Pergamon

Tetrahedron Vol. 51, No. 12, pp. 3423-3434, 1995

0040-4020/95 $9.50+0.00

0040-4020(95)00091-7

Highly Enantioselective Synthesis of (*R*)- and (*S*)-2-Amino-5-phosphonopentanoic Acids [(*R*)- and (*S*)-AP5] *via* Modified Seebach Imidazolidinones.

Oscar García-Barradas and Eusebio Juaristi*

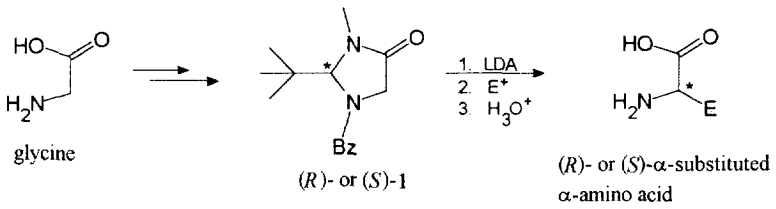
Departamento de Química, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Apartado Postal 14-740, 07000 México, D. F., México.

Abstract. The preparation of four new stereoisomeric 1-carbobenzyloxy-2-*tert*-butyl-3-(α-methylbenzyl)-1,3-imidazolidin-4-ones is described. Alkylation of the lithium enolates of these chiral glycine derivatives proceeds with high diastereoselectivity. In particular, the reaction of the *unlike* isomers, (2*R*,1'*S*)- and (2*S*,1'*R*)-**7**, afforded the desired phosphorylated products **9** with ≥ 98% diastereoselectivity. Hydrolysis of the alkylated products proceeds under relatively mild conditions to give enantiomerically pure α-substituted α-amino acids. Thus, hydrolysis of (2*R*,5*R*,1'*S*)-**9** and (2*S*,5*S*,1'*R*)-**9** provided the physiologically important, enantiopure amino phosphonic acids (*R*)-AP5 and (*S*)-AP5.

Introduction.

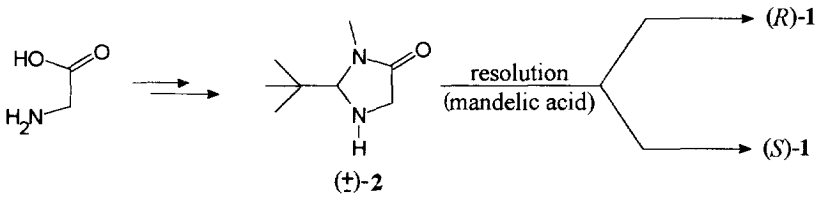
Among the available methods to synthesize α-amino acids in optically active form,[1] the use of chiral glycine derivatives (*R*)- and (*S*)-**1** has been particularly successful[2] (Scheme I).

Scheme I



Enantiomerically pure 1,3-imidazolidin-4-ones **1** were initially obtained *via* a multistep degradation of suitable precursors derived from serine[3a] or methionine.[3b] However, much better results were obtained by the resolution of the imidazolidinone **2** with mandelic acid,[4] followed by acylation under Schotten-Baumann conditions (Scheme II).

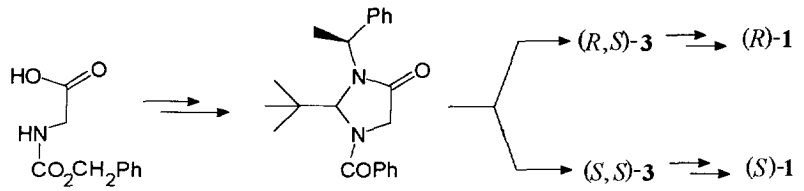
Scheme II



(±)-2

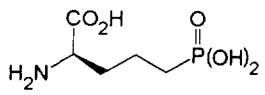
More recently, Juaristi, et al.[5] described an anternative route for the preparation of enantiomerically pure (*R*)- and (*S*)-**1**, *via* the separation of the diastereoisomeric mixture of (*R,S*)-**3** and (*S,S*)-**3** (Scheme III). Furthermore, it was pointed out that intermediates **3** could offer some advantages for the enantioselective synthesis of α-amino acids.[5,6]

Scheme III

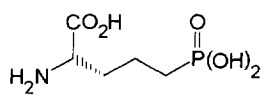


(*R,S*)- and (*S,S*)-**3**

In this paper we report the convenient application of closely related analogues of **3** in the highly enantioselective preparation of (*R*)- and (*S*)-2-amino-5-phosphonopentanoic acids [(*R*)- and (*S*)-**4**, so called (*R*)- and (*S*)-AP5], which are of substantial interest in medicinal chemistry as potent antagonist for the *N*-methyl-D-aspartic acid excitatory amino acid receptor.[7-9]



(*R*)-4



(*S*)-4

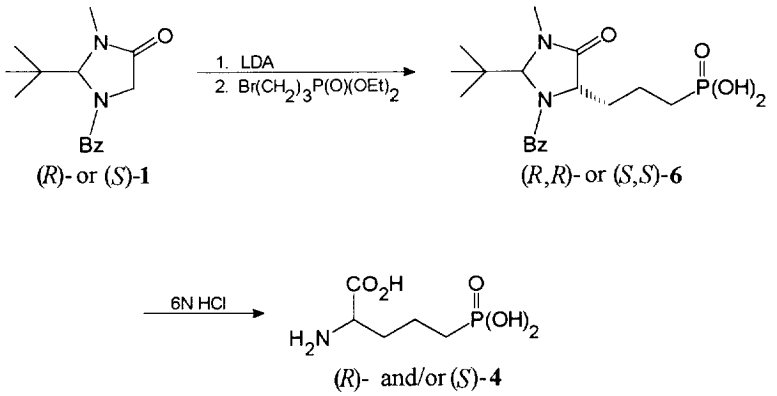
Results and Discussion

A. Partial Racemization in the Preparation of Scalemic AP5s *via* Imidazolidinones 1.

(*R*)- and (*S*)-2-*tert*-butyl-3-methyl-1,3-imidazolidin-4-ones **1** were prepared according to the procedure described by Fitzi and Seebach.[4a] Comparison of the optical rotations in our compounds with those in the literature[4a] suggested that their enantiomeric purities were higher than 99%.

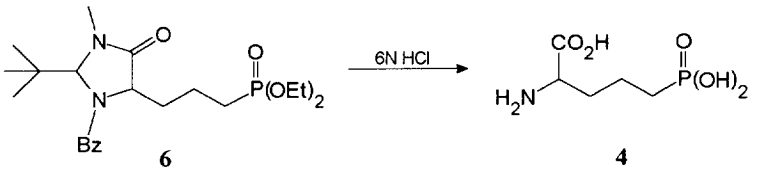
(*R*)- and (*S*)-**1** were then treated with lithium diisopropylamide (LDA), followed by addition of diethyl 3-bromopropylphosphonate (**5**) to afford the desired products of *trans* substitution, (*R,R*)-**6** and (*S,S*)-**6**, in 59.0% and 69.4% isolated yields, respectively (Scheme IV). Examination of the ^1H and ^{13}C NMR spectra of the crude products from these reactions indicates diastereoselectivities greater than 95%.

Scheme IV



Hydrolysis of (*R*,*R*)-**6** and (*S*,*S*)-**6** was carried out under acidic conditions (6N HCl), and the free aminophosphonic acid was obtained from Dowex ion-exchange resin.[2,3] Table I summarizes our results, the most salient features being that complete hydrolysis, within a reasonable time, required temperatures of hydrolysis equal to 140°C or higher.

Table I. Conditions Employed for the Hydrolysis of (*R*,*R*)- and (*S*,*S*)-**6**, and Optical Purity of the Isolated (*R*)-and (*S*)-AP5



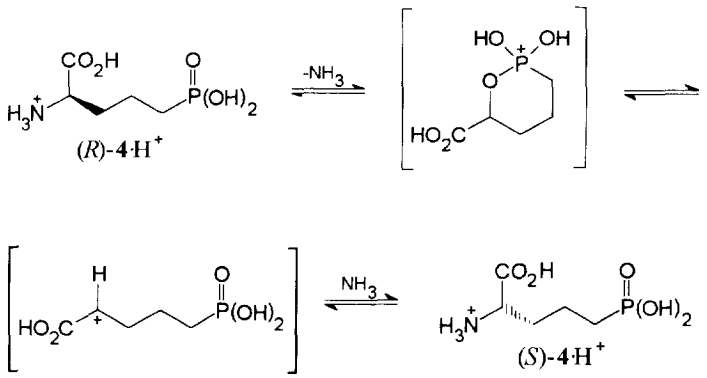
6 **4**

Substrate	Temperature (°C)	Reaction time (h)	Degree of hydrolysis	Optical purity of **4** (%)
(*S*,*S*)-**6**	180	8	complete	0
(*R*,*R*)-**6**	180	8	complete	0
(*S*,*S*)-**6**	90	4	null	---
(*S*,*S*)-**6**	120	4	partial[a]	---
(*S*,*S*)-**6**	140	6	complete	44
(*S*,*S*)-**6**	120	48	partial	29
(*R*,*R*)-**6**	140	6	complete	33

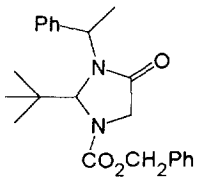
[a] *N*-Methyl amide of **4** was observed as the product.

However, partial racemization was observed al 140°C, and complete racemization was found at 180°C. We speculate that intramolecular participation of the phosphoryl group might be involved in the racemization process (Scheme V). Thus, anchimeric participation by the phosphoryl group could help explain the configurational lability of (*R*)- and (*S*)-**4** to the acidic conditions employed for hydrolysis; conditions that are usually compatible for the preparation of many other enantiopure α-amino acids.[2,3]

Scheme V



Be this as it may,[10] it was deemed necessary to search for milder conditions in order to carry out the hydrolysis step without racemization. In this regard, it seemed that imidazolidinone derivatives **7** would be more prone to hydrolysis,[4b,5,11] thus facilitating the isolation of the desired aminophosphonic acids in enantiomerically pure state.



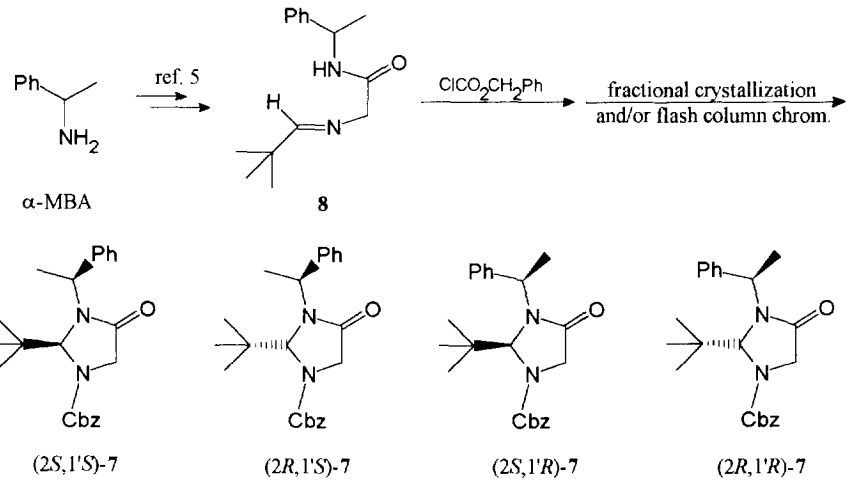
7 (stereochemistry not indicated)

B. Preparation of the Four Stereoisomers of 2-*tert*-Butyl-1-carbobenzyloxy-3-(α-methylbenzyl)-1,3-imidazolidin-4-one (7).

Scheme VI shows the reaction sequence used to convert either enantiomer of α-methylbenzylamine (α-MBA) into the appropriate enantiopure imidazolidinone.

Chiral imines (*R*)- and (*S*)-**8** were prepared from (*R*)- or (*S*)-MBA according to the published procedure.[5] Treatment with benzyl chloroformate afforded two diastereoisomeric heterocycles in a ratio close to 1:1. Thus, (2*S*,1'*S*)-**7** and (2*R*,1'*S*)-**7** were formed from (*S*)-MBA, and the pair (2*S*,1'*R*)-**7**/(2*R*,1'*R*)-**7** from (*R*)-MBA. The yield of combined cyclized products was 80% in both cases.

Scheme VI[a]



[a] Cbz = carbobenzyloxy group

The separation of the (2*S*,1'*S*)/(2*R*,1'*S*) mixture was achieved by flash chromatography to give the less polar diastereoisomer as a solid with mp 77-78°C and $[\alpha]_D^{28}$ = -36.2° (c = 1.05, CH_2Cl_2), and then the more polar isomer, mp 132-133°C, $[\alpha]_D^{28}$ = +114.0° (c = 1.13, CH_2Cl_2). Alternatively, fractional crystallization of the crude product from EtOAc-hexane (1:9) gave the polar isomer; the remaining mother liquor was then separated by chromatography, as described above.

The assignment of configuration of the cyclized diastereoisomers described in the previous paragraph was achieved by chemical correlation with known[5] (2*S*,1'*S*)-**3** and (2*R*,1'*S*)-**3**. Indeed, the less polar isomer with mp 77-78°C was hydrogenolyzed [H_2/Pd(C)] in quantitative yield to provide the expected amine-acetal, which was *N*-benzoylated under Schotten-Baumann conditions to give a derivative with mp 125-127°C and $[\alpha]_D^{28}$ = +59.8 (c = 1, CH_2Cl_2), corresponding to (2*S*,1'*S*)-**3**.[5] Therefore, the less polar imididazolidinone obtained from (*S*)-**8** must be (2*S*,1'*S*)-**7** (Scheme VIIa).

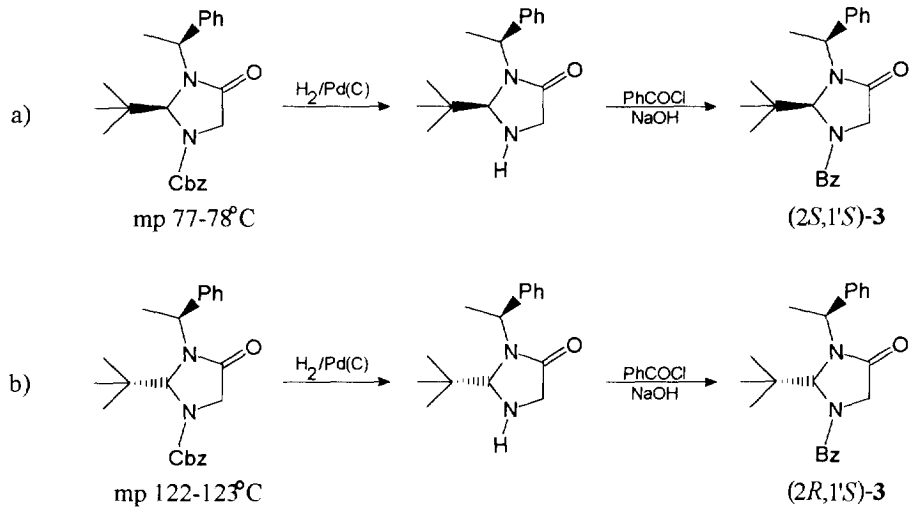
Similary, the more polar product with mp 132-133°C was converted to a benzoylated derivative with mp 186-187°C and $[\alpha]_D^{28}$ = +45.3 (c = 1, CH_2Cl_2), which corresponds to (2*R*,1'*S*)-**3** (Scheme VIIb).

Imidazolidinones (2*S*,1'*R*)-**7** and (2*R*,1'*R*)-**7** were prepared and separated in similar fashion (Scheme VI), with (*R*)-MBA as the starting chiral amine. These heterocyclic compounds are enantiomers of (2*R*,1'*S*)-**7** and (2*S*,1'*S*)-**7**, respectively, so that the assignment of their configuration was straightforward.

C. Highly Stereoselective Alkylation of (2*R*,1'*S*)-7 and (2*S*,1'*R*)-7, and Subsequent Hydrolysis to Enantiopure (*R*)-4 and (*S*)-4.

Imidazolidinones (2*R*,1'*S*)-**7** and (2*S*,1'*R*)-**7** were treated separately with LDA, and the resulting enolates were added to diethyl 3-bromopropylphosphonate (**5**). Spectroscopic analysis (^1H and ^{13}C NMR) indicated the formation of the desired alkylated products **9** with very high diastereoselectivity, ≥ 98%.

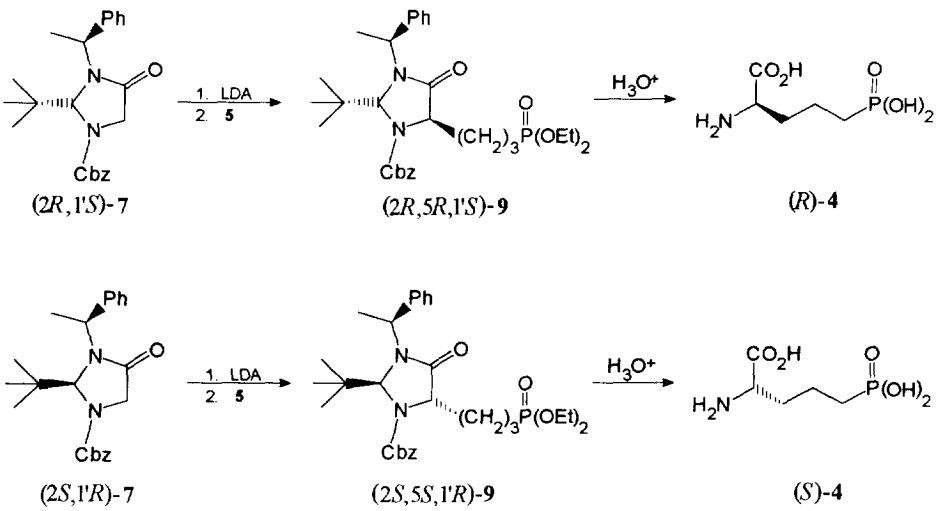
Scheme VII[a]



[a] Cbz = carbobenzyloxy. Bz = benzoyl.

That the configuration of this product is *trans* relative to the *tert*-butyl group at C(2) (Scheme VIII) could be established by hydrolysis to the expected aminophosphonic acids of known absolute configuration, as described below.

Scheme VIII



Adducts (2*R*,5*R*,1'*S*)-**9** and (2*S*,5*S*,1'*R*)-**9** were purified by flash chromatography (see Experimental) to afford the pure compounds in 64.8% and 63.5% yields, respectively. Hydrolysis to (*R*)-**4** and (*S*)-**4** proceeded conveniently with 6N HCl, at a temperature of 115°C for 16 h. Extraction with CH_2Cl_2 and treatment with propylene oxide (see Experimental) provided *enantiopure* (*R*)-(-)-AP5 and (*S*)-(+)-AP5, respectively, in 97.8% and 98.3% chemical yields (Scheme VIII).

Conclusions.

Imidazolidinones **7** proved to be convenient starting materials for the enantioselective synthesis of α-substituted α-amino acids. In particular, alkylation of lithium enolates **7**-Li proceeds with very high diastereoselectivity to give the products of addition *trans* to the *tert*-butyl group. Hydrolysis of the alkylated derivatives **9** can be carried out without racemization under relatively mild conditions, and with excellent yields. Thus, the use of (2*R*,1'*S*)-**7** and (2*S*,1'*R*)-**7** as chiral glycine precursors permitted a high-yield synthesis of enantiopure (*R*)- and (*S*)-AP5.[12]

Experimental Part

General. Melting points were determined in a Mel-Temp apparatus, in open capillary tubes and are not corrected. TLC: Merck-DC-F_{254}; detection by UV light. Flash column chromatography:[14] Merck silica gel (0.040-0.063 mm). Optical rotations were determined in a Perkin-Elmer 241 polarimeter, at the sodium D line (589 nm). ^{1}H NMR spectra: Jeol PMX-60 (60 MHz) and Jeol GSX-270 (270 MHz) spectrometers. ^{13}C NMR spectra: Jeol FX-90Q (22.49 MHz) and Jeol GSX-270 (67.8 MHz). ^{31}P NMR spectra: Jeol FX-90Q (36.23 MHz) and Jeol GSX-270 (109.25 MHz). Chemical shifts (δ) in ppm downfield from internal TMS reference (^{1}H and ^{13}C NMR spectra) and external H_3PO_4 reference (^{31}P NMR spectra); the coupling constants (J) are given in Hz. Elemental analyses were obtained at Galbraith Laboratories, Inc., TN.

(*R*)- and (*S*)-1-Benzoyl-2-*tert*-butyl-3-methyl-1,3-imidazolidin-4-one [(*R*)- and (*S*)-1] were prepared by benzoylation of (*S*)- and (*R*)-2-*tert*-butyl-3-methyl-1,3-imidazolidin-4-one [(*S*)- and (*R*)-**2**], according to the procedure of Fitzi and Seebach.[4a]

(*R*)-**1**, mp 143-146°C (lit.[4a] mp 143-144°C); $[\alpha]_D^{28}$ = -125.3 (c = 1, CH_2Cl_2) (lit.[4a] $[\alpha]_D$ = -126.0 (c = 1, CH_2Cl_2).

(*S*)-**1**, mp 145-146°C (lit.[4a] mp 143-144°C); $[\alpha]_D^{28}$ = +126.0 (c = 1, CH_2Cl_2) (lit.[4a] $[\alpha]_D$ = +127.5 (c = 1, CH_2Cl_2).

(*R*,*S*)- and (*S*,*S*)-1-Benzoyl-2-*tert*-butyl-3-(α-methylbenzyl)-1,3-imidazolidin-4-one [(*R*,*S*)- and (*S*,*S*)-3]: see the procedure described in ref. 5.

Diethyl 3-bromopropylphosphonate (5). In a 50-mL round-bottom Schlenk flask provided with magnetic stirrer and condenser, was placed 6.28 mL (12.5 g, 62 mmol) of 1,3-dibromopropane and heated to 120°C before the addition of 2.6 mL (2.5 g, 15.1 mmol) of triethylphosphite. The reaction mixture was stirred at 120°C during 1 h, and then heated to 160°C for 5 h. The crude product was allowed to cool to room temperature and was purified by distillation in a Kugelrohr apparatus, bp 110°C/5 mm (lit.[15] 110-116°C/0.02 mm) as a viscous, colorless liquid. ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.35 (t, J = 7.0 Hz, 6 H, CH_3CH_2), 1.6-2.4

(m, 4H, CH_2CH_2P), 3.55 (t, J = 7.0 Hz, 2H, CH_2Br), 4.15 (p, J = 7.0 Hz, 4H, CH_2CH_3). ^{13}C NMR (22.49 MHz, $CDCl_3$) δ 16.44 (d, $^3J_{P/C}$ = 6.1 Hz, CH_3CH_2), 24.35 (d, $^1J_{P/C}$ = 142.8 Hz, CH_2P), 25.98 (d, $^3J_{P/C}$ = 3.7 Hz, CH_2Br), 33.61 (d, $^2J_{P/C}$ = 18.3 Hz, CH_2CH_2P), 61.67 (d, $^2J_{P/C}$ = 6.1 Hz, CH_2CH_3). ^{31}P NMR (36.23 MHz, $CDCl_3$) δ 30.52.

(2*S*,5*S*)-(+)-1-Benzoyl-2-*tert*-butyl-3-methyl-5-(diethyl 3-propylphosphonate)-1,3-imidazolidin-4-one [(*S*,*S*)-6]. In a 50-mL Schlenk flask provided with magnetic bar and rubber septa was placed under nitrogen 25 mL of dry THF. The flask was submerged in a dry ice-acetone bath at -78°C before the addition of 0.31 mL (0.23 g, 2.26 mmol) of diisopropylamine and then 1.0 mL (0.16 g, 2.46 mmol) of 2.47 M *n*-butyl lithium in hexane.The resulting solution was stirred at -78°C for 20 min before the addition of 0.53 g (2.05 mmol) of imidazolidinone (*S*)-**1** in 10 mL of THF. The resulting orange solution of the desired enolate was stirred at -78°C for 1 h and was then treated with 0.57 g (2.2 mmol) of bromide **5**, and stirred at the same temperature for an additional hour. The reaction was quenched with 5 mL of saturated aqueous ammonium chloride and then 5 mL of water. Extraction with CH_2Cl_2, removal of water with Na_2SO_4 and concentration afforded the crude product, which was purified by flash chromatography [ethyl acetate/hexane/methanol (8:1:1)] to give 0.61 g (69.4 % yield) of (*S*,*S*)-**6** as a white solid with mp 82-85°C and $[\alpha]_D^{28}$ = +61.0 (c = 1, CH_2Cl_2). ^1H NMR (90MHz, $CDCl_3$) δ 0.9-1.5 (m, 21H, $C(CH_3)_3$ + $(CH_2)_3P$ + CH_2CH_3), 3.13 (s, 3H, N-CH_3), 4.1 (m, 4H, CH_2CH_3), 4.4 (broad, 1H, C(5)-**H**), 5.7 (s, 1H, C(2)-**H**), 7.5-7.8 (m, 5H, C_6H_5). ^{13}C NMR (22.49 MHz, $CDCl_3$) δ 15.75 (d, $^2J_{P/C}$ = 4.9 Hz, CH_2CH_2P), 16.44 (d, $^3J_{P/C}$ = 6.1 Hz, CH_2CH_3), 25.38 (d, $^1J_{P/C}$ = 142.8 Hz, CH_2P), 26.33 (s, $C(CH_3)_3$), 31.0 (s, $CH_2CH_2CH_2P$), 31.91 (s, $C(CH_3)_3$), 40.96 (s, N-CH_3), 60.95 (d, $^2J_{P/C}$ = 2.4 Hz, C(5)), 61.46 (d, $^2J_{P/C}$ = 6.1 Hz, CH_2CH_3), 80.12 (s, C(2)), 127.42 (s, C_{meta}), 128.94 (s, C_{ortho}), 131.64 (s, C_{para}), 136.57 (s, C_{ipso}), 170.92 (s, CO). ^{31}P NMR (36.23 MHz, $CDCl_3$) δ 30.49.

(2*R*,5*R*)-(-)-1-Benzoyl-2-*tert*-butyl-3-methyl-5-(diethyl 3-propylphosphonate)-1,3-imidazolidin-4-one [(*R*,*R*)-6]. Imidazolidinone (*R*)-**1** (0.53 g, 2.05 mmol) was metallated with LDA and treated with 0.57 g (2.2 mmol) of bromide **5** according to the procedure described above for the preparation of (*S*,*S*)-**6**. The same workup and purification protocol afforded 0.51 g (59 % yield) of pure (*R*,*R*)-**6** as a white solid, mp 83-85°C, $[\alpha]_D^{28}$ = -61.0 (c = 1, CH_2Cl_2). The ^1H, ^{13}C and ^{31}P NMR spectra were identical to those reported for (*S*,*S*)-**6**.

2-*N*-(2,2'-Dimethylpropyliden)amino-*N*'-((*R*)-α-methylbenzyl)acetamide [(*R*)-(+)-8]. According to the described procedure,[5] 2.44 g (13.7 mmol) of (*R*)-(+)-2-amino-*N*'-(α-methylbenzyl)acetamide was condensed with 2.98 mL (2.36 g, 27.4 mmol) of pivalaldehyde to afford 3.15 g (93.4 % yield) of (*R*)-**8** as a viscous, yellowish oil, $[\alpha]_D^{28}$ = +73.3 (c = 1, EtOH) (lit.[5] $[\alpha]_D^{29}$ = -73.8 (c = 1, EtOH) for (*S*)-**8**).

2-*N*-(2,2'-Dimethylpropyliden)amino-*N*'-((*S*)-α-methylbenzyl)acetamide [(*S*)-(-)-8]. According to the described procedure,[5] 1.5 g (8.4 mmol) of (*S*)-(-)-2-amino-*N*'-(α-methylbenzyl)acetamide was condensed with 1.83 mL (1.45 g, 16.8 mmol) of pivalaldehyde to afford 1.91 g (92 % yield) of (*S*)-**8** as a viscous, yellowish oil, $[\alpha]_D^{28}$ = -73.5 (c = 1, EtOH) (lit.[5] $[\alpha]_D^{29}$ = -73.8 (c = 1, EtOH)).

(2*RS*)-*tert*-Butyl-1-carbobenzyloxy-3-[(*S*)-α-methylbenzyl]-1,3-imidazolidin-4-one [(2*RS*,1'*S*)-7]. In a 250 mL Schlenk round-bottom flask, provided with magnetic stirrer and condenser, 1.5 g (6.1 mmol) of (*S*)-**8** was placed and dissolved in 150 mL of freshly distilled benzene. The resulting solution was heated to reflux before the addition of 0.96 mL (1.14 g, 6.7 mmol) of benzyl chloroformate. The reaction mixture was heated to reflux for 6 h, allowed to cool to room temperature, filtered and concentrated to provide a brown crystalline solid shown by ^{13}C NMR analysis to consist of a 54:46 mixture of the expected diastereoisomeric cyclized products. This mixture was separated by flash chromatography (eluent, EtOAc:hexane, 6:4) to give 0.58 g (25.1% yield) of the less polar isomer, identified as (2*S*,1'*S*)-**7** by chemical correlation with (2*S*)-**3** (see below), and 0.71 g (30.7 % yield) of the more polar isomer, identified as (2*R*,1'*S*)-**7** by chemical correlation with (2*R*)-**3** (see below).

(2*S*,1'*S*)-7: mp 77-78°C. $[\alpha]_D^{28}$ = -36.2 (c = 1.05, CH_2Cl_2). ^1H NMR (60 MHz, $CDCl_3$) δ 0.99 (s, 9H, $C(CH_3)_3$), 1,89 (d, J = 7.0 Hz, 3H, CH_3CH), 3.65 (d, J = 16.0 Hz, 1H, CHH'), 4.10 (d, J = 16.0 Hz, 1H, CHH'), 4.59 (q, J = 7.0 Hz, CH_3CH), 5.0 (s, 2H, CH_2Ph), 5.09 (s, 1H, C(2)-**H**), 7.15 (s, 10H, H_{arom}). ^{13}C NMR (22.49 MHz, $CDCl_3$) δ 17.3 (CH_3CH), 25.59 ($C(CH_3)_3$), 39.46 ($C(CH_3)_3$), 50.40 (**C**(5)), 55.76 (CH_3CH), 67.30 (OCH_2), 81.77 (**C**(2)), 126.41, 127.22, 127.60, 127.92, 128.19, 135.56, 140.55, 154.69, 170.83.

Anal. Calcd. for $C_{23}H_{28}N_2O_3$: C, 72.60; H, 7.42. Found: C, 72.43; H, 7.55.

(2R,1'S)-7: mp 132-133°C. $[\alpha]_D^{28}$ = +114.0 (c = 1.13, CH_2Cl_2). ^1H NMR (60 MHz, $CDCl_3$) δ 0.82 (s, $C(CH_3)_3$), 1,70 (d, J = 7.0 Hz, 3H, CH_3CH), 3.79 (d, J = 16.0 Hz, 1H, C(5)HH'), 4.25 (d, J = 16.0 Hz, 1H, C(5)HH'), 4.58 (q, J = 7.0 Hz, 1H, CH_3CH), 5.0 (s, 1H, C(2)-**H**), 5.1 (s, 2H, OCH2), 7.25 (s, 10H, H_{arom}). ^{13}C NMR (22.49 MHz, $CDCl_3$) δ 20.22 (CH_3CH), 25.53 ($C(CH_3)_3$), 39.13 ($C(CH_3)_3$), 50.78 (**C**(5)), 58.47 (CH_3CH), 67.68 (OCH_2), 83.66 (**C**(2)), 126.89, 127.98, 128.25, 128.41, 135.62, 140.92, 154.96, 171.21.

Anal. Calcd. for $C_{23}H_{28}N_2O_3$: C, 72.60; H, 7.42. Found: C, 72.29; H, 7.62.

Chemical Correlation of (2*S*,1'*S*)-7 with (2*S*,1'*S*)-3. In a hydrogenation flask was placed 0.3 g (0.8 mmol) of (2*S*,1'*S*)-7, 30 mL of ethyl acetate, and 0.03 g of 10% palladium on charcoal. The reaction mixture was hydrogenolyzed with H_2 at 50 atm for 4 h at room temperature, filtered over celite, and concentrated to give 0.198 g (quantitative yield) of the desired product as a viscous yellowish oil, which was dissolved in 20-mL of CH_2Cl_2 and placed in a 100-mL round-bottom flask provided with magnetic stirrer and two addition funnels. The flask was immersed in an bath at 0°C and then treated simultaneously with 0.1 mL (0.124 g, 0.88 mmol) of benzoyl chloride and 0.88 mL (0.035 g, 0.88 mmol) of 1N NaOH. The reaction mixture was allowed to react for 1.5 h at 0°C, and then washed with 20 mL of saturated, aqueous $NaHCO_3$ and with 20 mL of water. Extraction with two 20-mL portions of CH_2Cl_2 and the usual workup procedure afforded the crude product, which was recrystallyzed from EtOAc-hexane (8:2) to afford 0.135 g (47.8 % yield) of (2*S*,1'*S*)-**3** as a white, crystalline solid with mp 125-127°C (lit.[5] 126-127°C). $[\alpha]_D^{28}$ = +59.8 (c = 1, CH_2Cl_2), (lit.[5] $[\alpha]_D^{29}$ = +60.5 (c = 1, CH_2Cl_2)).

Chemical Correlation of (2*R*,1'*S*)-7 with (2*R*,1'*S*)-3. Following the same procedure described above for the conversion of (2*S*,1'*S*)-7 to (2*S*,1'*S*)-**3**, 0.2 g (0.53 mmol) of (2*R*,1'*S*)-7 was hydrogenolyzed with H_2/Pd(C) in 99.6 % yield. Benzoylation afforded then 0.098 g (53.2 % yield) of (2*R*,1'*S*)-**3** as a white, crystalline solid, mp 186-187°C (lit.[5] mp 185-186°C). $[\alpha]_D^{28}$ = +45.3 (c = 1, CH_2Cl_2), (lit.[5] $[\alpha]_D^{29}$ = +45.5 (c = 1, CH_2Cl_2)).

(2*RS*,1'*R*)-*tert*-Butyl-1-carbobenzyloxy-3-[(*R*)-α-methylbenzyl]-1,3-imidazolidin-4-one [(2*RS*,1'*R*)-7]. According to the procedure described above for (2*RS*,1'*S*)-7, 3.15 g (12.8 mmol) of (*R*)-**8** in 300 mL of benzene were treated with 2.01 mL (2.4 g, 14.08 mmol) of benzyl chloroformate to give 3.97 g (81.6 % yield) of the expected mixture of diastereoisomeric cyclized products in a 57:43 ratio. Flash chromatography (EtOAc-hexane, 6:4) provided 1.35 g (27.8 % yield) of the less polar diastereoisomer, whose configuration was assigned as (2*R*,1'*R*)-7 by comparison of its NMR spectra with those of enantiomer (2*S*,1'*S*)-7 (see above). Further elution of the column afforded 1.46 g (30 % yield) of the more polar isomer identified as (2*S*,1'*R*)-7 by comparison with ^1H and ^{13}C NMR spectra of enantiomer (2*R*,1'*S*)-**7**.

(2*R*,1'*R*)-7: mp 77-78°C. $[\alpha]_D^{28}$ = +35.8 (c = 1, CH_2Cl_2). ^1H and ^{13}C NMR spectra identical with those described above for (2*S*,1'*S*)-7. (for enantiomer, mp 77-78°C, $[\alpha]_D^{28}$ = -36.2 (c = 1.05, CH_2Cl_2).

(2*S*,1'*R*)-7: mp 132-133°C. $[\alpha]_D^{28}$ = -114.0 (c = 1, CH_2Cl_2). ^1H and ^{13}C NMR spectra identical with those described above for enantiomer (2*R*,1'*S*)-**7**.

Anal. Calcd. for $C_{23}H_{28}N_2O_3$: C, 72.60; H, 7.42. Found: C, 72.59; H, 7.53.

(2*R*,5*R*,1'*S*)-1-Carbobenzyloxy-2-*tert*-butyl-3-(α-methylbenzyl)-5-(diethyl 3-propylphosphonate)-1,3-imidazolidin-4-one [(2*R*,5*R*,1'*S*)-9]. In a 50-mL Schlenk flask was placed 15 mL of dry THF under nitrogen. The flask was immersed in a dry ice-acetone bath at -78°C and then 0.2 mL (1.45 mmol) of diisopropylamine followed by 0.63 mL (1.45 mmol) of 2.3 M *n*-BuLi was added. The resulting solution was stirred for 30 min before the addition of 0.5 g (1.32 mmol) of (2*R*,1'*S*)-7 in 15 mL of THF. The resulting enolate solution was stirred 1 h and then 0.38 g (1.45 mmol) of bromide **5** was added. The reaction mixture was stirred for 1 h, quenched with 5 mL of saturated aqueous ammonium chloride, extracted with two 20-mL portions of CH_2Cl_2, dried with Na_2SO_4, and concentrated. The crude product was purified by flash chromatography (EtOAc-hexane, 6:4) to give 0.48 g (64.8 % yield) of a colorless semisolid, $[\alpha]_D^{28}$ = +75.4 (c = 1, CH_2Cl_2). ^1H NMR (270 MHz, $CDCl_3$) δ 0.82 (s, 9H, C(**CH**$_3$)$_3$), 1.29 (t, J = 7.3 Hz, 6H, **CH**$_3$CH$_2$), 1.75 (d, J = 7.3 Hz, 3H, **CH**$_3$CH), 1.2-2.6 (broad, 6H, **CH**$_2$**CH**$_2$**CH**$_2$P), 4.05 (p, J = 7.3 Hz, 4H, CH$_3$**CH**$_2$), 4.17 (m, C(5)-**H**), 4.63 (q, J = 7.3 Hz, 1H, CH$_3$**CH**), 5.12 (d, J = 13.85 Hz, 2H, **CH**$_2$Ph), 5.17 (s, C(2)-**H**), 7.21-7.45 (m, 10H, **H**arom). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 16.47 (d, $^3J_{C/P}$ = 5.5 Hz, **CH**$_3$CH$_2$), 20.58 (s, **CH**$_3$CH), 25.62 (d, $^1J_{C/P}$ = 141.0 Hz, **CH**$_2$P), 26.08 (s, C(**CH**$_3$)$_3$), 30.33 (s, **CH**$_2$**CH**$_2$**CH**$_2$P), 40.51 (s, **C**(CH$_3$)$_3$), 59.84 (s, CH$_3$**CH**), 60.30 (d, $^2J_{C/P}$ = 2.2 Hz, CH$_3$**CH**$_2$), 61.40 (s, **C**(5)), 61.41 (d, $^2J_{C/P}$ = 12.1 Hz, CH$_2$**CH**$_2$**CH**$_2$P), 67.58 (s, **CH**$_2$Ph), 82.32 (s, **C**(2)), 127.10, 127.37, 128.46, 128.52, 128.69, 128.73, 135.63, 141.25, 153.47, 172.67 (**C**arom). ^{31}P NMR (36.23 MHz, $CDCl_3$) δ 31.19.

(2*S*,5*S*,1'*R*)-1-Carbobenzyloxy-2-*tert*-butyl-3-(α-methylbenzyl)-5-(diethyl 3-propylphosphonate)-1,3-imidazolidin-4-one [(2*S*,5*S*,1'*R*)-9]. The same procedure described for the preparation of (2*R*,5*R*,1'*S*)-**9** was followed with 0.5 g (1.32 mmol) of (2*S*,1'*R*)-**7**, to afford 0.47 g (63.5 % yield) of the desired product as a colorless semisolid, $[\alpha]_D^{28}$ = -75.7 (c = 2.88, CH_2Cl_2). The ^1H, ^{13}C, and ^{31}P NMR spectra were similar to those described for enantiomer (2*R*,5*R*,1'*S*)-**9**.

(*R*)-(-)-2-Amino-5-phosphonopentanoic Acid (*R*)-4. In a glass ampoule provided with magnetic stirrer was placed 0.3 g (0.54 mmol) of (2*R*,5*R*,1'*S*)-**9** and 3 mL of 6N HCl. The ampoule was sealed and heated for 16 h in a oil bath at 115°C. The reaction mixture was then allowed to cool to room temperature, extracted with two 10-mL portions of CH_2Cl_2, the aqueous phase was concentrated and the residue suspended in 10 mL of anh. hot ethanol, allowed to cool to room temperature and treated dropwise with propylene oxide[16] until the solution became turbid. At this point, the solution was heated to 50°C for 15 min, and the solid formed was filtered at vacuum. The remaining solid was recrystallized from EtOH/H_2O (1:1) to afford 0.104 g (97.8 % yield) of the desired (*R*)-AP5 as a white solid, mp 245°C. $[\alpha]_D^{28}$ = -22.0 (c = 1, 6N HCl) (lit.[8a] mp 245-246°C, $[\alpha]_D^{33}$ = -21.0 (c = 1, 6N HCl). ^1H NMR (270 MHz, D_2O) δ 1.4-1.8 (m, 4H), 1.8-2.1 (m, 2H), 3.97 (t, J = 5.9 Hz, 1H). ^{13}C NMR (67.8 MHz, D_2O) δ 27.97 (d, J = 3.3 Hz, $CH_2CH_2CH_2P$), 35.51 (d, J = 135.5 Hz, CH_2P), 40.22 (d, J = 17.7 Hz, CH_2CH_2P), 62.28 (s, CH), 181.48 (s, CO). ^{31}P NMR (109.25 MHz, D_2O) δ 30.81.

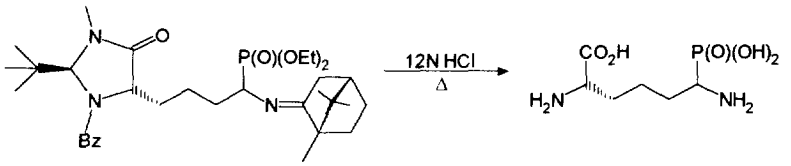
(*S*)-(+)-2-Amino-5-phosphonopentanoic Acid (*S*)-4. The same procedure described for the hydrolysis of (2*R*,5*R*,1'*S*)-**9** was carried out with 0.3 g (0.54 mmol) of (2*S*,5*S*,1'*R*)-**9** and 3 mL of 6N HCl to give 0.104 g (98.3 % yield) of (*S*)-**4** as a white solid, mp 245°C. $[\alpha]_D^{28}$ = +22.0 (c = 1, 6N HCl) (lit.[8a] mp 245-246°C, $[\alpha]_D^{33}$ = +21.0 (c = 1, 6N HCl)). The ^1H, ^{13}C, and ^{31}P NMR spectra were similar to those described for (*R*)-**4**.

Acknowledgments. We are indebted to G. Uribe for his help in recording several NMR spectra, to CONACYT (project 242-E) for financial support, and to A. Reyes, D. Seebach, A. Studer, and J. C. Vederas for useful discussions.

References and Notes

1. (a) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon Press: Oxford, 1989. (b) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539.
2. (a) Seebach, D.; Imwinkelried, R.; Weber, T. In *Modern Synthetic Methods*; Scheffold, R. Ed.; Springer-Verlag: Berlin, 1986; Vol. 4. (b) Seebach, D.; Juaristi, E.; Miller, D. D.; Schickli, C.; Weber, T. *Helv. Chim. Acta* **1987**, *70*, 237. (c) Seebach, D.; Dziadulewicz, E.; Behrendt, L.; Cantoreggi, S.; Fitzi, R. *Liebigs Ann. Chem.* **1989**, 1215-1232.
3. (a) Seebach, D.; Miller, D. D.; Müller, S.; Weber, T. *Helv. Chim. Acta* **1985**, *68*, 949. (b) Weber, T.; Aeschimann, R.; Maetzke, T.; Seebach, D. *Helv. Chim. Acta* **1986**, *69*, 1365.
4. (a) Fitzi, R.; Seebach, D. *Angew. Chem., Int. Edn. Engl.* **1986**, *25*, 345. (b) Fitzi, R.; Seebach, D. *Tetrahedron* **1988**, *44*, 5277.

5. Juaristi, E.; Rizo, B.; Natal, V.; Escalante, J.; Regla, I, *Tetrahedron Asymmetry* **1991**, *2*, 821.
6. Juaristi, E.; Anzorena, J. L.; Madrigal, D.; Boog, A.; Seebach, D. *to be published.*
7. (a) Evans, R. H.; Francis, A. A.; Jones, A. W.; Smith, D. A. S.; Watkins, J. C. *Br. J. Pharmacol.* **1982**, *75*, 65. See, also: (b) *Trends Neurosci.* **1987**, *10*, 263. (c) *Excitatory Amino Acid Receptors: Design of Agonists and Antagonists*, Krogsgaard-Larsen, P.; Hansen, J. J., Eds.; Harwood: Chichester, UK, 1992.
8. Two enantioselective syntheses of (*R*)-AP5 have been reported: (a) Ornstein, P. L. *J. Org. Chem.* **1989**, *54*, 2251. (b) Muller, M.; Mann, A.; Taddei, M. *Tetrahedron Lett.* **1993**, *34*, 3289.
9. For reports on the enantioselective preparation of lower analogues of AP5, see: (a) Schoellkopf, U.; Büsse, U.; Lonsky, R.; Hinrichs, R. *Liebigs Ann. Chem.* **1986**, 2150. (b) Shapiro, G.; Buechler, D.; Ojea, V.; Pombo-Villar, E.; Ruiz, M.; Weber, H.-P. *Tetrahedron Lett.* **1993**, *34*, 6255
10. In an experiment consistent with the mechanism proposed in Scheme V, enantiopure (+)-AP5 was heated to 180°C in 6N HCl to afford, as expected, racemic material. Interestingly, Vederas' group has recently described the preparation of enantiopure phosphonic analogues of diaminopimelic acid via hydrolysis of imidazolidinone precursors in refluxing concentrated HCl [Song, Y,; Niederer, D.; Lane-Bell, P.M.; Lam, L. K. P.; Crawley, S.; Palcic, M. M.; Pickard, M. A.; Pruess, D. L.; Vederas, J. C. *J. Org. Chem.* **1994**, *59*, 5784]. Nevertheless, the reaction was done in two stages and at lower temperatures. Furthermore, anchimeric participation by the phosphoryl group in this system would involve a less favorable seven membered ring.



11. The easier hydrolytic removal of the carbobenzoxy group relative to *N*-benzoyl[4b] should afford the NH acetal derivative, which readily hydrolyses under acidic conditions. If necessary, the α-methylbenzyl moiety would then be removed by hydrogenolysis.
12. Numerous synthetic applications of *N*-carbo-*t*-butoxy imidazolidinones[4,13] suggest that *N*-carbobenzoxy derivatives **7** should prove of general utility.
13. (a) Seebach, D.; Gees, T.; Schuler, S. *Liebigs Ann. Chem.* **1993**, 785. (b) Plenevaux, A.; Al-Darwich, M. J.; Lemaire, C.; Delefiore, G.; Comar, D. *Appl. Radiat. Isot.* **1994**, *45*, 361. (c) Studer, A.; Seebach, D. *Liebigs Ann. Chem.* In press.
14. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
15. Soloshonok, V. A.; Belokon, Y. N.; Kuzmina, N. A.; Maleev, V. I.; Svistunova, N. Y.; Solodenko, V. A.; Kukhar V. P. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1525.
16. Fieser, M. *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons, New York, **1986**, Vol. 12, p. 69.

(*Received in USA* 28 *September* 1994; *accepted* 23 *January* 1995)