 0.9 (*t*, *J* = 6, 6 H); 1.4 (*m*, 4 H); 1.65 (*m*, 4 H); 3.15 (*m*, 4 H); 3.95 (*s*, 3 H); 4.0 (*dt*, *J* = 7, 6, 4 H); 4.7 (*m*, 1 H); 5.1 (*s*, 2 H); 5.33 (*d*, *J* = 10, 1 H); 7.2–7.4 (*m*, 11 H); 7.5 (*m*, 2 H).

(S)-2 Amino-3-[2'-chloro-5-(phosphonomethyl)-1,1'-biphenyl-3-yl]propanoic Acid (**1a**) A soln. of **15a** (2.0 g, 36 mmol) in AcOH (38 ml) and 24% aq. HBr (33 ml) was stirred at *ca.* 65° for 72 h. About half of the solvent was evaporated *in vacuo*, and the pH was adjusted to 2 with conc. aq. NH_3. The amorphous product was filtered off. A soln. of this product in H_2O (25 ml) and conc. aq. NH_3 (0.5 ml) was added dropwise at 60° under stirring to 1M aq. HCl (4 ml) and THF (3 ml). Stirring was continued for 30 min at 60° and then at r.t. After 1 h, the crystals formed were filtered off and washed with H_2O: 1.03 g (76%; 97.8% ee) of (*S*)-**1a**, identical (m.p., TLC, $[\alpha]_D$, ^{1}H-NMR) to the product obtained by the former synthetic pathway [1].

(S)-2-Amino-3-[5-(phosphonomethyl)-1,1'-biphenyl-3-yl]propanoic Acid (**1b**). As described for (*S*)-**1a** with 0.24 g (0.4 mmol) of **15b**: (*S*)-**1b** (0.08 g, 59%), identical (m.p., TLC, $[\alpha]_D$, ^{1}H-NMR) to the product obtained by the former synthetic pathway [1].

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