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Enantioselective synthesis of (*S*)-2-amino-3-phosphonopropionic acid, (*S*)-AP-3, and (*R*)-2-amino-4-phosphonobutanoic acid, (*R*)-AP-4, via diastereoselective azidation of (4*R*,5*R*)-*trans*-*N*-[(diethoxyphosphoryl)propionyl]- and (4*R*,5*R*)-*trans*-*N*-[(diethoxyphosphoryl)butanoyl]hexahydrobenzoxazolidin-2-one

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Abstract—N-Acylation of readily available, enantiopure oxazolidinone (4*R*,5*R*)-**1b** with (diethoxyphosphoryl)propionyl chloride and (diethoxyphosphoryl)butanoyl chloride affords de title substrates (4*R*,5*R*)-**2** and (4*R*,5*R*)-**7**, respectively, which are azidated with high diastereoselectivity by means of the reaction between their sodium enolates (4*R*,5*R*)-**2**-Na and (4*R*,5*R*)-**7**-Na with trisyl azide. Removal of the chiral auxiliary from azidated products (4*R*,5*R*,2′*S*)-**3** and (4*R*,5*R*,2′*R*)-**8** followed by hydrogenation and hydrolysis of the resulting carboxylic acids (*S*)-**4** and (*R*)-**9** gave the pharmacologically relevant aminophosphonic acids (*S*)-AP-3 and (*R*)-AP-4 in good yield.

1. Introduction

Excitatory amino acids (EAA) are the most common neurotransmitters in the mammalian central nervous system (CNS).[1] Thus, EAA receptors offer an opportunity to develop therapeutic compounds for the treatment of several pathological conditions affecting the brain, such as Parkinson's and Alzheimer's diseases.[2,3] In this context, several studies have shown that phosphonic analogues of the aminodicarboxylic acids, glutamic acid, and their higher homologues, are modulators for the *N*-methyl-D-aspartate (NMDA) receptor site. Indeed, aminophosphonic acids AP-3, AP-4, AP-5, and AP-6 (Fig. 1) have demonstrated to be particularly potent.

The biological activity of these compounds has been shown to depend markedly on their stereochemical configuration. For example, the (*S*)-enantiomer of 2-amino-4-phosphonobutanoic acid AP-4 is 40 times more active than the (*R*)-enantiomer in the suppression of glutamate-mediated neurotransmission.[4] As a consequence, the asymmetric synthesis of aminophosphonic acids has been intensely pursued in recent years.[5]

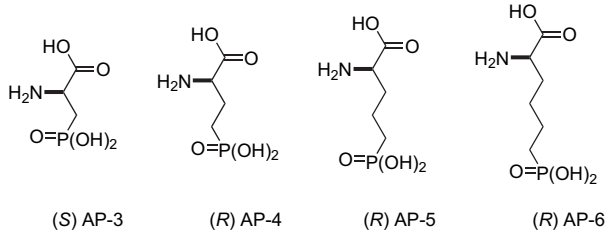

Figure 1.

Some years ago, we reported a convenient procedure for the preparation of both pairs of enantiomeric hexahydrobenzoxazolidin-2-ones **1a–d** from inexpensive cyclohexene oxide and (*S*)-α-phenylethylamine[6,7] (Fig. 2). We have also described the use of **1a–d** as effective chiral auxiliaries for the stereoselective alkylation, acylation, and aldol condensation of propionic and hydrocinnamic acids.[8] More recently, the application of oxazolidinones **1a–d** as chiral sulfinyl transfer reagents was also reported.[9]

Keywords: Chiral oxazolidinones; Aminophosphonic acids; Diastereoselective electrophilic amination; Enantioselective synthesis.
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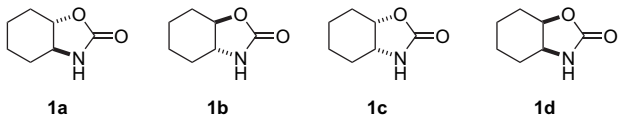


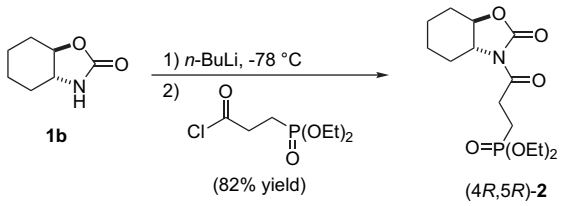
Figure 2.

We would like to communicate the use of *trans*-oxazolidinone (4*R*,5*R*)-**1b** for the enantioselective synthesis of (*S*)-AP-3 and (*R*)-AP-4.[10]

2. Results and discussion

2.1. Preparation of (4*R*,5*R*)-*trans*-*N*-[(diethoxyphosphoryl)propionyl]hexahydrobenzoxazolidin-2-one, (4*R*,5*R*)-2

trans-Hexahydrobenzoxazolidinone **1b** was N-acylated following the established protocol,[11] by treatment with *n*-butyllithium at −78 °C, followed by addition (−78 °C) of (diethoxyphosphoryl)propionyl chloride[12] to generate the *N*-propionyl derivative **2** (82% yield) (Scheme 1).

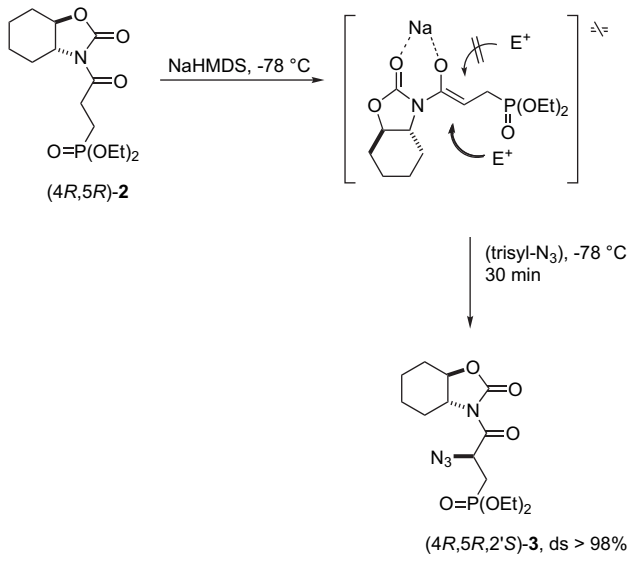


Scheme 1.

2.2. Diastereoselective azidation of (4*R*,5*R*)-2

From the various reagents available for the electrophilic amination of carbanionic substrates,[13] we chose to effect direct azide transfer to the sodium enolate of phosphorylated propionyl substrate (4*R*,5*R*)-**2**. Thus, the sodium enolate derived from oxazolidinone (4*R*,5*R*)-**2**, generated with sodium hexamethyldisilazide (NaHMDS), was treated with 1.1 equiv of 2,4,6-triisopropylbenzylsulfonyl azide (trisyl-N_3) at −78 °C for 30 min[14] (Scheme 2). Most gratifyingly, ^{1}H NMR analysis of the crude azidated product **3** showed a single set of signals, indicating a diastereomeric purity≥98%.

The absolute configuration of the newly created stereogenic center at C(2′) in product **3** was established to be (*S*) by means of chemical correlation with 2-amino-3-phosphonopropionic acid (AP-3) as discussed in Section 2.3. This result is consistent with the intermediacy of a (*Z*)-configured enolate,[15] where the sodium cation is chelated by both carbonyl



Scheme 2.

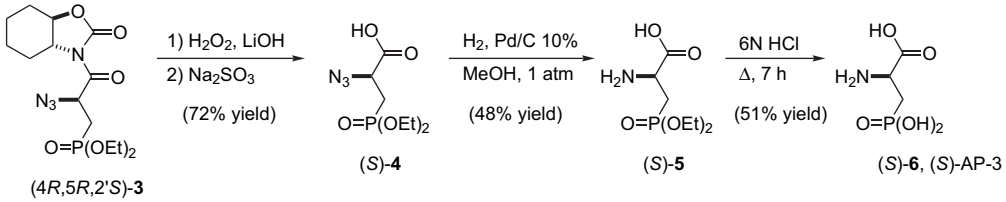
oxygens and the electrophile is incorporated from the less sterically hindered face of the enolate (Scheme 2).

2.3. Removal of the chiral auxiliary and hydrogenation/hydrolysis to give (*S*)-AP-3

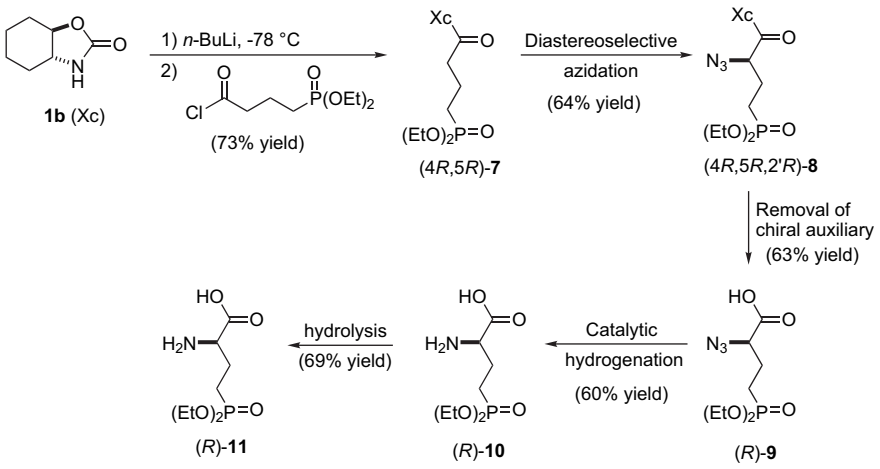
Isolation of the desired aminophosphonic acid (*S*)-AP-3 was accomplished in three steps, as outlined in Scheme 3. Thus, removal of the oxazolidinone chiral auxiliary was achieved by treatment of azide (4*R*,5*R*,2′*S*)-**3** with lithium hydroperoxide, as suggested by Evans and co-workers.[14,15] This reaction proceeded with 72% yield and the resulting azide-acid (*S*)-**4** was reduced by catalytic hydrogenation to afford α-amino acid (*S*)-**5** in 48% yield. Finally, hydrolysis of the diethyl phosphonate group was carried out with 6 N HCl under reflux for 7 h to give the expected aminophosphonic acid (*S*)-AP-3 [(*S*)-**6**, 51% yield], whose physical properties and optical rotation coincided with those reported in the literature.[10,16] The overall yield of the preparation of (*S*)-AP-3 from phosphorylated oxazolidinone (4*R*,5*R*)-**2** was 11.6%.

2.4. Enantioselective synthesis of (*R*)-2-amino-4-phosphonobutanoic acid, (*R*)-AP-4

In a further application of hexahydrobenzoxazolidinone **1b** in the enantioselective preparation of α-amino-ω-phosphonocarboxylic acids, (*R*)-2-amino-4-phosphonobutanoic acid, (*R*)-AP-4, was synthesized via N-acylation of **1b** with (diethoxyphosphoryl)butanoic acid chloride to give derivative (4*R*,5*R*)-**7**, which was then azidated, hydrogenated, and



Scheme 3.



Scheme 4.

hydrolyzed as described above in the case of (4*R*,5*R*)-**2**. (*R*)-2-Amino-4-phosphonobutanoic acid, (*R*)-AP-4, was isolated in 12.2% overall yield (Scheme 4).

3. Summary

The potential of hexahydrobenzoxazolidinones **1a**–**d** as effective chiral auxiliaries in the enantioselective synthesis of α-amino-ω-phosphonocarboxylic acids is demonstrated by the use of phosphoryl derivatives (4*R*,5*R*)-**2** and (4*R*,5*R*)-**7**, which were prepared by N-acylation of **1b**, for the highly stereoselective preparation of (2*S*)-amino-3-phosphonopropanoic acid, (*S*)-AP-3, and (2*R*)-amino-4-phosphonobutanoic acid, (*R*)-AP-4.

4. Experimental

4.1. General

Flasks, stirring bars, and hypodermic needles used for the generation and reactions of organometallic compounds were dried for ca. 12 h at 120 °C and allowed to cool in a desiccator over anhydrous $CaSO_4$. Anhydrous solvents were obtained by distillation from benzophenone/ketyl radical.[18] *n*-Butyllithium was titrated according to the method of Juaristi and co-workers.[19] TLC: Merck DC-F_{254} plates, detection UV light, iodine vapor or ninhydrin spray. Flash chromatography:[20] Merck silica gel (0.040–0.063 mm). Melting points: Melt Temp apparatus, not corrected. ^{1}H NMR spectra: Jeol Eclipse-400 (400 MHz), Bruker Ultra Shield (300 MHz), and Jeol GSX-270 (270 MHz) spectrometers; ^{13}C NMR spectra: Jeol Eclipse-400 (100 MHz) and Bruker Ultra Shield (75 MHz); ^{31}P NMR spectra: Jeol Eclipse-400 (162 MHz) and Bruker Ultra Shield (121 MHz) spectrometers; Chemical shifts δ are given in parts per million relative to Me_4Si as an internal reference, coupling constants are given in *J* (hertz). Mass spectra were obtained in a Hewlett–Packard HP-5986 instrument. High-resolution mass spectra (HRMS) were obtained at the Instituto de Química, UNAM, México on an HPLC 1100 coupled to MSD TOF Agilent Technologies mod. 1969A.

4.2. (4*R*,5*R*)-*trans*-*N*-[3′-(Diethoxyphosphoryl)propionyl]hexahydrobenzoxazolidin-2-one, (4*R*,5*R*)-2

A dry 250-mL two-necked flask provided with a magnetic stirrer, a dropping funnel, and a low-temperature thermometer was charged with a mixture of (4*R*,5*R*)-**1b** (1.8 g, 12.75 mmol) in dry THF (130 mL) under nitrogen. The solution was cooled to −78 °C in dry ice/acetone bath before the dropwise addition of a precooled solution of *n*-BuLi (5.31 mL, 2.4 M in hexane, 12.75 mmol). Stirring was continued for 2 h at −78 °C and then a precooled solution of (diethoxyphosphoryl)propionyl chloride (3.8 g, 16.57 mmol) in THF (50 mmol) was added dropwise. The reaction mixture was stirred at −78 °C for 1 h, and allowed to warm up to −30 °C with continued stirring during 3 h, and then quenched with saturated aqueous solution of NH_4Cl (30 mL). Water (120 mL) was added and the organic material was extracted with EtOAc (3×100 mL), dried with anhydrous Na_2SO_4, filtered, and evaporated. The crude product was purified by silica gel column chromatography (hexane/EtOAc, 80:20 to 50:50) to give 3.49 g (82% yield) of (4*R*,5*R*)-**2** as a colorless oil, $[\alpha]_D^{25}$ −47.0 (*c* 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.25 (t, J=7.0 Hz, 6H), 1.35 (m, 3H), 1.58 (m, 1H), 1.79 (m, 1H), 1.86 (m, 1H), 2.03 (m, 2H), 2.17 (m, 1H), 2.74 (m, 1H), 2.97 (m, 1H), 3.22 (m, 1H), 3.48 (ddd, $J^1 \approx J^2$=10.8 Hz, J^3=3.3 Hz, 1H), 3.81 (ddd, $J^1 \approx J^2$=11.5 Hz, J^3=3.6 Hz, 1H), 4.02 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.4 (d, $J_{C/P}$=6.2 Hz), 20.2 (d, $J_{C/P}$=144.5 Hz), 23.5, 23.7, 28.4, 28.8, 30.0 (d, $J_{C/P}$=2.3 Hz), 61.8 (d, $J_{C/P}$=6.9 Hz), 63.2, 81.6, 154.6, 173.5 (d, $J_{C/P}$=17.7 Hz). ^{31}P NMR ($CDCl_3$, 162 MHz) δ 31.7. MS (20 eV) *m*/*z* 334 (M^++1, 24), 236 (16), 193 (99), 165 (100), 137 (89), 96 (45), 81 (17), 55 (9). HRMS (FAB) calcd for $C_{14}H_{25}NO_6P$: 334.1420; found: 334.1425.

4.3. (4*R*,5*R*)-*trans*-*N*-[4′-(Diethoxyphosphoryl)butanoyl]hexahydrobenzoxazolidin-2-one, (4*R*,5*R*)-7

The same procedure described for the preparation of (4*R*,5*R*)-**2** was followed, with 2.0 g (14.2 mmol) of oxazolidinone **1b**, 5.1 mL of *n*-butyllithium (2.77 M in hexane, 14.2 mmol), and 4.12 g (17 mmol) of (diethoxyphosphoryl)-butanoic acid chloride to give 3.6 g (73% yield) of (4*R*,5*R*)-**7**

that was crystallized from CH_2Cl_2–AcOEt, mp 70–71 °C, $[\alpha]_D^{25}$ −52.8 (*c* 1.04, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz) δ 1.26 (t, J=7.0 Hz, 6H), 1.30 (m, 3H), 1.60 (m, 1H), 1.70–2.00 (m, 6H), 2.17 (m, 1H), 2.70–2.90 (m, 2H), 3.05 (m, 1H), 3.48 (ddd, $J^1 \approx J^2$=10.8 Hz, J^3=3.2 Hz, 1H), 3.82 (ddd, $J^1 \approx J^2$=11.5 Hz, J^3=3.5 Hz, 1H), 4.03 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.5, 16.5, 17.5 (d, $J_{C/P}$=4.6 Hz), 23.5, 23.7, 24.9 (d, $J_{C/P}$=141.3 Hz), 28.4, 28.9, 36.6 (d, $J_{C/P}$=16.3 Hz), 61.5, 61.6, 63.1, 81.4, 154.7, 174.3. ^{31}P NMR ($CDCl_3$, 121.5 MHz) δ 32.4. MS (20 eV) *m*/*z* 349 (M^++2, 1), 348 (M^++1, 6), 347 (M^+, 4), 302 (3), 250 (7), 207 (100), 179 (82), 165 (82), 152 (57), 151 (53), 125 (26), 123 (17), 96 (20). Elem. Anal. Calcd for $C_{15}H_{26}NO_6P$: C, 51.86; H, 7.55; N, 4.03; found: C, 52.00; H, 7.28; N, 4.03.

4.4. (4*R*,5*R*)-*trans*-*N*-[3′-(Diethoxyphosphoryl)-(2′*S*)-azidopropionyl]hexahydrobenzoxazolidin-2-one, (4*R*,5*R*,2′*S*)-3

A dry two-necked flask provided with magnetic stirrer, dropping funnel, and low-temperature thermometer was charged with a mixture of (4*R*,5*R*)-**2** (300 mg, 0.9 mmol) in THF (30 mL) under nitrogen. The solution was cooled to −78 °C in dry ice/acetone bath before the dropwise addition of a precooled solution of NaHMDS (0.9 mL, 1 M in hexane, 0.9 mmol). After 30 min at −78 °C a precooled solution of trisyl azide (306.5 mg, 0.99 mmol) in THF (5 mL) was added dropwise. The reaction mixture was stirred for 30 min before the addition of glacial acetic acid (0.24 mL, 4.14 mmol). The reaction mixture was allowed to warm up to room temperature and stirred for 3 h. Saturated aqueous NH_4Cl (5 mL) was added and the organic material was extracted with EtOAc (3×30 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated in a rotary evaporator. The crude product was purified by flash chromatography (hexane/EtOAc, 1:1) to yield 222 mg (66% yield) of azide (4*R*,5*R*,2′*S*)-**3** as a colorless oil, $[\alpha]_D^{25}$ −42.0 (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz) δ 1.33 (m, 6H), 1.40 (m, 3H), 1.66 (m, 1H), 1.88 (m, 2H), 2.20 (m, 2H), 2.51 (m, 1H), 2.60 (m, 1H), 3.59 (m, 1H), 3.98 (ddd, $J^1 \approx J^2$=11.3 Hz, J^3=3.3 Hz, 1H), 4.11 (q, J=7.2 Hz, 2H), 4.16 (q, J=7.1 Hz, 2H), 5.22 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.5 (d, $J_{C/P}$=6.2 Hz), 23.5, 23.7, 27.2 (d, $J_{C/P}$=142.7 Hz), 28.5, 28.6, 56.2 (d, $J_{C/P}$=1.5 Hz), 62.3 (d, $J_{C/P}$=4.1 Hz), 62.4 (d, $J_{C/P}$=4.1 Hz), 63.6, 82.1, 154.2, 171.0 (d, $J_{C/P}$=13.8 Hz). ^{31}P NMR ($CDCl_3$, 121 MHz) δ 26.4. MS (20 eV) *m*/*z* 375 (M^++1, 0.8), 346 (1.7), 249 (8.6), 205 (2.3), 178 (61), 150 (62), 122 (100), 97 (22), 81 (17), 58 (5.4). HRMS (FAB) calcd for $C_{14}H_{24}N_4O_6P$: 375.1433; found: 375.1436.

4.5. (4*R*,5*R*)-*trans*-*N*-[4′-(Diethoxyphosphoryl)-(2′*S*)-azidobutanoyl]hexahydrobenzoxazolidin-2-one, (4*R*,5*R*,2′*R*)-8

The same procedure described for the preparation of (4*R*,5*R*,2′*S*)-**3** was followed with 1.0 g (2.9 mmol) of (4*R*,5*R*)-**7**, 3.17 mL of LiHMDS (1 M in hexane, 3.2 mmol), 0.98 g (3.2 mmol) of trisyl azide, and 0.76 mL (13.2 mmol) of glacial acetic acid to give 712 mg (63.7% yield) of (4*R*,5*R*,2′*R*)-**8** as a slightly yellow oil, $[\alpha]_D^{25}$ −39.0 (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ 1.29 (t, J=7.1 Hz, 6H), 1.42 (m, 3H), 1.65 (m, 1H), 1.80–2.05 (m, 5H), 2.20 (m, 2H), 2.80 (m, 1H), 3.57 (ddd, $J^1 \approx J^2$=11.0 Hz, J^3=3.3 Hz, 1H), 3.94 (ddd, $J^1 \approx J^2$=11.5 Hz, J^3=3.6 Hz, 1H), 4.08 (m, 4H), 4.79 (dd, J^1=8.5 Hz, J^2=7.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.4, 16.5, 22.2 (d, $J_{C/P}$=142.2 Hz), 23.5, 23.7, 24.1 (d, $J_{C/P}$=3.1 Hz), 28.4, 28.6, 60.9 (d, $J_{C/P}$=17.6 Hz), 61.9 (m), 63.5, 82.2, 154.2, 171.6. ^{31}P NMR ($CDCl_3$, 162 MHz) δ 31.1. MS (20 eV) *m*/*z* 389 (M^++1, 2.1), 220 (6.1), 192 (62.2), 164 (46.2), 136 (100), 109 (16.1). HR-ESI-TOF *m*/*z* [**2a**·Na]$^+$ calcd for $C_{15}H_{25}N_4O_6PNa$: 411.1404; found: 411.1411 (1.73 ppm).

4.6. (2*S*)-Azido-3-(diethoxyphosphoryl)propionic acid, (*S*)-4

In a 100-mL flask provided with magnetic stirrer and nitrogen atmosphere was placed 856 mg (2.28 mmol) of azide (4*R*,5*R*,2′*S*)-**3** in 35 mL of THF and 11.5 mL of water. The resulting solution was cooled to 0 °C before the addition of 1.04 mL (9.12 mmol) of 30% H_2O_2 and 191.8 mg (4.56 mmol) of $LiOH \cdot H_2O$. The reaction mixture was stirred at 0 °C for 3 h and then 634 mg (5.02 mmol) of Na_2SO_3 in 6.0 mL of water was added. Immediately thereafter, 20 mL of 0.5 N solution of $NaHCO_3$ was added and the aqueous solution was extracted with EtOAc (2×50 mL) to remove the oxazolidinone auxiliary. The aqueous phase was acidulated to pH=2.0 with 1 N HCl and extracted with CH_2Cl_2 (3×50 mL). The organic extracts were combined, dried with anhydrous Na_2SO_4, and evaporated. The product (*S*)-**4** was purified by silica gel column chromatography (*i*-PrOH/MeOH/AcOH, 8:1:0.3) to give 417 mg (72% yield) of a colorless oil, $[\alpha]_D^{25}$ +44.1 (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ 1.32 (t, J=7.0 Hz, 6H), 2.19 (ddd, $J^1 \approx J^2$=16.5 Hz, J^3=9.2 Hz, 1H), 2.42 (ddd, J^1=19.1 Hz, J^2=15.4 Hz, J^3=4.4 Hz, 1H), 4.11–4.21 (m, 5H), 9.35 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.3 (d, $J_{C/P}$=23.7 Hz), 27.9 (d, $J_{C/P}$=144.5 Hz), 57.0 (d, $J_{C/P}$=3.8 Hz), 63.0 (d, $J_{C/P}$=6.9 Hz), 63.1 (d, $J_{C/P}$=6.9 Hz), 171.1 (d, $J_{C/P}$=15.3 Hz). ^{31}P NMR ($CDCl_3$, 162 MHz) δ 27.8. MS (20 eV) *m*/*z* 252 (M^++1, 38), 180 (60), 152 (35), 134 (8), 122 (100), 97 (52), 80 (26), 70 (30), 58 (13), 43 (70). HRMS (FAB) calcd for $C_7H_{15}N_3O_5P$: 252.0749; found: 252.0744.

4.7. (2*R*)-Azido-4-(diethoxyphosphoryl)butanoic acid, (*R*)-9

The same procedure described for the preparation of (*S*)-**4** was followed with 1.12 g (2.9 mmol) of (4*R*,5*R*,2′*R*)-**8**, 1.31 mL (11.57 mmol) of H_2O_2, 243 mg (5.8 mmol) of $LiOH \cdot H_2O$, and 802 mg (6.4 mmol) of Na_2SO_3 to give 483 mg (63% yield) of (*R*)-**9** as a pale yellow oil, $[\alpha]_D^{25}$ +32.4 (*c* 1.02, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz) δ 1.30 (t, J=7.0 Hz, 6H), 2.00 (m, 4H), 3.98 (br, 1H), 4.08 (q, J=7.0 Hz, 2H), 4.10 (q, J=7.0 Hz, 2H), 9.36 (br, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.4, 16.5, 21.6 (d, $J_{C/P}$=141.2 Hz), 25.0, 62.3, 62.4, 63.2 (d, $J_{C/P}$=16.4 Hz), 174.5. ^{31}P NMR ($CDCl_3$, 121 MHz) δ 32.6. MS (20 eV) *m*/*z* 26.5 (M^+, 16.6), 236 (10.5), 219 (8.5), 192 (62.7), 164 (43.8), 136 (100), 128 (51.1), 109 (26.1), 100 (45.1), 82 (20.2), 72 (16.2), 54 (41.0), 44 (56.9). HR-ESI-TOF *m*/*z* [**2a**·Na]$^+$ calcd for $C_8H_{16}N_3O_5PNa$: 288.07198; found: 288.07231 (1.15 ppm).

4.8. (2*S*)-Amino-3-(diethoxyphosphoryl)propionic acid, (*S*)-5

In a hydrogenation flask were placed 370 mg (1.47 mmol) of (*S*)-**4**, 30 mL of methanol, and 37 mg of 10% Pd/C. The flask was pressurized with hydrogen (1 atm) and shaken at room temperature for 1 h. The reaction mixture was filtered over Celite and the filtrate was evaporated in a rotary evaporator. The residue was purified by silica gel column chromatography *i*-PrOH/MeOH/NH_4Cl (6:1:0.5) to give 160 mg (48% yield) of (*S*)-**5** as a waxy solid with mp 123–125 °C, $[\alpha]_D^{25}$ +14.7 (*c* 1.02, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ 1.29 (t, J=7.0 Hz, 3H), 1.30 (t, J=7.0 Hz, 3H), 2.42 (ddd, $J^1 \approx J^2$=15.4 Hz, J^3=10.6 Hz, 1H), 2.58 (m, 1H), 3.86 (m, 1H), 4.08 (q, J=7.0 Hz, 2H), 4.12 (q, J=7.0 Hz, 2H), 7.01 (br, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.4, 26.4 (d, $J_{C/P}$=139.2 Hz), 49.8, 62.7, 172.2 (d, $J_{C/P}$=15.3 Hz). ^{31}P NMR ($CDCl_3$, 162 MHz) δ 29.9. MS (20 eV) *m/z* 226 (M^++1, 3), 180 (100), 152 (45), 138 (7), 124 (55), 106 (35), 97 (8), 83 (6), 57 (7), 45 (74). HRMS (FAB) calcd for $C_7H_{17}NO_5P$: 226.0844; found: 226.0841.

4.9. (2*R*)-Amino-4-(diethoxyphosphoryl)butanoic acid, (*R*)-10

The same procedure described for the preparation of (*S*)-**5** was followed with 483 mg (1.8 mmol) of (*R*)-**9**, 25 mL of methanol, and 48.3 mg of 10% Pd/C to give 262 mg (60% yield) of (*R*)-**10** as a white solid, mp 152–154 °C, $[\alpha]_D^{25}$ −8.24 (*c* 3.64, H_2O); lit.[10c] $[\alpha]_D^{25}$ +9.22 (*c* 5.0, H_2O) for the (*S*)-enantiomer. ^1H NMR (D_2O, 300 MHz) δ 1.30 (t, J=7.0 Hz, 6H), 1.80–2.20 (m, 4H), 3.78 (dd, J^1=J^2=5.4 Hz, 1H), 4.12 (q, J=7.2 Hz, 2H), 4.14 (q, J=7.2 Hz, 2H). ^{13}C NMR (D_2O, 75 MHz) δ 15.8, 15.9, 20.3 (d, $J_{C/P}$= 140.0 Hz), 23.7 (d, $J_{C/P}$=3.8 Hz), 54.7 (d, $J_{C/P}$=19.1 Hz), 63.8 (d, $J_{C/P}$=1.3 Hz), 63.9 (d, $J_{C/P}$=1.3 Hz), 173.6. ^{31}P NMR (D_2O, 121 MHz) δ 34.4.

4.10. (2*S*)-Amino-3-phosphonopropionic acid, (*S*)-6

In a 25-mL flask provided with magnetic stirrer were placed 174 mg (0.77 mmol) of (*S*)-**5** and 4.0 mL of 6 N HCl. The reaction mixture was heated to reflux for 7 h, allowed to cool to room temperature, and concentrated in a rotary evaporator. The residue was redissolved in 6.0 mL of ethanol and treated with 2.0 mL of propylene oxide. The resulting suspension was heated to 50 °C for 2 h, and concentrated in a rotary evaporator to give a white solid, which was redissolved in 1.0 mL of water and crystallized upon addition of 3.0 mL of ethanol to give 67 mg (51% yield) of amino acid (*S*)-**6** [(*S*)-AP-3], mp 224–226 °C, $[\alpha]_D^{25}$ −12.0 (*c* 1.0, 1 N NaOH); lit.[10d] $[\alpha]_D^{25}$ +12.6 (*c* 0.75, 1 N NaOH) for the (*R*)-enantiomer.[16] $[\alpha]_{Hg}^{25}$ −54.0 (*c* 1.0, 1 N NaOH); lit.[10d] $[\alpha]_{Hg}^{25}$ +58.9 (*c* 1.0, 1 N NaOH) for the (*R*)-enantiomer.[16] ^1H NMR (D_2O, 270 MHz) δ 2.09 (m, 1H), 2.30 (ddd, $J^1 \approx J^2$=16.5 Hz, J^3=3.9 Hz, 1H), 4.14 (ddd, J^1=15.1 Hz, J^2=9.8 Hz, J^3=3.9 Hz, 1H). ^{13}C NMR (D_2O, 67 MHz) δ 28.1 (d, $J_{C/P}$=130.9 Hz), 49.7 (d, $J_{C/P}$=4.2 Hz), 171.9 (d, $J_{C/P}$=12.5 Hz). ^{31}P NMR (D_2O, 109 MHz) δ 18.6.

4.11. (2*R*)-Amino-4-phosphonopropionic acid, (*R*)-11

The same procedure described for the preparation of (*S*)-**6** was followed with 224 mg (0.94 mmol) of (*R*)-**10** and 5.1 mL of 6 N HCl to give 119 mg (69% yield) of amino acid (*R*)-**11** [(*R*)-AP-4] as a white solid, mp 206–208 °C, $[\alpha]_D^{25}$ −25.0 (*c* 1.0, 6 N HCl); lit.[10c] $[\alpha]_D^{25}$ +27.6 (*c* 3.0, 6 N HCl) for the (*S*)-enantiomer. ^1H NMR (D_2O, 400 MHz) δ 1.71 (m, 2H), 2.13 (m, 2H), 4.03 (dd, J^1=J^2=5.7 Hz, 1H). ^{13}C NMR (D_2O, 100 MHz) δ 23.4 (d, $J_{C/P}$= 133.8 Hz), 24.5, 53.7 (d, $J_{C/P}$=16.0 Hz), 172.3. ^{31}P NMR (D_2O, 162 MHz) δ 25.4.

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