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NMR and X-Ray Crystallographic Studies of Linear and Cyclic Aminomethanephosphinates

Edgar González-Juárez, Armando Ortega-Guevara, Irma Linzaga-Elizalde, and Jaime Escalante

Centro de Investigaciones Químicas, Universidad Autónoma del Estado de Morelos, Av. Universidad 1001, Cuernavaca, Mor. CP 62210, México

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ABSTRACT: *We report the preparation of four diastereoisomeric pairs of ethyl {[(3-hydroxypropyl)-amino](aryl)methyl}phenylphosphinates. In two cases, the phosphinates were transformed to 1,4,2-oxazaphosphepane heterocycles through one-pot intramolecular esterification. The analogous reaction with formaldehyde gave the six-membered ethyl (1,3-oxazinan-3-ylmethyl)phenylphosphinate, which could be transformed in a posterior reaction to the corresponding aminomethanephosphinic acid. The new compounds were characterized by IR, ^{1}H, ^{13}C, and ^{31}P NMR.* © 2006 Wiley Periodicals, Inc. Heteroatom Chem 17:81–87, 2006; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20179

INTRODUCTION

As analogues of amino acids, aminophosphonic, and aminophosphinic acids **1** are of considerable interest due to their properties in agrochemistry as plant growth regulators and herbicides [1]. Some derivatives have properties as inhibitors of aspartic proteases [2,3], or ligases [4], and monoesters have been used in analytical chemistry for the solvent extraction of metals [5–7]. The aminomethanephosphonic acid derivatives of 2-aminoethanol substrates have been starting materials for the preparation of six-membered heterocyclic 1,4,2-oxazaphosphinanes **2**, which are interesting for the preparation of enantiopure phosphonic acid [8–10]. Recently we have reported the preparation of a series of diethyl {[(3-hydroxypropyl)amino](aryl) methyl}phosphonates **3**, as intermediate materials for seven-membered 1,4,2-oxazaphosphepane **4** [11]. In this work, we present the preparation and structural characterization of new ethyl {[(3-hydroxypropyl)amino](aryl)methyl}phenylphosphinates **5–8**, two seven-membered 1,4,2-oxazaphosphepanes **9,10**, and (1,3-oxazinan-3-ylmethyl)phenylphosphinate **11**.

Correspondence to: Irma Linzaga-Elizalde; e-mail: linzaga@ciq.uaem.mx.
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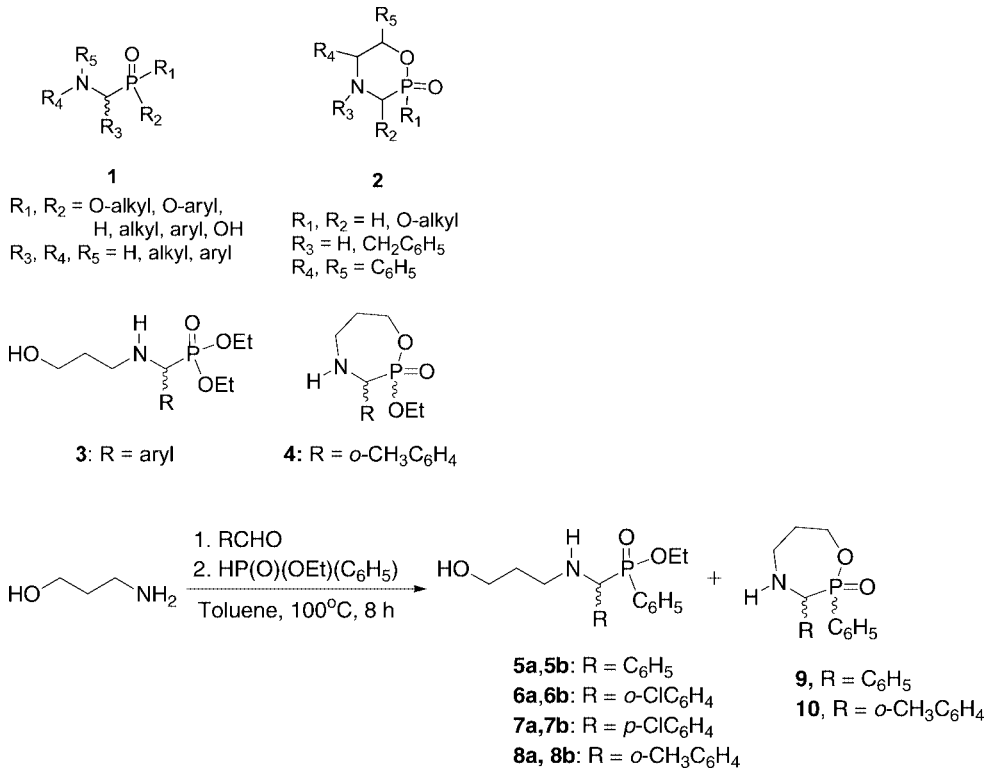
RESULTS AND DISCUSSION

Ethyl {[(3-hydroxypropyl)amino](aryl)methyl} phenylphosphinates were prepared by addition of ethyl phenylphosphinate to the Schiff base precursors in toluene using reflux. According to this procedure, we obtained the diastereomeric mixtures of aminomethylphosphinates **5–8** in good yields (Scheme 1), which were separated by column chromatography. Such compounds exhibit two chiral centers at C (CHP) and P [P((O)(OEt)(C_6H_5)], which determine their formation as a mixture of two diastereoisomers (**a** and **b**), each being a racemic mixture of enantiomers.

Compounds **5–8** have similar IR and NMR spectroscopic data. In the IR spectra, the absorption bands characteristic of NH and OH (3382–3404 cm^{-1}), P=O (1206–1215 cm^{-1}), and P—O_{Et}



SCHEME 1

(1026–1034 cm^{-1}) groups are noted in the expected areas. In general in the ^1H NMR spectra [12,13], the P—OEt moiety gives rise to ABM_3X spin systems. The signal for the CHP hydrogen atom is a doublet at 4.0–4.9 ppm with $^2J_{HP} = 14.4–17.2$ Hz. The less polar diastereoisomers give the smallest coupling constants and the upfield–shiftfield signal corresponds to the more polar diastereoisomers. This may be attributed to the fact that the methyne proton is localized at the same side as the phenyl group, this causing a highfield shift. The NH and OH protons give the same chemical shift. In all cases, the methylene protons alpha to CH_2OH show two complex multiplets and in some cases the remaining methylene protons show two distinct signals too. The ^{13}C NMR spectra of these compounds display some interesting features: a doublet for the methyl group in the P—OEt moiety at ≈16.4–16.8 ppm with $^3J_{CP} = 4.5–6.1$ Hz and a further doublets for the methylene group at 61.6–62.3 ppm with $^2J_{CP} = 6.1–7.6$ Hz. The signals for the NCH_2 group have chemical shifts of δ 47.1–47.9 ppm with $^3J_{CP} \approx 12.1–15.2$ Hz. The magnitude of these coupling constants suggests that the trans-conformation is predominant for the P—C—N—C fragment. The CH_2OH methylene group is shielded, $\delta = 62.9–63.8$ ppm. The doublets at 58.2–64.1 ppm with $^1J_{CP} \approx 106.3–109.3$ Hz evidence that the P—C bonds have been formed. The ^{31}P NMR shifts range from $\delta = 37.8–41.3$ ppm, of which the downfield shifts correspond to the most polar diastereoisomers.

Diastereoisomers **6a** and **6b** provided single crystals and were subjected to X-ray crystallographic analyses [14] (Fig. 1). The hydrogen atoms bonded to the carbon and nitrogen atom in the H—N—C—H moiety are *anti*, the P=O and the hydrogen atoms in the NH groups are parallel, the OH group is oriented toward the nitrogen atom, and the C2 carbon atom is in a trans conformation relative to the phosphorus atom, which confirms the C—P coupling in the ^{13}C NMR spectrum for **6a** and **6b**.

Interestingly, when the reaction shown in Scheme 1 is carried out in the presence of benzaldehyde and refluxed for 24 h, a mixture of the aminomethylphosphinates (**5a** + **5b**) and 1,4,2-oxazaphosphephane (**9**) was obtained. When the reaction was carried out with *o*-tolualdehyde in the same conditions, aminomethylphosphinates (**8a** + **8b**) and 1,4,2-oxazaphosphephane (**10**) were generated. The corresponding mixtures were separated by column chromatography.

In the ^1H NMR spectra, the absence of the signals for the —OCH_2CH_3 group in **9** and **10** is notable. The coupling constants for the —CHP— fragment

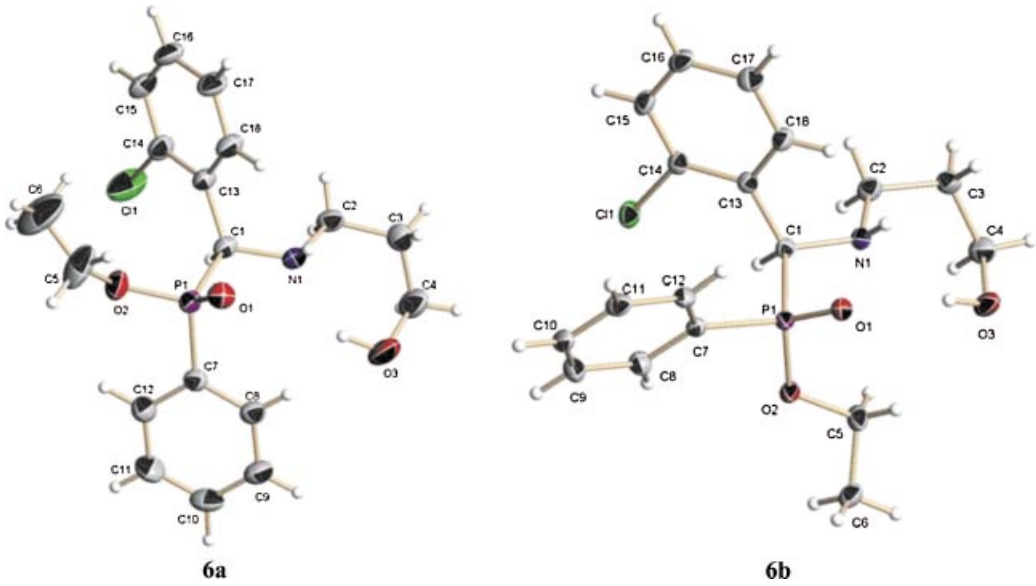


FIGURE 1 Perspective view of the molecular structures of diastereoisomers **6a** and **6b**.

have diminished in relation to the acyclic precursors ($^2J_{HP} = 14.8$ Hz for **9** and 2.8 Hz for **10**). Furthermore, a sharp signal is characteristic for the NH group. The $-CH_2-$ groups show different signals for every proton in both cases. In the case of compound **10**, the coupling constants for the $-NCH_2-$ group for the signal at 2.98 ppm are, $J = 2.7$, 9.1, 11.2 Hz and those for the signal at 3.54 ppm are $J = 3.3$, 6.5, 10.6 Hz, only considering H—H coupling in both the cases. From this, it can be concluded that the compounds have chair conformations.

In the ^{13}C NMR spectra, the most interesting chemical shift changes are seen for the —N—C—P— fragment, because the lowfield shift at 68.2 ppm for **9** (d, $^1J_{CP} = 97.4$ Hz) and 60.5 ppm for **10** (d, $^1J_{CP} = 85$ Hz) compared with the acyclic structures **5a,b** and **8a,b**. The $-NCH_2-$ group only shows a single signal, in contrast to acyclic structures that normally give a double. This may be because they are not in a trans conformation. The ^{31}P NMR chemical shifts are at 45.4 and 41.6 ppm and are upfield shifted when compared to the acyclic structures counterparts. In conclusion, the NMR data support the chair-conformation in solution.

Crystals of the oxazaphosphephane derivative of benzaldehyde were subjected to an X-ray crystallographic analysis [15]. This seven-membered ring has a chair-conformation with the P-phenyl and C-phenyl groups syn-equatorial, which is common for 2,3-disubstituted cycloheptane analogues (Fig. 2).

When 2 mol of formaldehyde was used instead of benzaldehyde for the reaction shown in Scheme 1, (1,3-oxazinan-3-ylmethyl)phenylphosphinate **11** was

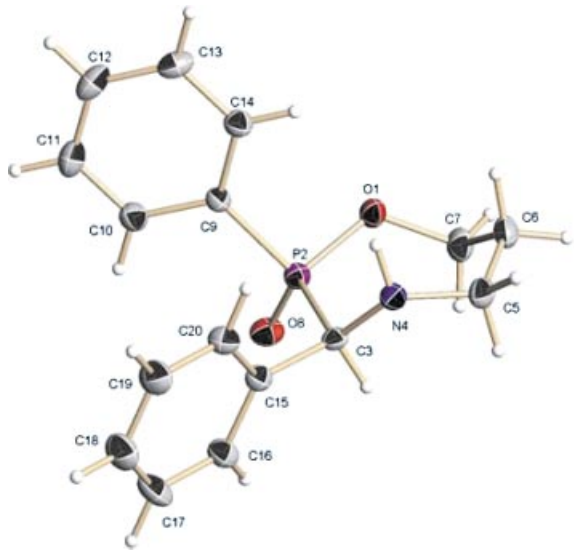
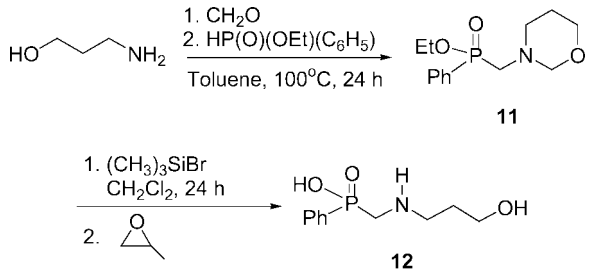


FIGURE 2 Molecular structure of compound **9**.

isolated with 63% yield. A related 1,3-oxazine derivative from diethylphosphite has been obtained in our laboratory [11]. The molecular structure of **11** was evidenced by characteristic IR-absorptions of the P=O (1211 cm^{-1}) and —P—O—C—C— (1123 cm^{-1}) bands. In the ^1H NMR spectrum, the two doublets for $-NCH_2O-$ (an AB system at 4.2 and 4.34 ppm with $J = 10$ Hz) and a doublet of doublets for every proton in $-NCH_2P-$ (at 3.22 ppm with $J = 7.6$ Hz and $^2J_{HP} = 15.6$ Hz, and 3.3 ppm with $J = 9.6$ Hz and $^2J_{HP} = 15.8$ Hz) make the difference when



SCHEME 2

compared to the other derivatives discussed so far. The chemical shift measured in the ^{31}P NMR spectrum is $\delta = 39.6$ ppm.

Phosphinate **11** can be transformed to the aminomethanephosphinic acid **12** through a hydrolysis reaction with bromotrimethylsilane and propylene oxide (Scheme 2). This compound shows bands at 3339, 1625, 1501, 1439, 1358, 1176, 1133, 1067 cm^{-1} in the IR spectrum, which are characteristic for —OH and —P(O)OH groups. Accordingly in the ^1H and ^{13}C NMR spectra, the signals corresponding to the POEt and $-NCH_2O-$ groups are missing, and the doublet for the $-CH_2P-$ is located at 3.24 ppm with $J = 10$ Hz. The signal in the ^{31}P NMR spectrum is displaced at 20.6 ppm.

In conclusion, we have prepared four diastereoisomeric pairs of ethyl {[(3-hydroxypropyl)-amino](aryl)methyl}phenylphosphinates by addition of ethyl phenyl phosphinate to the imine derivatives of benzaldehyde. In these reactions it was observed that the benzaldehyde and *o*-tolualdehyde generated seven-membered 1,4,2-oxazaphosphepane heterocycles via an intramolecular esterification. With formaldehyde, an ethyl (1,3-oxazinan-3-yl-methyl)phenylphosphinate derivative is obtained.

EXPERIMENTAL

General Methods

Materials were obtained from commercial suppliers and were used without further purification. NMR studies were carried out with Varian Gemini 200 and Varian Inova 400 instruments. Standards were TMS (internal, ^1H, ^{13}C) and H_3PO_4 (external, ^{31}P). Chemical shifts are stated in parts per million; they are positive, when the signal is shifted to higher frequencies than the standard. COSY and HETCOR experiments have been carried out in order to assign the ^1H and ^{13}C spectra completely. IR spectra have been recorded on a Bruker Vector 22 FT spectrophotometer. Mass spectra were obtained on HP 5989A and Jeol JMS 700 equipments. X-ray diffraction studies were performed on a Bruker-APEX diffractometer with a CCD area detector at 100 K ($\lambda_{Mo K\alpha} = 0.71073$ Å, monochromator: graphite).

General Procedure for Ethyl {[(3-Hydroxyproyl)-amino](aryl)methyl }phenylphosphinates

A mixture of aldehyde (1 mol) and 3-amine-1-propanol (1 mol) in toluene is heated to reflux in a Dean–Stark distillation. When the calculated amount of H_2O has separated, was added to the resulting imine mixture the ethyl phenyl phosphinate (1 mol) and then heated to 100°C for 3 h. Then, the reaction mixture was allowed to cool to room temperature, the solvent was evaporated, and the crude product was chromatographed (dichloromethane: methanol 98:2) to obtain the diastereoisomers **5a,b–8a,b**.

Ethyl {[(3-Hydroxypropyl)amino](phenyl)methyl}-phenylphosphinates **5a + 5b**. According to the general procedure, 3-amino-1-propanol (0.500 g, 6.7×10^{-3} mol) was treated with benzaldehyde (0.711 g, 6.7×10^{-3} mol) and ethyl phenyl phosphinate (1.140 g, 6.7×10^{-3} mol) in 25 mL of toluene (2.050 g, 92.5% after percolation).

5a (less polar, as a colorless liquid, 0.958 g, 43.0%, after column chromatography): IR ν 3386, 1210, 1121, 1033 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.20 (t, 3H, $J = 7.0$ Hz), 1.53–1.62 (m, 1H), 1.64–1.74 (m, 1H), 2.63 (ddd, 1H, $J = 3.8$ Hz, $J = 6.6$ Hz, $J = 10.6$ Hz), 2.75 (ddd, 1H, $J = 3.8$, 8.2, 12.0 Hz), 3.65 (dd, 1H, $J = 4.6$, 6.2 Hz), 3.87–3.98 (m, 2H), 4.10 (d, 1H, $^2J_{HP} = 15.2$ Hz), 7.22–7.65 (m, 10H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ 16.6 (d, $^3J_{CP} = 6.1$ Hz), 30.9, 47.9 (d, $^3J_{CP} = 15.2$ Hz), 61.9 (d, $^2J_{CP} = 7.6$ Hz), 63.8, 64.1 (d, $^1J_{CP} = 106.3$ Hz), 128.2, 128.3, 128.5, 128.6, 128.7, 128.9, 129.0, 132.5, 132.6, 132.8, 132.9, 134.6. ^{31}P ($CDCl_3$, 161.8 MHz) δ 38.7 ppm. MS (FAB) *m/z* 334, 165, 164, 91, 77.

5b (more polar, as a crystalline solid, mp = 67–69°C, 0.466 g, 21%, after column chromatography): IR ν 3382, 1206, 1122, 1026 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.34 (t, 3H, $J = 7.0$ Hz), 1.58–1.67 (m, 1H), 1.72–1.82 (m, 1H), 2.70–2.78 (m, 2H,), 3.29 (br s, 2H), 3.72–3.75 (m, 2H), 3.99 (dq, 1H, $J = 7.2$ Hz), 4.16 (dq, 1H, $J = 7.2$ Hz), 4.2 (d, 1H, $^2J_{HP} = 17.2$ Hz), 7.08–7.49 (m, 10H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ 16.4 (d, $^3J_{CP} = 4.6$ Hz), 30.8, 47.49 (d, $^3J_{CP} = 13.7$ Hz), 61.6 (d, $^2J_{CP} = 6.0$ Hz), 63.3, 63.5 (d, $^1J_{CP} = 106.3$ Hz), 127.7, 127.8 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 132.5, 132.6. ^{31}P NMR ($CDCl_3$, 80.9 MHz), δ 40.5. MS (FAB) *m/z* 334, 165, 164, 91, 77.

Ethyl {(2-Chlorophenyl)[(3-hydroxyproyl)amino]-methyl}phenylphosphinates **6a + 6b**. According to the general procedure, 3-amino-1-propanol (0.500 g, 6.7×10^{-3} mol) was treated with *o*-chlorobenzaldehyde (0.942 g, 6.7×10^{-3} mol) and ethyl phenyl phosphinate (1.140 g, 6.7×10^{-3} mol) in 25 mL of toluene (2.107 g, 86.0%, after percolation).

(S)-Ethyl {(S*)-(2-Chlorophenyl)[(3-hydroxypropyl)amino]methyl}phenylphosphinate*, **6a**. (Less polar, as a crystalline solid, mp = 58–60°C, 0.373 g, 15%, after column chromatography): IR (cm^{-1}) ν 3390, 1215, 1121, 1034 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.12 (t, 3H, $J = 7.0$ Hz), 1.50–1.57 (m, 1H), 1.59–1.68 (m, 1H), 2.54 (ddd, 1H, $J = 4.4$, 7.2, 11.6 Hz), 2.75 (ddd, 1H, $J = 4.4$, 7.4, 12 Hz), 3.04 (br s, 2H), 3.59 (ddd, 2H, $J = 3.2$ Hz, 4.4 Hz, 7.6 Hz), 3.80–3.87 (m, 2H), 4.82 (d, 1H, $^2J_{HP} = 15.2$ Hz), 7.25–7.78 (m, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ 16.5 (d, $^3J_{CP} = 4.6$ Hz), 30.9, 47.3 (d, $^3J_{CP} = 13.7$ Hz), 58.4 (d, $^1J_{CP} = 109.3$ Hz), 61.8 (d, $^2J_{CP} = 6.0$ Hz), 63.3, 127.3, 128.6, 128.7, 129.1, 129.4, 129.6, 132.2, 132.3, 132.8, 135.4 (d, $^2J_{CP} = 6.0$ Hz). ^{31}P NMR ($CDCl_3$, 80.95 MHz),

(R)-Ethyl {(S*)-(2-Chlorophenyl)[(3-hydroxypropyl)amino]methyl}phenylphosphinate* **6b**. (More polar, as a crystalline solid, mp = 97–100°C, 0.236 g, 9.7%, after column chromatography): IR (cm^{-1}) ν 3388, 1214, 1120, 1033 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.37 (t, 3H, $J = 7$ Hz), 1.59–1.68 (m, 1H), 1.75–1.85 (m, 1H), 2.69–2.81(m, 2H), 3.17 (br s, 2H), 3.72–3.81 (m, 2H), 4.02–4.12 (m, 1H), 4.19–4.29 (m, 1H), 4.90 (d, 1H, $^2J_{HP} = 16.8$ Hz), 7.12–7.53 (m, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ 16.8 (d, $^3J_{CP} = 4.5$ Hz), 30.8, 47.5 (d, $^3J_{CP} = 12.1$ Hz), 58.2 (d, $^1J_{CP} = 106.3$ Hz), 62.3 (d, $^2J_{CP} = 6.1$ Hz), 63.5, 127.2, 128.1, 128.3, 129.2, 129.4, 129.5, 132.5 (d, $^1J_{CP} = 9.2$ Hz), 132.7, 135.0 (d, $^2J_{CP} = 7.6$ Hz). ^{31}P NMR ($CDCl_3$, 161.81 MHz), δ 40.0. MS (FAB) *m/z* 370, 368, 369, 200, 199, 198, 125, 77.

Ethyl {(4-Chlorophenyl)[(3-hydroxypropyl)-amino]methyl}phenylphosphinates **7a + 7b**. According to the general procedure, 3-amino-1-propanol (0.500 g, 6.7×10^{-3} mol) was treated with *p*-chlorobenzaldehyde (0.942 g, 6.7×10^{-3} mol) and ethyl phenyl phosphinate (1.140 g, 6.7×10^{-3} mol) in 25 mL of toluene (1.950 g, 79.7% after percolation).

7a (less polar, as a colorless liquid, 0.280 g, 11.5%, after column chromatography): IR ν 3399, 1213, 1122, 1093, 1034 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.23 (t, 3H, $J = 7$ Hz), 1.53–1.62 (m, 1H), 1.63–1.73 (m, 1H), 2.57–2.63 (m, 1H), 2.64–2.72 (m, 1H), 3.01 (br s, 2H), 3.63 (dd, 2H, $J = 5.2$, 5.4 Hz), 3.87–4.05 (m, 2H), 4.07 (d, $^2J_{HP} = 15.6$ Hz), 7.16–7.64 (m, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ 16.5 (d, $^3J_{CP} = 6$ Hz), 31.0, 47.4 (d, $^3J_{CP} = 13.6$ Hz), 61.6 (d, $^2J_{CP} = 6.1$ Hz), 63.2, 63.5 (d, $^1J_{CP} = 107.8$ Hz), 127.8, 128.01, 128.07, 128.1, 128.3, 128.4, 132.3, 132.4, 132.5. ^{31}P NMR ($CDCl_3$, 80.95 MHz), δ 38.1. MS (FAB) *m/z* 370, 369, 368, 200, 199, 198, 125.

7b (more polar, as a colorless liquid, 0.243 g, 10.0%, after column chromatography): IR ν 3404, 1214, 1121, 1092, 1033 (cm^{-1}). ^1H NMR ($CDCl_3$, 400 MHz) δ 1.33 (t, 3H, $J = 7$ Hz), 1.57–1.66 (m, 1H), 1.69–1.79 (m, 1H), 2.69 (dd, 2H, $J = 5.8$, 11.6 Hz), 3.06 (br s, 2H), 3.68–3.71 (m, 2H), 3.94–4.00 (m, 1H), 4.12–4.19 (m, 1H) 4.14 (d, 1H, $^2J_{HP} = 17.2$ Hz), 7.0–7.52 (m, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ 16.4 (d, $^3J_{CP} = 6.1$ Hz), 31.2, 47.1 (d, $^3J_{CP} = 13.6$ Hz), 61.7 (d, $^2J_{CP} = 6.8$ Hz), 62.9, 63.3 (d, $^1J_{CP} = 107$ Hz), 128.1, 128.2, 128.3, 129.7, 129.8, 132.5, 132.6, 133.5, 133.7. ^{31}P NMR ($CDCl_3$, 161.81 MHz), δ 40.4. MS (FAB) *m/z* 370, 369, 368, 200, 299, 298, 125, 77.

Ethyl {[(3-Hydroxyproyl)amino](2-methylphenyl)-methyl}phenylphosphinates **8a + 8b**. According to the general procedure, 3-amino-1-propanol (0.500 g, 6.7×10^{-3} mol) was treated with *o*-tolualdehyde (0.805 g, 6.7×10^{-3} mol) and ethyl phenyl phosphinate (1.140 g, 6.7×10^{-3} mol) in 25 mL of toluene (percolation afforded 2.187 g, 94.7%).

8a (less polar, column chromatography afforded 0.348 g, 15% as a colorless liquid): IR (cm^{-1}) ν 3384, 1212, 1121, 1031. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.16 (t, 3H, $J = 7.2$ Hz), 1.49–1.58 (m, 1H), 1.59–1.68 (m, 1H), 2.22 (s, 3H), 2.54 (ddd, 1H, $J = 4.2$, 7.2, 11.4 Hz), 2.72 (ddd, 1H, $J = 4.0$, 7.9, 11.8 Hz), 2.92 (br s, 2H), 3.60–3.63 (m, 2H), 3.81–3.90 (m, 2H), 4.41 (d, 1H, $^2J_{HP} = 15.2$ Hz), 7.13–7.68 (m, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ 16.5 (d, $^3J_{CP} = 6.0$ Hz), 19.9, 31.0, 47.7 (d, $^3J_{CP} = 15.2$ Hz), 58.6 (d, $^1J_{CP} = 109.3$ Hz), 61.7 (d, $^3J_{CP} = 6.1$ Hz), 63.7, 126.5 (d, $J = 3.0$ Hz), 127.5 (d, $J = 4.6$ Hz), 127.8, 128.5, 128.7, 130.5, 132.4 (d, $^1J_{CP} = 9.1$ Hz), 132.8, 133.2, 137.8 (d, $J = 6.1$ Hz). ^{31}P NMR ($CDCl_3$, 80.95 MHz), δ 38.5. MS (FAB) *m/z* 348, 179, 178, 176, 105, 91.

8b (more polar, column chromatography afforded 0.400 g, 17.3% as a colorless liquid): IR (cm^{-1}) ν 3386, 1215, 1120, 1032. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.35 (t, 3H, $J = 7.2$ Hz), 1.56–1.64 (m, 1H), 1.69–1.79 (m, 1H), 2.16 (s, 3H), 2.67–2.79 (m, 2H), 3.17 (br s, 2H), 3.7 (dd, 2H, $J = 5.2$, 10.4 Hz), 3.93–4.0 (m, 1H), 4.14–4.24 (m, 1H), 4.49 (d, 1H, $^2J_{HP} = 16.8$ Hz), 7.0–7.5 (m, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ 16.7 (d, $^3J_{CP} = 6.1$ Hz), 19.9, 31.0, 47.6 (d, $^3J_{CP} = 13.6$ Hz), 58.77 (d, $^1J_{CP} = 107.8$ Hz), 61.9 (d, $^3J_{CP} = 6.1$ Hz), 63.5, 126.31, 126.34, 127.7, 128.2, 128.3, 130.4, 132.7, 132.8 (d, $^1J_{CP} = 9.1$ Hz), 133.0, 137.6 (d, $^2J_{CP} = 6.1$ Hz). ^{31}P NMR ($CDCl_3$, 80.95 MHz), δ 41.3. MS (FAB) *m/z* 348, 179, 178, 102.

(2S,3R*)-2,3-Diphenyl-1,4,2-oxazaphosphepane 2-oxide* **9**

According to the general procedure, 3-amino-1-propanol (0.250 g, 3.35×10^{-3} mol) was treated with benzaldehyde (0.353 g, 3.35×10^{-3} mol) and ethyl phenyl phosphinate (0.561 g, 6.7×10^{-3} mol) in 25 mL of toluene (24 h reflux). Column chromatography afforded **9** as a crystalline solid (0.133 g, 13.8%), mp = 190–193°C.

IR (cm^{-1}) ν 3309, 1214, 1154, 1122, 1043 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.84 (s, 1H), 193 (dq, 1H, $J = 3.2$, 6.4 Hz), 2.27–2.38 (m, 1H), 2.98 (ddd, 1H, $J = 2.4$, 12.4 Hz), 3.50–3.52 (m, 1H), 3.54–3.56 (m, 1H), 4.34–4.45 (m, 1H), 4.44 (d, 1H, $^2J_{HP} = 14.8$ Hz), 4.68 (q, 1H, $J = 11.3$ Hz), 6.94–7.54 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ 33.1, 52.5, 66.2 (d,$^2J_{CP} = 5.1$ Hz), 68.2 (d, $^1J_{CP} = 97.4$ Hz), 127.3, 127.4, 127.6, 127.7, 127.8, 128.0, 128.3, 128.4, 132.4, 133.0 (d, $^1J_{CP} = 8.6$ Hz), 136.8. ^{31}P NMR ($CDCl_3$, 161.8 MHz), δ 45.4.

3-(2-Methylphenyl)-2-phenyl-1,4,2-oxazaphosphepane 2-oxide **10**

According to the general procedure, 3-amino-1-propanol (0.500 g, 6.7×10^{-3} mol) was treated with *o*-tolualdehyde (0.805 g, 6.7×10^{-3} mol) and ethyl phenyl phosphinate (1.140 g, 6.7×10^{-3} mol) in 25 mL of toluene (24 h reflux). Column chromatography afforded as a colorless liquid (0.265 g, 13%).

IR (cm^{-1}) ν 3434, 3318, 1213, 1124, 1072, 1019 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.75 (s, 3H), 2.19–2.27 (m, 1H), 2.49–2.59 (m, 1H), 2.67 (br s, 2H), 2.98 (ddd, $J = 2.7$, 9.1, 11.2 Hz), 3.54 (ddd, $J = 3.3$, 6.5, 10.6 Hz), 4.13 (d, $^2J_{HP} = 2.8$ Hz), 4.18–4.29 (m, 1H), 4.66–4.73 (m, 1H), 6.85–7.70 (m, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ 19.2, 34.1, 48.2, 60.5 (d, $^1J_{CP} =$ 85 Hz), 67.0 (d, $^2J_{CP} = 6.1$ Hz), 126.3 (d, $J_{CP} = 2.3$ Hz), 127.3 (d, $J_{CP} = 2.2$ Hz), 127.6 (d, $J_{CP} = 12.2$ Hz), 128.0 (d, $J_{CP} = 3.8$ Hz), 129.71, 129.73, 131.3 (d, $^1J_{CP} =$ 9.1 Hz), 131.9 (d, $J_{CP} = 2.3$ Hz), 134.7, 135.1 (d, $J_{CP} = 7.6$ Hz). ^{31}P NMR ($CDCl_3$, 80.95 MHz), δ 41.6. MS (FAB) *m/z* 303, 302, 301 160, 154, 105, 91, 77.

Ethyl (1,3-Oxazinan-3-ylmethyl)-phenylphosphinate **11**

According to the general procedure, 3-amino-1-propanol (0.100 g, 1.3×10^{-3} mol) was treated with formaldehyde (0.079 g, 2.6×10^{-3} mol) and ethyl phenyl phosphinate (0.226 g, 1.3×10^{-3} mol) in 25 mL of toluene (24 h reflux). Column chromatography afforded as a colorless liquid (98:2, CH_2Cl_2: CH_3OH) (0.227 g, 63%).

IR (cm^{-1}) ν 3455, 1211, 1123, 1039 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.30 (t, $J = 7.2$ Hz), 1.60–1.66 (m, 2H), 2.94–3.07 (m, 2H), 3.22 (dd, 1H, $^2J_{HP} = 7.6$, $^2J = 15.6$ Hz), 3.3 (dd, 1H, $^2J_{HP} = 9.6$, $^2J = 15.8$ Hz), 3.82 (dd, 1H, $J = 5.6$, 5.2 Hz), 3.86–3.96 (m, 1H), 4.07–4.17 (m, 1H), 4.20 (d, 1H, $J = 10$ Hz), 4.34 (d, 1H, $J = 10$ Hz), 7.46–7.85 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ 16.5 (d, $^3J_{CP} = 6$ Hz), 21.5, 50.7 (d, $^1J_{CP} = 121.5$ Hz), 51.6 (d, $^3J_{CP} = 6$ Hz), 60.9 (d, $^2J_{CP} = 6.1$), 67.7, 85.8 (d, $^3J_{CP} = 9.1$ Hz), 128.3, 128.4, 131.8, 131.9, 132.2. ^{31}P NMR ($CDCl_3$, 80.95 MHz), δ 39.6. MS (FAB) *m/z* 270, 269, 268, 100, 70, 42.

{[(3-Hydroxypropyl)amino]methyl}phenylphosphinic Acid **12**

To a cold solution of **11** (0.200 g, 7×10^{-4} mol) in anhydrous dichloromethane (0.5 mL) trimethylsilylbromide (0.58 g, 3.78×10^{-3} mol) was added. After stirring the mixture at room temperature for 24 h, the solvent was removed under reduced pressure and water (5 mL) was added to the residue. After 24 h, the water was evaporated under reduced pressure and propylene oxide (3 mL) was added. After stirring the mixture at room temperature for 1 h, the solvents were evaporated and the product was recrystallized from methanol to give **12** as a white solid (0.161 g, yield: 95%, mp = 238–240°C).

IR (KBr) ν 3339, 1625, 1501, 1439, 1358, 1177, 1133, 1076 cm^{-1}. ^1H NMR (D_2O, 400 Hz) δ 1.75–1.81 (m, 2H), 3.09 (dd, 2H, $J = 7.2$ Hz), 3.24 (d, 2H, $J = 10$ Hz), 3.55–3.58 (m, 2H), 7.50–7.74 (m, 5H). ^{13}C (D_2O, 100 MHz) δ 27.3, 46.9 (d, $^1J_{CP} = 92.6$ Hz), 48.1 (d, $^3J_{CP} = 6$ Hz), 59.3, 128.8, 129.0, 131.2, 131.3, 132.3 (d, $J_{CP} = 3.1$ Hz). ^{31}P ($CDCl_3$, 161.8 MHz) δ 20.6 ppm. MS (FAB) *m/z* 231, 230, 229, 155, 138, 88, 76.

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[13] Failla, S.; Finocchiaro, P.; Consiglio, G. A. Heteroat Chem 2000, 493, 11.
[14] *(S*)-ethyl{(S*)-(2-chlorophenyl)[(3-hydroxypropyl)amino]methyl}phenylphosphinate*: Crystal data for $C_{18}H_{23}ClNO_3P$ (**6a**), $M_r = 367.79$ gmol^{-1}, $0.26 \times 0.29 \times 0.63$ mm^3, monoclinic, space group $P2(1)/c$, $a = 10.6614(10)$, $b = 22.584(2)$, $c = 7.9990(8)$ Å, $\alpha = 90$, $\beta = 96.1180(10)$, $\gamma = 90°$, $V = 1915.0(3)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.276$ g/cm^3, $\theta = 25.00°$, 3373 independent reflections, $R_1 = 0.0456$ for 3373 reflections with $I > 2\ \sigma(I)$ and $wR_2 = 0.1245$ for all data, 290 parameters. Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-258573.

(R)-ethyl {(S*)-(2-chlorophenyl)[(3-hydroxypropyl)amino]methyl}phenylphosphinate*: Crystal data for $C_{18}H_{23}ClNO_3P$ (**6b**), $M_r = 367.79$ gmol^{-1}, $0.28 \times 0.32 \times 0.54$ mm^3, triclinic, space group $P\bar{1}$, $a = 8.3128(13)$, $b = 9.6458(15)$, $c = 11.6712(19)$ Å, $\alpha = 77.028(3)$, $\beta = 84.668(3)$, $\gamma = 86.752(3)°$, $V = 907.4(2)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.346$ g/cm^3, $\theta = 25.00°$, 2921 independent reflections, $R_1 = 0.0341$ for 2921 reflections with $I > 2\ \sigma(I)$ and $wR_2 = 0.0893$ for all data, 226 parameters. Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-58572.
[15] *(2S*,3R*)-2,3-Diphenyl-1,4,2-oxaphosphepane 2-oxide*: Crystal data for $C_{16}H_{18}NO_2P$ (**9**), $M_r = 287.28$ gmol^{-1}, $0.18 \times 0.21 \times 0.40$ mm^3, orthorhombic, space group $P2(1)2(1)2(1)$, $a = 5.9766(9)$, $b = 8.7777(13)$, $c = 28.317(4)$ Å, $\alpha = 90$, $\beta = 90$, $\gamma = 90°$, $V = 1485.6(4)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.284$ g/cm^3, $\theta = 25.00°$, 2616 independent reflections, $R_1 = 0.0309$ for 2616 reflections with $I > 2\ \sigma(I)$ and $wR_2 = 0.0686$ for all data, 185 parameters. Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-258574.