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# General approach to the synthesis of optically active 2-carboxy-4-[3′-(diethoxyphosphinyl)propyl]-5-alkylpiperazines (CPP analogues)

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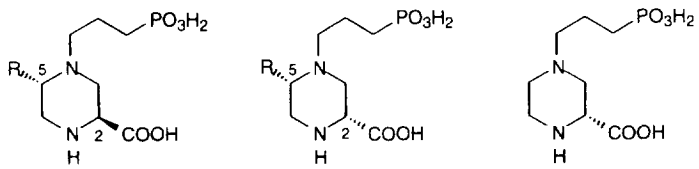
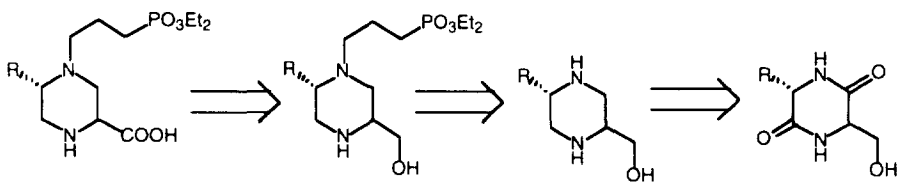
***Abstract:*** General stereospecific syntheses of the optically active title compounds are described. The procedures presented are based on readily available starting materials, such as piperazine alcohols, and can be arranged for multigram quantities. © 1997 Elsevier Science Ltd

The pharmacological action of the excitatory amino acids (EAA), L-glutamate and L-aspartate, is well documented.[1] In this context, 2-carboxy-4-(3-phosphonopropyl) piperazine (CPP) has been identified as a potent and selective antagonist of the *N*-methyl-D-aspartate (NMDA) subtype of the glutamate receptor.[2] Recently we have published[3] the first stereocontrolled synthesis of (*R*)-CPP starting from *cyclo*-Sar-Ser; following our interest in the field of NMDA antagonists we have carried out the preparation of 5-alkyl substituted CPP-analogues **1** and **2**.




**1** **2** **(*R*)-CPP**

A reliable retrosynthetic analysis for **1** and **2** suggested a correlation between the diastereomerically defined precursor, 2-carboxy-5-alkyl-4-[3′-(diethoxyphosphinyl)propyl]-piperazine, and 2-hydroxymethyl piperazine, that can be prepared by reduction of serine-containing diketopiperazine (Scheme 1). The availability of enantiomers of both the amino acids should enable the preparation of all the four possible stereoisomers.




**Scheme 1.**

For a synthesis that could be applied on a multigram scale and follows also the rule of atom economy, the main problem is the differentiation of the two nitrogen atoms in the piperazine ring. The presence of the hydroxy group in the piperazine alcohols suggested the use of *N,O*-acetals as a protection and differentiation of the nitrogen atom in the 1-position of the heterocyclic ring. After this step, the oxazolidine ring should be removed and the hydroxymethyl group oxidised after the preliminary protection of the *N*(1) atom and the quaternization of the *N*(4) atom. The complete synthesis of **1** (R=*i*-

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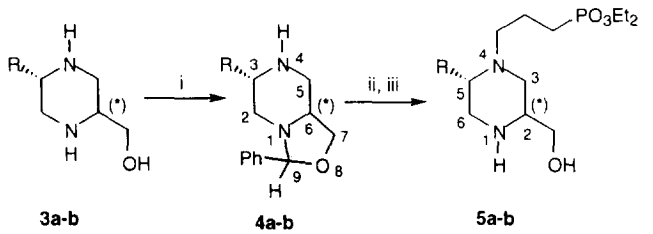
Pr) and **2** (R=*i*-Bu) is presented here as a representative example. However, the procedures reported can be applied to 5-alkyl-2-hydroxymethyl piperazines as general method.

After a first attempt to prepare the *N,O*-acetonide derivatives of the aminoalcohols **3a–b**, we preferred to employ PhCHO owing to the better stability of *N,O*-benzylidene acetal ring and to minimize the formation of byproduct (Scheme 2). Thus, the treatment of **3a** and **3b** with freshly distilled PhCHO in the presence of 5 Å molecular sieves in benzene at reflux for 30 min afforded the oxazolidines **4a–b** in high yields after bulb to bulb distillation. Concerning the structures **4a–b**, NOE experiments confirmed the presence of the oxazolidine ring involving the *N*(1) atom, thus excluding the formation of a six membered ring involving *N*(4) atom. As shown by the GLC and $^1$H NMR analysis, the products **4a–b** are a mixture of two epimers at C(9) in 85/15 ratio for **4a** and in 55/45 ratio for **4b**. The alkylation at *N*(4) atom was carried out using $Br(CH_2)_3PO(OEt)_2$ in the presence of $Na_2CO_3$ in various solvents: best results were obtained using refluxing MeOH. After 24 h, the alkylphosphonates **5a** and **5b** were recovered in 65–78% yield after chromatographic purification. In the subsequent step, the *N,O*-acetal ring was removed by acid hydrolysis with 10% aq HCl at room temperature overnight.

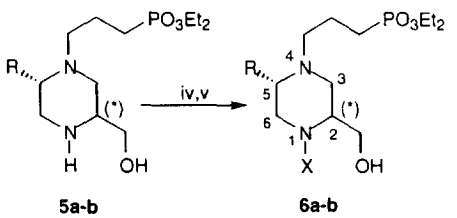



| 3-5 | R | (•) |
|---|---|---|
| a | i-Pr | S |
| b | i-Bu | R |

**Reagents and conditions:** i) PhCHO, 5Å molecular sieves, 1/2 h reflux. ii) $Br(CH_2)_3PO(OEt)_2$, $Na_2CO_3$, MeOH, 24 h reflux. iii) HCl 10%, 12 h rt

**Scheme 2.**

Treatment of **5a** with $(Boc)_2O$ and $Na_2CO_3$ in presence of catalytic $NH_2OH$ in $CH_2Cl_2/H_2O$ gave, in quantitative yield, the *N*-Boc derivative (2*S*,5*S*)-**6a**. When the same treatment was applied to 2-hydroxymethyl piperazines, having the (2*R*,5*S*) configuration, the reactions afforded the *N*-Boc derivatives in very low yields. Other methodologies for Boc-group introduction did not give satisfactory results. The use of the ethoxycarbonyl group, less hindered than Boc-group, for protecting the *N*(1) atom, allowed us to overcome this problem. Thus, the treatment of **2c** with ClCOOEt, in benzene at 0°C for 1 h, afforded the **6b** compound in 59% yield (Scheme 3).

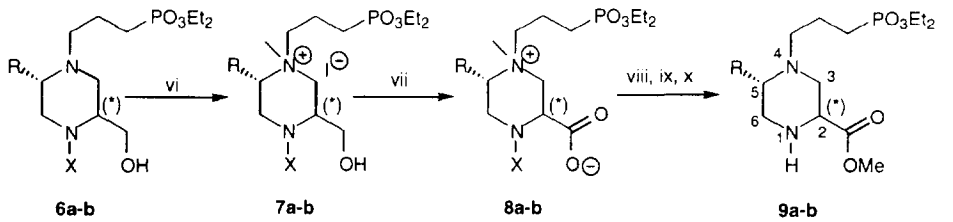



| 6 | R | X | (•) |
|---|---|---|---|
| a | i-Pr | Boc | S |
| b | i-Bu | COOEt | R |

**Reagents and conditions:** iv) $Boc_2O$, $CH_2Cl_2/H_2O$, $Na_2CO_3$, $NH_2OH$ (cat), rt, 8 h. v) ClCOOEt, benzene 0° C, 1h

**Scheme 3.**

The ammonium salts **7a** and **7b** were obtained by adding MeI to the N(1)-protected aminoalcohols **6a** and **6b** at r.t. in MeOH, for 24–48 h. Then the crude products were dissolved in water and washed with $CH_2Cl_2$ affording the pure ammonium salts that were isolated in 83–94% yield respectively (Scheme 4).




**6a-9a**: R = *i*-Pr, X = Boc, (5S,2S); **6b-9b**: R = *i*-Bu, X = COOEt, (5S,2R)

**Reagents and conditions:** vi) MeI, MeOH, rt., 12 h. vii) $NaIO_4$, Acetone/$H_2O$, $RuCl_3$ (cat), 0°C to rt., 1 h. viii) AcOH. ix) Xylene/MeCN, 140°C, 72 h. x) HCl(g), MeOH, 24 h.

Scheme 4.

The compounds **7a** and **7b** were then oxidised following the Sharpless procedure[4] with sodium periodate in the presence of catalytic amounts of $RuCl_3$.[5] The oxidation mixtures were filtered on Celite pad, affording, after removal of inorganic salts, the crude acids **8a–b** in 65–88% yield, as light brown foams. The structures of acids **8a–b** were confirmed by $^1H$ NMR analysis and by elementary analysis. Attempts to carry out the demethylation of these crude acids using PhSNa[6] were however unsuccessful. Thus, demethylation was achieved by using the acetate anion as nucleophile: the crude oxidation products were then lyophilised from acetic acid solutions affording the acetates. Heating at 140°C for 72 h of the acetates in xylene/acetonitrile as solvent afforded the corresponding demethylated amino acids, which were recovered in satisfactory yields from the reaction mixture as methyl esters **9a** and **9b**, by treatment with HCl in MeOH at rt.[7] Measurements of $^1H$ and $^{13}C$ NMR spectra carried out at various temperatures (from 20° to 50°C) have indicated that both compounds **9a** and **9b** have a diastereoisomeric purity ≥97%. Subsequent treatment with 6 N HCl (reflux, 12 h) restored the phosphonic acid moiety and removed the *N*(1) protecting group. However, the recovery of **1** or **2** as free amino acids by using ion exchange chromatography gave poor results, the target compounds being recovered only in small quantities.[8]

## Experimental section

Melting and boiling points are uncorrected. Bulb to bulb distillations were carried out with a Büchi GRK-51 apparatus equipped with a vacuum controller Büchi B-168. Elemental analyses were performed on a Perkin–Elmer 420 B analyzer. Optical rotations were measured with a Perkin–Elmer 241 automatic polarimeter in a 1 dm tube. GC analyses of the reaction products were carried out on a Perkin–Elmer 8600 gas-chromatograph on fused silica megabore columns (15 m × 0.53 mm) DB-1, DB-5 (J&W), operating with a He flow rate of 9 mL/min. The $^1H$ NMR (300 MHz), $^{13}C$ NMR (75.4 MHz) and $^{31}P$ (121.4 MHz) Fourier transform spectra were obtained with a Varian VXR-300 spectrometer on $CDCl_3$ solutions (unless otherwise specified). All reactions involving air sensitive materials were carried out under argon atmosphere; all reagents and solvents employed were reagent grade materials purified by standard methods and distilled before use. (2*S*,5*S*)-2-Hydroxymethyl-5-*iso*-propylpiperazine, **3a**, $[\alpha]_D^{25}$ +5.61 (c 1, $CHCl_3$), and (2*R*,5*S*)-2-hydroxymethyl-5-*iso*-butylpiperazine, **3b**, $[\alpha]_D^{25}$ +4.9 (c 9, $CHCl_3$) were prepared as previously reported.[9]

*General procedure for **4a** and **4b***

A solution of 5-alkyl-2-hydroxymethylpiperazine **3a** and **3b** (11.4 mmol) and freshly distilled benzaldehyde (12.5 mmol) in dry benzene (40 mL) was placed in a 100 mL two-necked-flask and heated at reflux in presence of activated molecular sieves (5 Å), under $N_2$ atmosphere. After 1 h the mixture was concentrated at reduced pressure (20 mBar) and the crude product bulb to bulb distilled (150°C) to give pure (GLC) protected piperazine **4a** and **4b**.

*(3S,6S,9RS)-9-Phenyl-3-*iso*-propyl-1,4-diaza-8-oxa[4.3.0.]bicyclononane* **4a**

94%, colourless oil. $^1$H NMR δ: 85/15 mixture of two diastereoisomers, 7.48–7.41 (m, 2H, Ph), 7.39–7.24 (m, 3H, Ph), 5.51 (s, 0.15H, PhC*H*), 4.60 (s, 0.85H, PhC*H*), 4.24 (t like, 0.15H, NCHC$H_2$O), 4.05 (t like, 0.85H, NCHC$H_2$O), 3.66 (dd like, 1H, NCHC$H_2$O), 3.22 (dd like, 1H), 2.72 (t like, 1H), 2.68 (dd like, 1H), 2.63–2.52 (m, 1H), 2.50–2.43 (m, 1H), 1.88 (t like, 1H), 1.60–1.46 [m, 1H, C*H*(CH$_3$)$_2$] 1.40 (bs, 1H, N*H*), 0.95 [d, 3H, *J*=6, CH(C$H_3$)$_2$], 0.85 ppm [d, 3H, *J*=6, CH(C$H_3$)$_2$]. $^{13}$C NMR δ: 138.7, 129.0, 128.2, 127.4, 96.3, 69.4, 68.6, 62.3, 60.1, 56.7, 56.4, 50.7, 48.0, 47.4, 31.4, 19.1 ppm. Calculated for $C_{15}H_{22}N_2O$: C, 73.13; H, 9.0; N, 11.37. Found: C, 73.0; H, 8.93; N, 11.41.

*(3S,6R,9RS)-9-Phenyl-3-*iso*-butyl-1,4-diaza-8-oxa[4.3.0.]bicyclononane* **4b**

72%, colourless oil. $^1$H NMR δ: 55/45 mixture of two diastereoisomers, 7.50–7.41 (m, 2H, Ph), 7.39–7.29 (m, 3H, Ph), 5.57 (s, 0.55H, PhC*H*), 5.20 (s, 0.45H, PhC*H*), 3.98–3.79 (m, 2H, NCHC$H_2$O), 3.25–3.15 (m, 1H), 3.10–2.91 (m, 2H), 2.91–2.82 (m, 1H), 2.50 (t like, 1H), 2.22–2.10 (m, 1H), 1.80 (bs, 1H, NH), 1.75–1.65 [m, 1H, CH$_2$C*H*(CH$_3$)$_2$], 1.42–1.11 [m, 2H, C$H_2$CH(CH$_3$)$_2$], 0.92 [d, 3H, *J*=6, CH$_2$CH(C$H_3$)$_2$], 0.83 ppm [d, 3H, *J*=6, CH$_2$CH(C$H_3$)$_2$]. $^{13}$C NMR δ: 136.8, 128.5, 127.6, 126.0, 99.0, 96.4, 90.2, 65.8, 63.8, 60.2, 55.6, 54.0, 51.0, 49.6, 43.7, 42.0, 24.5, 24.3, 23.2, 22.5, 22.2 ppm. Calculated for $C_{16}H_{24}N_2O$: C, 73.81; H, 9.29; N, 10.76. Found: C, 73.90; H, 9.11; N, 10.37.

*General procedure for* **5a** *and* **5b**

Protected piperazines **4a** and **4b** (6.1 mmol) were dissolved in absolute methanol (50 mL) and sodium carbonate (9.4 mmol) and diethyl (bromopropyl) phosphonate (12.5 mmol) were added. The reaction was refluxed for 24 h under $N_2$ atmosphere. After filtration, the methanol solution was concentrated under reduced pressure. The brown oil residue was placed on a silica gel column and eluted with AcOEt/$CH_2Cl_2$/MeOH 7/1/2. The crude compound was dissolved in 10% aq HCl (30 mL) and stirred at r.t. for 12 h. Then, the aqueous solution was made alkaline with KOH and extracted with $CH_2Cl_2$ several times. The collected organic phases were dried ($Na_2SO_4$) and the solvent eliminated under vacuum affording pure (TLC: AcOEt/$CH_2Cl_2$ 7/3) *N*-alkylated piperazine methanols **5a** and **5b**.

*(2S,5S)-2-Hydroxymethyl-4-[3′-(diethoxyphosphinyl)propyl]-5-*iso*-propylpiperazine* **5a**

65%; $[\alpha]_D^{25}$ +21.8 (c 0.6, $CHCl_3$); $^1$H NMR δ: 4.19–4.00 [m, 4H, P(OC$H_2$CH$_3$)$_2$], 3.85 (dd, 1H, $J_1$=11, $J_2$=3, C$H_2$OH), 3.41 (dd, 1H, $J_1$=11, $J_2$=5, C$H_2$OH), 2.95–2.66 (m, 4H), 2.38–2.25 (m, 2H), 2.24–2.12 (m, 2H), 2.10–1.99 (m, 1H), 1.98–1.88 (m, 1H), 1.80–1.62 (m, 5H), 1.25 [t, 6H, *J*=7, P(OCH$_2$C$H_3$)$_2$], 0.86 [d, 3H, *J*=7, CH(C$H_3$)$_2$], 7.76 ppm [d, 3H, *J*=7, CH(C$H_3$)$_2$]; $^{13}$C NMR δ: 64.1, 61.3, 59.9, 54.9, 52.6, 50.3, 47.0, 26.3, 24.4, 22.5, 19.8, 19.1, 16.3 ppm; $^{31}$P NMR δ: 32.9 ppm. Calculated for $C_{15}H_{33}N_2O_4P$: C, 53.56; H, 9.89; N, 8.33. Found: C, 53.57; H, 9.85; N, 8.36.

*(2R,5S)-2-Hydroxymethyl-4-[3′-(diethoxyphosphinyl)propyl]-5-*iso*-propylpiperazine* **5b**

78%; $[\alpha]_D^{25}$ +27.8 (c 2.5, $CHCl_3$); $^1$H NMR δ: 4.15–4.02 [m, 5H, P(OC$H_2$CH$_3$)$_2$+C$H_2$OH], 3.90–3.81 (dd like, 1H, C$H_2$OH), 3.65–3.43 (m, 2H), 2.72–2.60 (m, 2H), 2.58–2.37 (m, 4H), 2.38–2.30 (m, 1H), 1.80–1.62 (m, 5H), 1.55–1.40 [m, 2H, C$H_2$CH(CH$_3$)$_2$], 1.25–1.16 [m, 1H, C*H*(CH$_3$)$_2$], 1.28 [t, *J*=7, 6H, P(OCH$_2$C$H_3$)$_2$], 0.89 [d, *J*=7, 3H, CH(C$H_3$)$_2$], 0.80 ppm [d, *J*=7, 3H, (C$H_3$)$_2$]; $^{13}$C NMR δ: 71.2, 65.9, 65.6, 59.7, 58.5, 57.5, 52.7, 52.2, 45.8, 25.5, 24.1, 22.8, 19.8, 16.6 ppm; $^{31}$P NMR δ: 34.1 ppm. Calculated for $C_{16}H_{35}N_2O_4P$: C, 54.84; H, 10.07; N, 7.99. Found: C, 54.8; H, 10.1; N, 8.03.

*(2S, 5S)-1-(*tert*-Butoxycarbonyl)-2-hydroxymethyl-4-[3′-(diethoxyphosphinyl)propyl]-5-*iso*-propylpiperazine* **6a**

A solution of compound **5a** (1.0 g, 3.0 mmol) in $CH_2Cl_2$ (15 mL), solid $Boc_2O$ (0.65 g, 3.0 mmol), $Na_2CO_3$ (0.6 g, 5.7 mmol) and $NH_2OH \cdot HCl$ (10% mol) in $H_2O$ (15 mL) were mixed together and stirred for 48 h at r.t. The organic and aqueous layers were separated and the aqueous layer extracted with $CH_2Cl_2$ (20 mL). The combined organic phases were washed with $H_2O$, dried ($Na_2SO_4$)

then evaporated under reduced pressure. The crude product was purified by flash chromatography (AcOEt/$CH_2Cl_2$ 2/8) to furnish the protected **6a** (1.25 g, 97%) having: $[\alpha]_D^{25}$ −1.65 (c 3.25, $CHCl_3$); $^1$H NMR δ: 4.0–3.85 [m, 4H, $P(OCH_2CH_3)_2$], 3.81 (dd, $J_1$=14, $J_2$=8, 1H, $CH_2OH$), 2.82 (dd, $J_1$=14, $J_2$=4, 1H, $CH_2OH$), 2.65–2.55 (m, 3H), 2.42–2.35 (m, 1H), 2.28–2.10 (m, 2H), 2.05–1.09 (mb, 3H), 1.65–1.40 (m, 5H), 1.34 [s, 9H, $C(CH_3)_3$], 1.19 [t, 6H, $J$=7, $P(OCH_2CH_3)_2$], 0.78 [d, $J$=7, 3H, $CH(CH_3)_2$], 0.72 ppm [d, $J$=7, 3H, $CH(CH_3)_2$]; $^{13}$C NMR δ: (mixture of two conformers) 155.4, 81.7, 66.7, 63.4, 61.1, 61.0, 58.1, 55.0, 53.9, 53.6, 52.0, 51.7, 50.5, 27.4, 25.9, 24.0, 23.9, 22.2, 22.1, 19.6, 18.3, 18.2, 17.9, 17.8, 16.2, 16.1. ppm. Calculated for $C_{20}H_{41}N_2O_6P$: C, 55.86; H, 9.92; N, 6.2. Found: C, 55.93; H, 10.03; N, 6.31.

*(2R,5S)-1-Ethoxycarbonyl-2-hydroxymethyl-[4-(3'-(diethoxyphosphinyl)propyl]-5-iso-butylpiperazine* ***6b***

To a solution of amino alcohol **5b** (1 g, 2.8 mmol) and $NEt_3$ (0.4 g, 3.9 mmol), in dry benzene, ClCOOEt (0.3 g, 2.8 mmol) was added at 0°C under $N_2$. The mixture was stirred at 0°C for 1 h then at r.t. for an additional hour. The white solid formed was filtered off and the resulting solution washed with 10% aq. HCl (3×10 mL). The aqueous solutions were made alkaline with solid KOH, saturated with NaCl and extracted with $CH_2Cl_2$ several times. The collected organic phases were dried ($Na_2SO_4$) and the solvent was eliminated under vacuum affording the product **6b** (0.7 g, 59%), pure (TLC, AcOEt/MeOH 85/15) having: $[\alpha]_D^{25}$ +83.01 (c 3.95, $CHCl_3$), $^1$H NMR δ 4.15–3.98 (m, 8H), 3.88–3.80 (m, 2H), 3.08 (d like, 1H), 2.85–2.72 (m, 2H), 2.38–2.24 (m, 1H), 2.23–2.08 (m, 2H), 1.85–1.53 (m, 5H), 1.50–1.37 (m, 1H) 1.30 [t, 7H, $J$=7, $P(OCH_2CH_3)_2$+$CH_2CH(CH_3)_2$], 1.23 (t, 3H, $J$=7, $COOCH_2CH_3$), 1.12–1.01 [m, 1H, $CH(CH_3)_2$], 0.89 [d, 3H, $CH(CH_3)_2$] 0.86 ppm [d, 3H, $J$=7, $CH(CH_3)_2$]; $^{13}$C NMR δ: 155.8, 64.4, 63.7, 61.4, 61.3, 58.2, 56.2, 52.7, 52.3, 51.5, 46.0, 40.2, 25.0, 23.8, 21.8 19.1 16.4 ppm. Calculated for $C_{19}H_{39}N_2O_6P$: C, 54.0; H, 9.31; N, 6.63. Found: C, 53.90; H, 9.40; N, 6.60.

*(2S,5S)-1-(*tert*-Butoxycarbonyl)-2-hydroxymethyl-4-[3'-(diethoxyphosphinyl)propyl]-4-methyl-5-*iso*-propyl piperazinium iodide* ***7a***

Methyl iodide (2 mL, 21 mmol) was added to the protected derivates **6a** (1.0 g, 2.3 mmol) in MeOH (20 mL). After 18 h under stirring, all the volatile products were eliminated under reduced pressure and the residues partitioned between $CH_2Cl_2$ and $H_2O$. The organic layers were discarded and the aqueous phases concentrated under vacuum affording pure (TLC) ammonium salt **7a**: (1.1 g, 83%), $[\alpha]_D^{25}$ +65.3 (c 1.35, $CH_3COOH$); $^1$H NMR ($D_2O$) δ: 4.13–4.00 [m, 6H, $P(OCH_2CH_3)_2$+$CH_2OH$], 3.82 (dd like, 2H), 3.22 (s, 1.2H, N–Me), 2.90 (s, 1.8H, N–Me), 2.90–2.70 (m, 2H), 2.60–2.40 (m, 1H), 2.30–2.10 (m, 1H), 1.88–1.60 (m, 4H), 1.35 (m, 3H), 1.26 [s, 9H, $C(CH_3)_3$], 1.11 [t, 6H, $J$=7, $P(OCH_2CH_3)_2$], 0.89 [d, $J$=7, 3H, $CH(CH_3)_2$], 0.75 ppm [d, $J$=7, 3H, $CH(CH_3)_2$]; $^{13}$C NMR ($D_2O$) δ: 146.8, 79.3, 67.6, 61.5, 61.4, 61.1, 59.8, 58.0, 56.2, 46.2, 46.0, 25.0, 23.8, 19.1, 18.9, 16.4, 16.0, 17.2, 16.3 ppm. Calculated for $C_{21}H_{44}N_2O_6PI$: C, 43.60; H, 7.67; N, 4.84. Found: C, 43.3; H, 7.65; N, 4.88.

*(2R,5S)-1-Ethoxycarbonyl-2-hydroxymethyl-4-[3'-(diethoxyphosphinyl)propyl]-4-methyl-5-*iso*-butyl piperazinium iodide* ***7b***

Methyl iodide (4 mL, 42 mmol) was added to the protected derivates **6b** (0.65 g, 1.5 mmol) in MeOH (20 mL). After 48 h the reaction was worked up as previously described for **7a** to afford pure (TLC) ammonium salt **7b**: (0.8 g, 94%), $[\alpha]_D^{25}$ +52.4 (c 2.5, $CH_3COOH$); $^1$H NMR ($D_2O$) δ: 4.11–3.94 [m, 8H, $P(OCH_2CH_3)_2$+$OCH_2CH_3$+$CH_2OH$], 3.86–3.60 (m, 3H), 3.55–3.38 (m, 3H), 3.35–3.20 (m, 2H), 3.06 (s, 1.3H, N–Me), 2.95 (s, 1.7H, N–Me), 2.05–1.75 (m, 3H), 1.70–1.58 (m, 2H), 1.49–1.32 (m, 2H), 1.19 [t, 6H, $J$=7, $P(OCH_2CH_3)_2$], 1.12 (t, 3H, $J$=7, $OCH_2CH_3$) 0.87 [d, 3H, $J$=7, $CH(CH_3)_2$], 0.84 ppm [d, 3H, $J$=7, $CH(CH_3)_2$]; $^{13}$C NMR ($D_2O$) δ: 152.0, 77.3, 68.6, 68.0, 59.7, 59.4, 49.2, 48.4, 48.1, 42.7, 34.2, 34.1, 31.7, 29.3, 29.1, 24.7, 24.6, 24.5 ppm. Calculated for $C_{20}H_{42}N_2O_6PI$: C, 42.56; H, 7.5; N, 4.96. Found: C, 42.48; H, 7.41; N, 5.01.

*(2S,5S)-1-(*tert*-Butoxycarbonyl)-2-carboxy-4-[3'-(diethoxyphosphinyl)propyl]-4-methyl-5-*iso*-propyl piperazinium* ***8a***

Under stirring at 0°C, $NaIO_4$ (3.5 g, 11 mmol) in water (40 mL) and $RuCl_3$ hydrate (0.08 g) were added to ammonium salt **7a** (1 g, 1.7 mmol) in acetone (60 mL). The reaction mixture was stirred for 1 h at 0°C and for an additional hour at r.t., then quenched with *iso*-propanol (4 mL). After 2 h, the reaction mixture was filtered through a Celite pad and the filtrate concentrated under vacuum. The residue was dissolved in $H_2O$ (10 mL) and washed with $CCl_4$ (2×20 mL) and $CH_2Cl_2$ (2×25 mL), then the organic phase was discarded and the aqueous solution evaporated to give **8a** (0.65 g, 82%), $[\alpha]_D^{25}$ +43.21 (c 1.35, $CH_3COOH$); $^1H$ NMR ($D_2O$) δ: 4.1–3.9 [m, 4H, $P(OCH_2CH_3)_2$], 3.3–3.5 (m, 3H), 2.3–2.4 (m, 3H), 2.1 (s, 1.6H, N–$CH_3$), 2.3–2.1 (m, 3H), 1.8 (s, 1.4H, N–$CH_3$), 1.6–1.4 (m, 3H), 1.33 [s, 9H, $C(CH_3)_3$], 1.12–1.15 [t, *J*=7, 6H, $PO(CH_2CH_3)_2$], 0.84 [d, *J*=7, 3H, $CH(CH_3)_2$], 0.80 ppm [d, *J*=7, 3H, $CH(CH_3)_2$]; $^{13}C$ NMR ($D_2O$) δ: 185.9 148.6, 75.8, 72.1, 63.0, 55.3, 49.2, 41.5, 37.9, 36.7, 32.1, 30.3, 28.3, 28.5, 25.6, 25.4, 24.1, 22.6, 21.5 ppm; Calculated for $C_{21}H_{41}N_2O_7P$: C, 54.3; H, 8.9; N, 6.03. Found: C, 54.22; H, 9.01 N, 6.1.

*(2R,5S)-1-(Ethoxycarbonyl)-2-carboxy-4-[3'-(diethoxyphosphinyl)propyl]-4-methyl-5-*iso*-butyl piperazinium* ***8b***

Under stirring at 0°C, $NaIO_4$ (4.6 g, 11 mmol) in water (40 mL) and $RuCl_3$ hydrate (0.08 g) were added to ammonium salt **7b** (1.2 g, 2.2 mmol) in acetone (60 mL). The reaction was worked up as previously described for **8a** to afford to give **8b** (0.60 g, 59%): $[\alpha]_D^{25}$ +24.1 (c 1.27, $CH_3COOH$); $^1H$ NMR ($D_2O$) δ: 4.12–3.91 [m, 8H, $P(OCH_2CH_3)_2$+$OCH_2CH_3$+$CH_2OH$], 3.50–3.34 (m, 2H), 3.30–3.13 (m, 2H), 3.08–2.99 (m, 1H), 2.98 (s, 1.5H, N–$CH_3$), 2.75 (s, 1.5H, N–$CH_3$), 2.06–1.73 (m, 4H), 1.64–1.43 (m, 2H), 1.42–1.24 (m, 1 H), 1.17 [t, *J*=7, 6H, $PO(CH_2CH_3)_2$], 1.05 (t, *J*=7, 3H, $OCH_2CH_3$), 0.83 [d, *J*=7, 3H, $CH(CH_3)_2$], 0.80 ppm [d, *J*=7, 3H, $CH(CH_3)_2$]; $^{13}C$ NMR ($D_2O$) δ: 165.2, 151.9, 80.7, 68.4, 66.9, 61.2, 60.2, 58.5, 49.2, 48.3, 42.0, 33.8, 31.2, 30.0, 28.5, 24.3, 23.6, 22.2 ppm; Calculated for $C_{20}H_{39}N_2O_7P$: C, 53.3; H, 8.73; N, 6.22. Found: C, 53.28; H, 8.80; N, 6.31.

*(2S,5S)-2-Carboxymethyl-4-[3'-(diethoxyphosphinyl)propyl]-5-*iso*-propylpiperazine* ***9a***

The crude acid **8a** (0.34 g, 0.8 mmol) was treated with glacial acetic acid (0.05 g, 0.82 mmol). After 3 h the acetic solution were lyophilised affording pure (TLC) protected acetate (0.38 g, 0.78 mmol).The acetate (0.05 g, 0.78 mmol) was suspended in xylene/acetonitrile (85/15, 100 mL) and heated, under stirring, at 140°C. After 26 h, the reaction mixture was evaporated under vacuum and the residue treated with $H_2O$ and extracted with $Et_2O$ (2×10 mL). The organic phase was discarded and the aqueous layers recovered and evaporated under vacuum. The residue was dissolved in dry MeOH and gaseous HCl was added after 24 h at room temperature: the reaction mixture was reduced to half of the volume and treated with ion exchange resin ($OH^-$ form) until pH 8–9. The resine was partitioned between $CH_2Cl_2$ (2×10 mL) and $H_2O$ (2×10 mL), the organic phase then dried ($Na_2SO_4$) and the solvent eliminated under vacuum affording pure (TLC) methylesters **9a** (0.10 g, 39%): $[\alpha]_D^{25}$ +5.6 (c 1.53, $CH_3COOH$); $^1H$ NMR (DMSO-$d_6$) δ: 4.12–4.00 [m, 4H, $P(OCH_2CH_3)_2$], 3.86 (s, 3H, $OCH_3$), 3.65 (dd, 1H, $J_1$=9, $J_2$=3, $CHCOOCH_3$), 3.41–3.19 (m, 3H), 2.73–2.51 (m, 4H), 2.30 (bs, 1H, N*H*), 2.15–1.85 (m, 4H), 1.52–1.37 [m, 1H, $CH(CH_3)_2$], 1.16 [t, 6H, *J*=7, $PO(CH_2CH_3)_2$], 0.89 [d, *J*=7, 3H, $CH(CH_3)_2$], 0.85 ppm [d, *J*=7, 3H, $CH(CH_3)_2$]; $^{13}C$ NMR δ: 172.0, 64.9, 64.7, 63.5, 62.3, 56.0, 52.6, 50.4, 30.7, 23.6, 20.0, 19.3, 17.0, 16.3 ppm. Calculated for $C_{16}H_{33}N_2O_5P$: C, 52.70; H, 9.13; N, 7.69. Found: C, 52.50; H, 9.21; N, 7.63.

*(2R,5S)-2-Carboxymethyl-4-[3'-(diethoxyphosphinyl)propyl]-5-*iso*-butyl piperazine* ***9b***

As previously described for **9a**, from the crude acid **8b** (0.59 g, 1.3 mmol) pure (TLC) methylesters **9b** was recovered, (0.29 g, 61%); $[\alpha]_D^{25}$ +2.7 (c 1, $CH_3COOH$), $^1H$ NMR (DMSO-$d_6$) δ: 4.21–4.01 [m, 4H, $P(OCH_2CH_3)_2$], 3.80 (s, 3H, $OCH_3$), 3.55 (dd, 1H, $J_1$=9, $J_2$=3, $CHCOOCH_3$), 3.32–3.13 (m, 3H), 2.83–2.59 (m, 4H), 2.42 (bs, 1H, N*H*), 2.20–1.90 (m, 4H), 1.64–1.43 [m, 3H, $CH_2CH(CH_3)_2$],

1.04 [t, 6H, PO($CH_2CH_3$)$_2$], 0.83 [d, $J$=7, 3H, CH($CH_3$)$_2$], 0.80 ppm [d, $J$=7, 3H, CH($CH_3$)$_2$]; $^{13}$C NMR (DMSO-$d_6$) δ: 175.2, 66.2, 63.5, 61.9, 55.8, 55.5, 54.8, 54.0, 50.0, 45.9, 23.7, 22.3, 21.6, 20.0, 19.2 ppm. Calculated for $C_{17}H_{35}N_2O_5P$: C, 53.95; H, 9.32; N, 7.40. Found: C, 54.11; H, 9.23; N, 7.37.

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