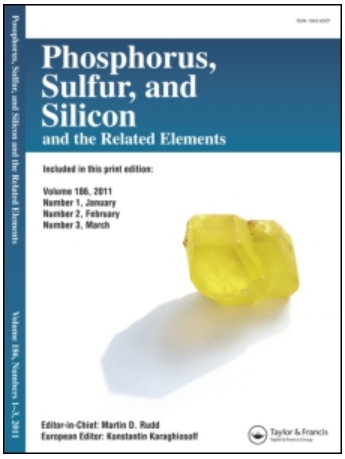

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

THREE-COMPONENT CONDENSATION OF ω-HYDROXY-*L*-α-AMINOCARBOXYLIC ACIDS, WATER AND PHOSPHORUS TRICHLORIDE OR METHYLDICHLOROPHOSPHINE

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To cite this Article Natchev, Ivan A.(1988) 'THREE-COMPONENT CONDENSATION OF ω-HYDROXY-*L*-α-AMINOCARBOXYLIC ACIDS, WATER AND PHOSPHORUS TRICHLORIDE OR METHYLDICHLOROPHOSPHINE', Phosphorus, Sulfur, and Silicon and the Related Elements, 37: 3, 149 — 157
To link to this Article: DOI: 10.1080/03086648808079030
URL: http://dx.doi.org/10.1080/03086648808079030

Phosphorus and Sulfur, 1988, Vol. 37, pp. 149–157
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THREE-COMPONENT CONDENSATION OF ω-HYDROXY-*L*-α-AMINOCARBOXYLIC ACIDS, WATER AND PHOSPHORUS TRICHLORIDE OR METHYLDICHLOROPHOSPHINE

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(Received June 28, 1987; in final form January 6, 1988)

Three-component condensation has been carried out of the ethyl esters of the *N*-acetylated *L*-tyrosine, *L*-DOPA, *L*-serine, *L*-threonine, and 4-hydroxy-*L*-proline, with equivalent amounts of water and phosphorus trichloride or methyldichlorophosphine, followed by alkaline hydrolysis of the blocking groups to hydroxyphosphonyl and methylphosphinyl derivatives. It has been found that condensation of α,β-dihydroxy aryl derivatives with equivalent amounts of water and phosphorus trichloride leads to the isolation of the corresponding 1,3,2-dioxaphospholes.

RESULTS AND DISCUSSION

The versatile biological activity of the phosphinyl analogues of the natural aminocarboxylic acids[1] has prompted our efforts to obtain a similar class of compounds, where the *L*-aminocarboxylic part of the corresponding natural-acid molecule would be preserved.

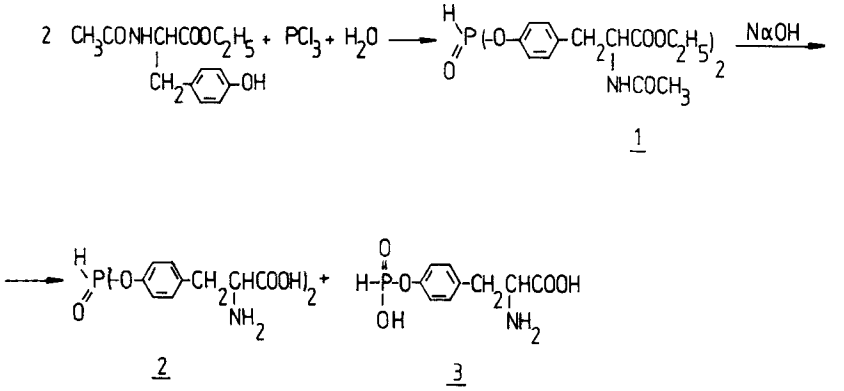
The introduction of the hydrophosphoryl group can be achieved via the reactive lateral groups of: the hydroxymethyl-containing *L*-serine, *L*-threonine, *L*-4-hydroxyproline, *I*-tyrosine, and 3-(3,4-dihydroxyphenyl)-*L*-alanine (DOPA); the amino- and guanidino-containing groups *L*-lysine, *L*-ornithine, 1,4-diamino-*L*-butanoic acid, guanidineacetic acid, creatine, and creatinine, as well as modification at the SH-group of cysteine. It would be interesting to synthesize and study the biological activity of the above amino acids, modified in their lateral chain with the residue of methylphosphinic acid —HP(O)CH_3—, or methylphosphonic acid —HOP(O)CH_3—.

Our Laboratory has launched a special program for synthesis of esters, amides and sulphides of phosphorous, methylphosphonic and methylphosphinic acid with the aid of ω-substituted *L*-α-aminocarboxylic acids.

In our previous papers,[2,3] we have discussed the possibilities for synthesizing diphenylphosphite and phenyl methylphosphonite by three-component condensation of phenol, water and phosphorus trichloride, or methyldichlorophosphine. In this work, we apply this method to the phenol-group-containing *L*-tyrosine and 3-(3,4-dihydroxyphenyl)*L*-alanine, as well as the model compounds pyrocatechol, 2,3-dihydroxypyridine, 3,4-dihydroxyphenylacetic acid ethyl ester, and 2,2′-biphenol. Studies have been continued further to include the hydroxyl-group-containing *L*-α-aminocarboxylic acids serine, threonine and hydroxyproline.

In order to enhance the three-component condensation of *N*-acetyl-*L*-tyrosine ethyl ester, water and phosphorus trichloride, it is recommended that 1 mol phosphorus trichloride is added dropwise for 2.0–2.5 hours to a boiling dioxan solution of 2 mols tyrosine derivative and 1 mol water. Throughout the interaction, a continuous nitrogen current should be passed through the reaction mixture, so that the hydrogen chloride released be removed from the system. It is also essential that quantity of water used should meet stoichiometrical requirements; otherwise the yields will drop considerably. During the interaction, no presence of phosphorous acid in the reaction mixture was discovered. Most probably, it is only one of the chlorine atoms of phosphorous trichloride that is initially hydrolyzed to the dichloroanhydride of phosphorous acid —$HP(O)Cl_2$, which then reacts with the phenol group of *L*-tyrosine. The activation of the second chlorine atom would require some heating. When the experiment was carried out at temperatures below zero (−5 + 0°C), or at ambient temperature (25°C), and when the above quantitative ratio of the components were used (i.e. tyrosine : water : phosphorus trichloride = 2 : 1 : 1), besides the diphosphite **1**, the presence of a product with a phosphorus-chlorine bond was observed, which proved to be very unstable and impossible to isolate in its pure form. Upon alkali treatment, this product led to the isolation of the monoester **3**, which is identical with that obtained below. Further proof is provided by the fact that, upon low-temperature three-component condensation, two mols hydrogen chloride are releated per two 2 mols tyrosine derivative,: 1 mol water and 1 mol phosphorus trichloride. Reversely, when three-component condensation is carried out with the reaction mixture boiling, 3 mols hydrogen chloride are released. However, when a double quantity of water is used in the low-temperature condensation, the monoester **3** is obtained as the main product, whereas high-temperature condensation affords the diphosphite **1** as the main product in a rather low yield. In this case, again, no presence of phosphorous acid in the reaction mixture is observed. When the ratio tyrosine : water : phosphorus trichloride is changed to 2 : 3 : 1, the diphosphite **1** and the monophosphite **3** are isolated in traces.

It is not the purpose of this work to investigate the mechanism of three-component condensation of phenols, water and phosphorus trichloride. A



SCHEME 1

separate exhaustive study of this mechanism is under way and the results will be published shortly.

Hydrolysis of the diphosphite **1** was carried out by treatment with sodium hydroxide. It turned out that the hydrolytic stability of one of the P—O—Ar groups and of the NH—$COCH_3$ group is almost the same. The diphosphite **2** and the monophosphite **1** were isolated in yields of about 40% and 35%, respectively.

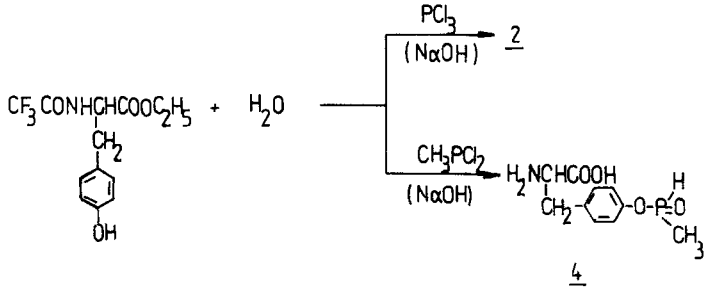
All attempts at using enzyme-catalyzed methods with the enzymes α-chymotrypsin, protease, acylase, etc., were unsuccessful. However, these enzymes have been employed quite successfully in our laboratory to hydrolyze the protective groups of other similar substrates, containing —P(O)(OH)R groups (cf. our previous publications). A possible assumption would be that the phosphorus-bound hydrogen atom causes the inhibition of the hydrolysis enzymes used.

As the hydrolysis of **1** in non-selective, we had to replace the acetyl group with the more easily hydrolyzable *N*-trifluoroacetyl group. When *N*-trifluoroacetyl-*L*-tyrosine ethyl ester is used under the above conditions and without isolation of the intermediate product the phosphite **2** (Scheme 2) is obtained in a yield of about 85% after alkaline hydrolysis. It is identical with the product obtained above.

Analogously, when the ratio *N*-trifluoroacetyl-*L*-tyrosine ethyl ester:water:methyldichlorophosphine = 1:1:1 is used, followed by alkaline hydrolysis, the methylphosphinic acid ester **4** is isolated. The reaction mechanism is most probably identical with that in which phosphorus trichloride participates. When analogous experiments were carried out at different temperatures and quantities of water used, the deviations in the yield of the end product **4** corresponded almost exactly to the deviations in the conditions applied. The reactivity of methyldichlorophosphine in this interaction is rather less pronounced towards *L*-tyrosine, hence the product **4** is isolated with a yield of approx. 70% (Scheme 2).

Before starting work on the three-component condensation of the *L*-tyrosine derivative *L*-DOPA-3-(3,4-dihydroxyphenyl)-*L*-alanine, we carried out treatment of catechol and 2,3-dihydroxypyridine, the metabolite of *L*-DOPA-3,4-dihydroxyphenylacetic acid ethyl ester, and 2,2′-biphenol.

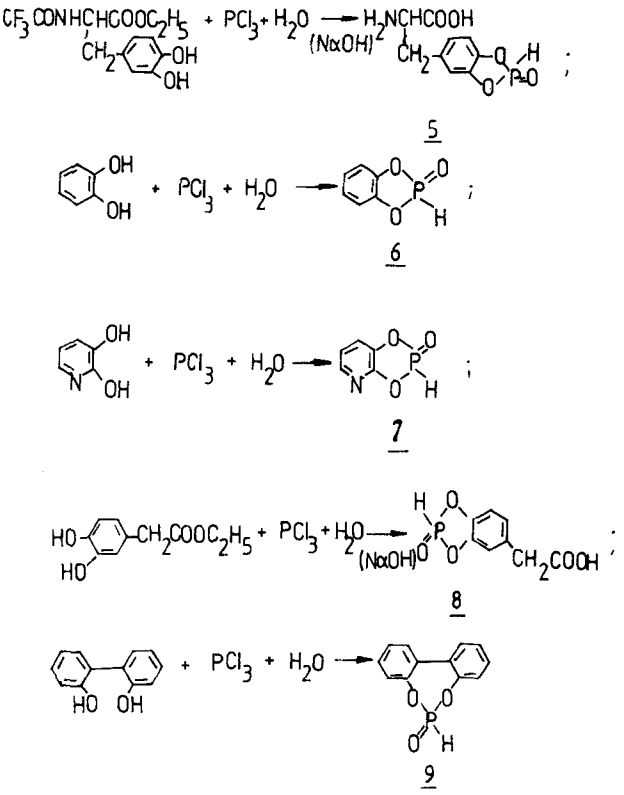
It could be assumed that, since a stepwise substitution occurs of the chlorine atoms of phosphorus trichloride, cyclization with the adjacent second phenol



SCHEME 2

group would take place to the corresponding 1,3,2-dioxaphosphole derivative. When conditions analogous to the above were used and the ratio 1,2-dihydroxyaryl:water:phosphorus trichloride was 1:1:1, the corresponding 1,3,2-dioxaphosphole derivatives, **6–9**, were isolated with very high yields (over 95%) from catechol, 2,3-dihydroxy-pyridine, 3,4-dihydroxyphenylacetic acid ethyl ester, and 2,2′-biphenol, respectively. The only exception from these excellent yields was observed in the formation of the sevenmembered dioxaphosphepine ring of **9**, where a phosphorus-containing oligomeric compound was isolated as the second product. Using other aryl derivatives with two far-removed hydroxy groups also resulted in the isolation of oligomeric products. Three-component condensation of diphenols with far-removed hydroxyl groups (e.g. 1,3-, 1,4- and 4,4′-), water and phosphorus trichloride in a quantitative ratio (1:1:1) is at the moment being conducted in our laboratory. The results will appear separately.

Three-component condensation of *N*-trifluoroacetyl-3-(3,4-dihydroxyphenyl)-*L*-alanine ethyl ester, water and phosphorus trichloride affords yields which are by 10–15% higher than those with *L*-tyrosine. This could possibly be accounted for with the lack of any spatial hindrance of the reaction centre of the *L*-DOPA-α,β-dihydroxy structure. The isolation of the intermediate protected *L*-DOPA is quite unnecessary. The 1,3,2-dioxaphosphole **5** is isolated in a yield of about 90% upon alkali treatment.



SCHEME 3

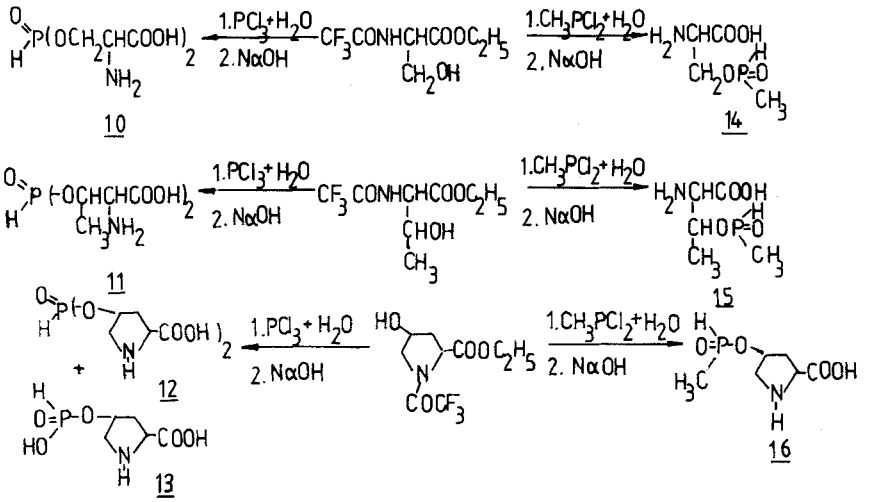
Treatment of *N*-trifluoroacetyl-*L*-serine ethyl ester with water and phosphorus trichloride does not proceed as smoothly as with aromatic hydroxy derivatives. Despite repeated experiments carried out with varying conditions of three-component condensation and amounts of the components used, we failed to obtain the di(seryl)phosphite **10** in yields higher than 50%. Some unstable chlorine derivatives are isolated as the main sideproducts, which, upon alkali treatment, release the starting serine. All our attempts at esterifying phosphorous acid with the same protected serine were unsuccessful.

An analogous interaction is observed between 1 mol *N*-trifluoroacetyl-*L*-serine ethyl ester, 1 mol water and 1 mol methyldichlorophosphine to the methylphosphinite **14**. Despite the weaker activity of methyldichlorophosphine under the conditions of three-component condensation, the yield of the phosphinite **14** is approx. 60%.

Analogously, the secondary alcohol *N*-trifluoroacetyl-*L*-threonine ethyl ester in combination with phosphorus trichloride, methyldichlorophosphine and water and after hydrolysis of the protective groups affords the products **11** and **15** in yields of 40 and 55%, respectively.

Treatment of *N*-trifluoroacetyl-trans-4-hydroxy-*L*-proline ethyl ester with water and phosphorus trichloride, or methyldichlorophosphine, is rather complicated due to both the instability of hydroxyproline under the conditions of three-component condensation, and to certain steric hindrances created by the bulky pyrrolidine residue. When this treatment is conducted at over 60°C, side products are obtained and the yield of the dipyrrolylphosphite **12** is only 10–12%. When a dioxan solution of hydroxyproline, water and phosphorus trichloride (2:1:1) is treated at 40–45°C, two products are isolated: the diphosphite **12** (yield approx. 35%) and the monoester **13** (yield approx. 45%).

The interaction of equimolar quantities of *N*-trifluoro-acetyl-trans-4-hydroxy-*L*-proline ethyl ester, water and methyldichlorophosphine proceeds more smoothly,



SCHEME 4

but the yields are relatively low. A subsequent alkaline hydrolysis leads to the isolation of the methylphosphinite **16** in a yield of about 55%.

Treatment of lower alcohols, as methanol, ethanol, propanol, etc., with water and phosphorus trichloride, or methyldichlorophosphine (mol ratio 2:1:1 and 1:1:1, respectively), afford very low yield.

Pseudo-rotation mechanism of hydrolysis of 5-membered cyclic esters of phosphoric acid is described by Westheimer in a review.[4] In this sence we can explain our unsuccessful attempt to use in the three-component condensation ($PCl_3 + H_2O + ROH$) ethylene glycol and glycerine to form the corresponding 1,3,2-dioxaphospholes. On the other hand, in the case with the 6-membered substituted phosphorinanes. Nifantiev *et al.*[5] treated 1,2-alkylidene-α-*D*-xylofuranose with phosphorus trichloride to give the corresponding 2-chlorine-1,3,2-dioxaphosphorinane derivative which after treating with water led to the alkylidene phosphite with a yield of 45%. When we carried out the three-component condensation with the same furanose, the yield of phosphorinane 2-oxide reached 85%. The synthesis of the respective 1,3,2-dioxaphosphorinanes 2-oxides by three-component condensation and their physiological activity are the subject of other papers.

Three-component condensation of mono- and 1,2-dihydroxyaromatic derivatives, water and phosphorus trichloride, or methylchlorophosphine, would be very suitable for experiments aimed at the synthesis of diarylphosphites and aryl methylphosphonites, where the use of alcohols or dioles has its drawbacks.

EXPERIMENTAL

1. General notes: IR-spectra, elemental analysis, HPLC, $[\alpha]_D^{20}$, and molecular weight—on a Perkin–Elmer instrument; ^{1}H NMR-spectra—on Brucker or Jeol-100 MHz; Mass-spectra—on Varian or LKB-900; m.p.'s measured on a Koefler apparatus; TLC—silica gel film "Merck", phosphomolybdate detection; reagents and solvents—from "Fluka", "Merck" and "Aldrich".

IR-spectra of known compounds have been compared with those of the same compounds, obtained by standard methods. All spectra within the range 4000–400 cm^{-1} were found to be completely identical.

2. Synthesis of the di(tyrosyl)phosphite **1**. Phosphorus trichloride (13.73 g, 0.1 M) is added dropwise for 3.0–3.5 hours to boiling dioxan (150 ml), containing *N*-acetyl-*L*-tyrosine ethyl ester (50.26 g, 0.1 M) and water (1.80 g, 0.1 M). A continuous current of dry argon or nitrogen is passed through the reaction mixture. The volatile components are then removed in vacuum and the oily residue is placed on a silica gel column (eluent chloroform : methanol = 9:1).

0,0′-Bis(*N*-acetyl-*L*-ethyltyrosinate) phosphite, **1**: $C_{26}H_{33}N_2O_9P$; 46.84 g (85.4%); b.p. oil, which does not distill without decomposition above 120°C/6.10^{-4} Torr; IR (film): 3300–3120, 2340, 1740, 1650, 1260, 1185, 1000–890, 840, 750, 630; ^{1}H NMR ($CDCl_3$): 1.18 and 1.23 (6 H, s, $COCH_3 \times 2$), 1.28 and 1.42 (6 H, t, $OCH_2CH_3 \times 2$), 4.1–4.4 (10 H, m, $OCH_2CH_3 \times 2$,$CH_2CH \times 2$), 7.1–7.5 (8 H, m, $C_6H_4 \times 2$), 6.12 (1 H, s, NH), [7.13 (1 H, d, $J_{H-P} = 540$ Hz), exchanged by D_2O + NaOD]; M.w., calc'd/found: 548.529/550; R_f: 0.56 (DMF : $CHCl_3$: MeOH = 2:6:1); $[\alpha]_D^{20}$: +77.3°, $c = 0.1$, MeOH;

Calc'd:	C 56.93	H 6.06	N 5.11%
Found:	C 57.18	H 5.93	N 5.18

3. Synthesis of the phosphites **2** *and* **3**. The diphosphite **1** (54.78 g, 0.1 M) is heated for 60 mins. in 2 N NaOH (150 ml) in a water bath. After cooling, acidification and vacuum distillation, the resinous mass is crystallized fractionally from ethanol to the products:

0,0′-Bis-(*L*-tyrosinyl)phosphite, **2**: $C_{18}H_{21}N_2O_7P$; 16.86 g (41.3%); m.p. 246–250°C (decomp.); IR

(KBr): 3100–2720, 2340, 1605, 1550, 1260, 1180, 1010–900, 840, 750, 630; ^{1}H NMR (D_2O + NaOD): 4.1–4.4 (6 H, m, $CH_2CH \times 2$), 7.1–7.5 (8 H, m, $C_6H_4 \times 2$), plus seven exchangeable protons; M.w. calc'd/found: 408.344/410; R_f: 0.32 (*n*-BuOH:AcOH:H_2O = 9:1:1) and 0.66 (*n*-BuOH:25%NH_4OH = 4:1); $[\alpha]_D^{20}$ +71..3°, *c* = 0.1, 0.1 N NaOH;

Calc'd: C 57.94 H 5.18 N 6.86%

Found: C 53.16 H 4.93 N 6.90%

The product is completely soluble in the more organic solvents and also has a good solubility in water.

0-Hydroxyphosphinyl-*L*-tyrosine, **3**; $C_9H_{12}NO_5P$; 8.38 g (34.2%); m.p., decomp.. at above 250°C; IR (KBr): 3010–2820, 2450–2350, 1605, 1255, 1205, 1020–900, 845, 750, 635; ^{1}H NMR (D_2O + NaOD): 4.1–4.3 (3 H, m, CH_2CH), 7.1–7.5 (4H, m, C_6H_4), plus five exchangeable protons, [in DMSO-d_6: 6.48 (1 H, d, J_{H-P} = 520 Hz), 10.2–10.6 (1 H, br, 8.POH)]; R_f: 0.44 (*n*-BuOH:AcOH:H_2O = 9:1:1); $[\alpha]_D^{20}$: +70.3°, *c* = 0.1, 0.1 N NaOH;

Calc'd: C 44.09 H 4.93 N 5.71%

Found: C 44.26 H 4.77 N 5.80%

The product is readily soluble in water, slightly soluble in DMF and hexametapol, and insoluble in common organic solvents, except in EtOH/NaOEt and *t*-BuOH/NaOBu-*t*.

4. Synthesis of the diphosphite **2**. The same procedure as in Item 1 is applied, only now *N*-trifluoroacetyl-*L*-tyrosine ethyl ester is used. The volatile components are removed in vacuum and the resinous residue is heated with 0.5 N NaOH on a water bath until a homogeneous solution is obtained. After the above work-up, 0,0'-bis(*L*-tyrosinyl)phosphite is obtained in a yield of 85.3% (34.83 g).

5. Synthesis of the methylphosphinite **4**. Methyldichlorophosphine (12.86 g, 0.11 M), dissolved in chloroform (120 ml), is added dropwise for 4 hours to a boiling solution of *N*-trifluoroacetyl-*L*-tyrosine ethyl ester (30.53 g, 0.1 M) in dioxan (300 ml) and water (1.8 g, 0.1 M). The volatile components are then removed in vacuum and the residue is heated with 0.5 N NaOH on a water bath, until a homogeneous solution is obtained. After cooling, acidification and evaporation in vacuum to dryness, the residue crystallizes from ethanol to give:

0-Methylphosphinyl-*L*-tyrosine, **4**: $C_{10}H_{14}NO_4P$; 17.34 g (71.3%; m.p. 218–220°C (decomp.); IR (KBr): 3100–2860, 2460, 1610, 1305, 1260, 1240, 845, 760, 635; ^{1}H NMR (D_2O + NaOD): 1.33 (2 H, d, *J* = 18 Hz, PCH_3), 4.1–4.4 (3 H, m, $CHCH_2$), 7.1–7.1 (4 H, m, C_6H_4), plus four exchangeable protons; Mass-spect. (M^+/e): 243.200/243; R_f: 0..62 (*n*-BuOH:AcOH;H_2O = 9:1:1); $[\alpha]_D^{20}$: +83.2°, *c* = 0.1, 0.1 N NaOH;

Calc'd: C 49.39 H 5.80 N 5.76%

Found: C 49.56 H 5.60 N 5.55%

6. Synthesis of the dioxaphospholes **5–9**. Phosphorus trichloride (13.71 g, 0.1 M) is added dropwise for 4 hours to a boiling solution of each of the 1,2-dihydroxy aryl derivatives (0.1 M): *N*-trifluoroacetyl-3-(3,4-dihydroxy-phenyl)-*L*-alanine ethyl ester, catechol, 2,3-dihydroxypyridine, 2,2'-biphenol, and 3,4-dihydroxyphenylacetic acid ethyl ester, in dioxan that contains water (1.8 g, 0.1 M). A continuous current of dry argon or nitrogen is passed through the reaction mixture. After evaporation in vacuum to dryness (in the presence of *L*-DOPA and phenylacetic acid ethyl ester), the reaction mixture is treated with 0.5 N NaOH for 30 mins. at 60°C and the following products are isolated, respectively:

3-(1,3,2-Benzodioxaphosphol-5-yl-2-oxo)-*L*-alanine, **5**: $C_9H_{10}NO_5P$; 21.75 g (88.7%); m.p. 218–220°C (decomp.); IR (KBr): 3010–2820, 2445, 1610, 1260–1200, 1010–960, 940, 820, 730, 630; ^{1}H NMR (D_2O + NaOD): 4.1–4.4 (3 H, m, CH_2CH), 6.9–7.4 (3 H, m, C_6H_3), plus four exchangeable protons; Mass-spect. (M^+/e): 243.156/243; R_f: 0.44 (*n*-BuOH:AcOH:H_2O = 9:1:1); $[\alpha]_D^{20}$ +88.7, *c* = 1, 0.1 N NaOH;

Calc'd: C 44.46 H 4.15 N 5.76%

Found: C 44.71 H 3.92 N 5.82%

1,3,2-Benzodioxaphosphole 2-oxide, **6**: $C_6H_5O_3P$; 15.0 g (96.1%); b.p. 131°C/12 mm Hg; 64–

65°C/2.10^{-2} mm Hg[6]; 116°C/8 mm Hg[7]; Mass-spect. (M^+/e): 156.079/156;

Calc'd: C 46.17 H 3.23%

Found: C 46.01 H 3.5%

Pyridino [2,3-*b*][1,3,2] dioxaphosphole 2-oxide, **7**: $C_5H_4NO_3P$; 14.87 g (94.7%); viscous oil, b.p. 120°C/6.10^{-4} Torr; Mass-spect. (M^+/e): 157.066/157;

Calc'd: C 34.24 H 2.57 N 8.92%

Found: C 34.00 H 2.90 N 8.88%

Dibenzo[d, f][1,3,2]dioxaphosphepine 6-oxide, **9**: $C_{12}H_9O_3P$; 17.00 g (73.2%); viscous oil, b.p. 120°C/6.10^{-4} Torr; Mass-spect. (M^+/e): 232.175/232;

Calc'd: C 62.08 H 3.91%

Found: C 61.77 H 4.11%

(1,3,2-Benzodioxaphosphol-5-yl-2-oxide)acetic acid, **8**: $C_8H_7O_5P$; 20.58 g (96.1%); m.p.: decomp. at about 150°C; Mass-spect. (M^+/e): 214.114/214;

Calc'd: C 44.88 H 3.29%

Found: C 44.96 H 3.56%

7. Synthesis of the diphosphites **10–12** *and the monophosphite* **13**. The procedure in Item 2 is followed with 0.2 M of each of the *N*-trifluoroacetylated esters of *L*-serine, *L*-threonine and trans-*L*-hydroxyproline (the latter 40–45°C). An analogous work-up affords the products **10** and **11**. Hydroxyproline gives the products **12** and **13**:

0,0'Bis(*L*-serinyl)phosphite, **10**: $C_6H_{13}N_2O_7P$; 12.63 g (49.3%); m.p. 233–235°C (decomp.); IR (KBr): 3120–2940, 2350, 1610, 1250, 1110–960; ^{1}H NMR (D_2O + NaOD): 1..31 and 1.45 (4 H, d, J = 6 Hz, $CH_2 \times 2$), 4.03 and 4.11 (2 H, t, CH × 2), plus seven exchangeable protons; Mass-spect. (M^+/e): 256.152/256; R_f: 0.44 (*n*-BuOH: AcOH: H_2O = 9:1:1); $[\alpha]_D^{20}$ +22.3°, c = 10, 1 N HCl;

Calc'd: C 28.13 H 5.12 N 10.94%

Found: C 28.55 H 5.43 N 11.01%

0,0'-Bis(*L*-threoninyl)phosphite, [2S,3R-(−)threonine], **11**: $C_8H_{17}N_2O_7P$; 11.43 g (40.2%); m.p.: decomp. at about 240°C; IR (KBr): 3120–2930, 2355, 1605, 1245, 1110–960; ^{1}H NMR (D_2O + NaOD): 1.22 and 1.32 (6 H, d, J = 8 Hz, $CHCH_3 \times 2$), 3.9–4.4 (4 H, m, CHCH × 2), plus seven exchangeable protons; Mass-spect. (M^+/e): 284.205/284; R_f: 0.50 (*n*-BuOH: AcOH: H_2O = 9:1:1); $[\alpha]_D^{20}$ −92.3°, c = 1, 0.1 N NaOH;

Calc'd: C 33.81 H 6.03 N 9.86%

Found: C 33.99 H 5.84 N 10.00%

The product is easily soluble in water, slightly soluble in DMF, DMSO and hexametapol, and insoluble in common organic solvents.

0,0'-Bis(trans-4-oxy-*L*-prolinyl)phosphite, [(2S,4R)-(−)-4-hydroxy-2-pyrrolidinecarboxylic acid], **12**: $C_{10}H_{17}N_2O_7P$; 10.85 g (35.2%); m.p. 248–251°C (decomp.); IR (KBr): 3100–2895, 2345, 1600, 1505, 1240, 1110–980; ^{1}H NMR (D_2O + NaOD): 1.72 (4 H, m, $CH_2 \times 2$), 2.76 (4 H, d, J = 9 Hz, $NHCH_2 \times 2$), 3.9–4.4 (4 H, m, CHOP and NHCHCOOH × 2), plus five exchangeable protons; Mass-spect. (M^+/e): 308.227/308; R_f: 0.56 (*n*-BuOH: AcOH: H_2O = 9:1:1); $[\alpha]_D^{20}$ −72.3°, c = 1, 0.1 N NaOH;

Calc'd: C 38.97 H 5.56 N 9.09%

Found: C 39.19 H 5.29 n 9.18%

0-Trans-4-oxy-*L*-prolinyl phosphorus acid, **13**: $C_5H_{10}NO_4P$; 8.19 g (45.7%); m.p.: decomp. at approx. 280°C; IR (KBr): 3110–2890, 2800–2450, 2350, 1600, 1500, 1250, 1110–960; ^{1}H NMR (D_2O + NaOD): 1.69 (2 H, dd, CH_2), 2.73 (2H, d, J = 9 Hz, $NHCH_2CH$), 3.98 (1 H, m, CHOP), 4.36 (1 H, t, CHCOOH), plus four exchangeable protons; Mass-spect. (M^+/e): 179.113/179; R_f: 0.56 (*n*-BuOH: AcOH: H_2O = 9:1:1),

Calc'd: C 33.53 H 5.63 N 7.82%

Found: C 33.81 H 5.55 N 7.94%

8. Synthesis of the methylphosphinites **14–16**. Methyldichlorophosphine (14.03 g, 0.12 M), dissolved in dioxan, is added dropwise for 4 hours to boiling dioxan (200 ml), which contains water (1.8 g, 0.1 M) and one of the ethyl esters of the *N*-trifluoroacetyl derivatives of *L*-serine, *L*-threonine and 4-hydroxy-*L*-proline (0.1 M). With hydroxyproline the addition is performed at 40–45°C. A continuous current of dry argon or nitrogen is passed through the reaction mixture. When addition is completed, boiling is kept up for another hour, followed by evaporation in vacuum to dryness. Sodium hydroxide (0.5 N, 120 ml) is then added to the reaction residue and the mixture is heated on a water bath for 30 mins. After cooling, acidification and evaporation in vacuum to dryness, the reaction residue is subjected to a two-fold recrystallization from ethanol. The following products are isolated, respectively:

0-Methylphosphinyl-*L*-serine, **14**: $C_4H_{10}NO_4P$; 9.84 g (58.9%); m.p. 186–189°C; IR (KBr): 3120–2920, 2330, 1605, 1320, 1240, 1100–960; ^{1}H NMR (D_2O + NaOD): 1.88 (3 H, d, J = 18 Hz, PCH_3), 4.10 (1 H, t, $CHCH_2$), 4.26 (2 H, d, J = 8 Hz, $CHCH_2$), plus four exchangeable protons; Mass-spect. (M^+/e): 167.102/167; R_f: 0.60 (*n*-BuOH:AcOH:H_2O = 9:1:1); $[\alpha]_D^{20}$ +82.3°, c = 1, 0.1 N NaOH;

Calc'd:	C 28.75	H 6.03	N 8.38%
Found:	C 29.36	H 6.00	N 8.56%

The product is readily soluble in water, DMF, DMSO and hexametapol, slightly soluble in dioxan, ethanol and methanol, and insoluble in ether, chloroform and hexane.

0-Methylphosphinyl-*L*-threonine, **15**: $C_5H_{12}NO_4P$; 10.16 g (56.1%); m.p. 184–186°C (decomp.); IR (KBr): 3120–2910, 2325, 1600, 1320, 1245, 1110–965; ^{1}H NMR (D_2O + NaOD): 1.29 (3 H, d, J = 8 Hz, $CHCH_3$), 1.91 (3 H, d, J = 18 Hz, PCH_3), 4.1–4.4 (2 H, m, $CHCH$), plus four exchangeable protons; Mass-spect. (M^+/e): 181.129/181; R_f: 0.64 (*n*-BuOH:AcOH:H_2O = 9:1:1); $[\alpha]_D^{20}$: −75.3°, c = 1, 0.1 N NaOH;

Calc'd:	C 33.16	H 6.68	N 7.75%
Found:	C 33.51	H 6.43	N 7.69%

0-Methylphosphinyl-trans-4-oxy-*L*-proline, **16**: $C_6H_{12}NO_4P$; 10.38 g (53.8); m.p. about 260°C (decomp.); IR (KBr): 3200–2860, 2340, 1610, 1320, 1235, 1120–980; ^{1}H NMR (D_2O + NaOD): 1.71 (2H, dd, $CHCH_2$), 2.01 (3 H, d, J = 18 Hz, PCH_3), 2.82 (2 H, d, J = 9 Hz, $NHCH_2$), 3.96 (1 H, m, CHOP), 4.44 (1 H, t, $CHCOOH$), plus three exchangeable protons; Mass-spect. (M^+/e): 193.140/193; R_f: 0.64 (*n*-BuOH:AcOH:H_2O = 9:1:1); $[\alpha]_D^{20}$: −92.3°, c = 1, 0.1 N NaOH;

Calc'd:	C 37.31	H 6.26	N 7.25%
Found:	C 37.56	H 6.01	N 7.31%

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