Stereospecific intramolecular cyclization of diethyl (*R*)-2-(*N*-benzylidene)-aminobutyl phosphite into (3*R*,5*R*)-2-ethoxy-2-oxo-3-phenyl-5-ethyl-1,4,2-oxazaphosphorinane in the presence of hydrogen chloride

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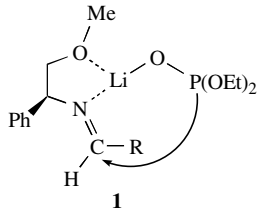
Diethyl (*R*)-2-(*N*-benzylidene)aminobutyl phosphite, formed in reaction of (*R*)-(+)-2-(*N*-benzylidene)aminobutan-1-ol with diethyl chlorophosphite, undergoes stereospecific intramolecular cyclization to give P-epimeric (3*R*,5*R*)-2-ethoxy-2-oxo-3-phenyl-5-ethyl-1,4,2-oxazaphosphorinanes as final reaction products.

Interest in the stereoselective synthesis of α-aminophosphonates is mainly determined by the necessity of obtaining α-aminophosphonic acids in a nonracemic form. These latter, which are structural analogues of α-amino carboxylic acids, attract special attention due to their interesting biological properties.[1,2] Among the known syntheses of nonracemic α-aminophosphonates, stereoselective addition reactions of organic P^{III} compounds with reagents containing the C=N bond are most significant. However, only an intermolecular version of this addition reaction was considered previously. Smith and co-workers[3] considered the formation of a complex and/or chelated intermediate **1** to be the starting points leading to high diastereoselectivity of the addition reaction of lithium diethyl phosphite to aldimines, derived from ethers of (*R*)-(–)-2-phenylglycinol and aldehydes.



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We considered the integration of the P^{III} atom and the imino group linked by a covalent bond in one molecule in the presence of a source of chirality in the reacting system, which could result in cyclization by the intramolecular diastereoselective interaction of the above reaction centres. To study this type of cyclization and its stereochemistry, diethyl (*R*)-2-(*N*-benzylidene)aminobutyl phosphite **2** was chosen as a model system. A six-membered 1,4,2-oxazaphosphorinane-type heterocyclic compound was expected as a reaction product. The compounds of this type can be easily transformed into free α-amino phosphonic acids.[4]

For the preparation of phosphite **2**, we studied the reaction of (*R*)-(+)-2-(*N*-benzylidene)aminobutan-1-ol **3** with diethyl chlorophosphite. According to the ^{31}P NMR data of the crude reaction mixture, the process† performed in a chloroform solution resulted in two phosphorus containing products **A** (upfield δ_P) and **B** (downfield δ_P) at the **A**:**B** ratio equal to 2:1. Both reaction products were isolated by column chromatography as stable colourless crystalline compounds. The X-ray data‡ suggest that products **A** and **B** present two stereoisomers of (3*R*,5*R*)-2-ethoxy-2-oxo-3-phenyl-5-ethyl-1,4,2-oxazaphosphorinane **6** (Figure 1), epimeric at the P atom.

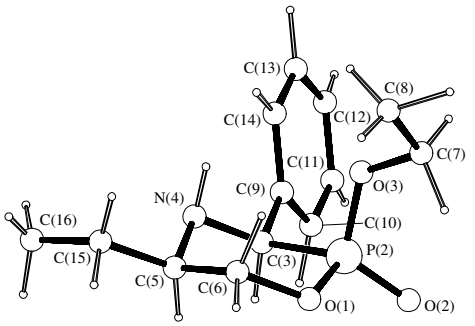
The most probable way of formation of P-epimeric 1,4,2-oxazaphophorinanes **6** in the reaction of imine **3** and diethyl chlorophosphite is presented in Scheme 1. Phosphite **2** formed at the first stage of reaction gives immonium salt **4** with HCl formed in the course of the reaction. Under the above reaction conditions, salt **4** undergoes intramolecular cyclization, which resulted in the formation of quasiphosphonium salt **5**. The latter transformed into products **6** (**A** and **B**) according to the second step of the Arbuzov-type reaction. This reaction pathway is confirmed by the data given below. The reaction of imine **3** with diethyl chlorophosphite in the presence of Et_3N in benzene or diethyl ether gave diethyl (*R*)-2-(*N*-benzylidene)aminobutyl phosphite **2**, which was identified by spectral data.§ The reaction performed in the same solvents but with no external acceptor of

† To a solution of 1.30 g (8 mmol) of diethyl chlorophosphite in 10 ml of $CHCl_3$, a solution of 1.47 g (8 mmol) of **3** {$[\alpha]_D^{20}$ +28.0° (*c* 13.2, MeOH), **3** prepared from (*R*)-(–)-2-aminobutan-2-ol with $[\alpha]_D^{20}$ –7.0° (neat) and benzaldehyde according to the known procedure[6]} in 10 ml of $CHCl_3$ in a dry argon atmosphere was added dropwise with cooling (0 °C) and stirring. After stirring for 10 min at this temperature, the reaction mixture was warmed slowly to room temperature and additionally stirred for 1 h. Then, it was evaporated to dryness in a vacuum. The residue was purified by column chromatography (silica gel, toluene–acetonitrile, 4:1). 1,4,2-Oxazaphosphorinanes **6** were isolated in 76% overall yield (1.70 g) as individual epimers **A** and **B** and as a mixture.

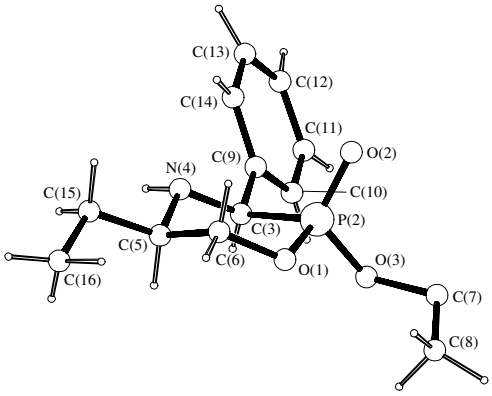
Epimer **6A**: mp 123 °C, R_f 0.66 (Silufol, toluene–MeCN, 1:1), $[\alpha]_D^{20}$ +83.2° (*c* 2.2, EtOH). ^{1}H NMR (Bruker WM-250, 250 MHz, CD_3CN) δ: 0.94 (t, 3H, MeCC, $^3J_{HH}$ 7.5 Hz), 1.07 (t, 3H, MeCO, $^3J_{HH}$ 7.1 Hz), 1.40 (m, 2H, CCH_2C), 3.05 (m, 1H, C^5–H^{ax}), 3.67 (m, 1H, MeC*H*O), 3.84 (m, 1H, MeC*H*′O), 4.02 (ddd, 1H, C^6–H^{ax}, $^3J_{HP}$ 1.7 Hz, $^3J_{H–H^{eq}}$ –10.7, $^3J_{H–H^{ax}}$ 10.7 Hz), 4.23 (ddd, 1H, C^6–H^{eq}, $^3J_{HP}$ 18.9 Hz, $^2J_{HH^{ax}}$ –10.7 Hz, $^3J_{H–H^{ax}}$ 3.0 Hz), 4.28 (d, 1H, HCP, $^3J_{HP}$ –12.7 Hz), 7.34–7.49 (m, 5H, C_6H_5). ^{31}P NMR (Bruker MSL-400, 162 MHz, CD_3CN) δ: 14.7. Found (%): C, 58.22; H, 7.63; N, 4.95; P, 11.78. Calc. for $C_{13}H_{20}NO_3P$ (%): C, 57.97; H, 7.49; N, 5.20; P, 11.51.

Epimer **6B**: mp 97–98 °C, R_f 0.63 (Silufol, toluene–MeCN, 1:1), $[\alpha]_D^{20}$ +50.6° (*c* 1.1, EtOH). ^{1}H NMR, δ: 0.92 (t, 3H, MeCC, $^3J_{HH}$ 7.5 Hz), 1.31 (t, 3H, MeCO, $^3J_{HH}$ 7.0 Hz), 1.52 (m, 2H, CCH_2C), 2.97 (m, 1H, C^5–H^{ax}), 4.08–4.28 (m, 3H, MeCH_2O, C^6–H^{eq}), 4.40 (d, 1H, HCP, $^3J_{HP}$ –16.0 Hz), 4.43 (ddd, 1H, C^6–H^{ax}, $^3J_{HP}$ 3.3 Hz, $^2J_{HP^{eq}}$ –11.5 Hz, $^3J_{H–H^{ax}}$ 11.5 Hz), 7.35–7.62 (m, 5H, C_6H_5). ^{31}P NMR, δ: 16.6. Found (%): C, 58.15; H, 7.21; N, 4.92; P, 11.85.

‡ *Crystallographic data for* **6A** *and* **6B**: at +20 °C crystals of $C_{13}H_{20}NO_3P$ (**6A**) are orthorhombic, space group $P2_12_12_1$, a = 5.829(3) Å, b = = 9.958(5) Å, c = 23.73(1) Å, V = 1378(1) Å^3, Z = 4, M = 269.28, d_{calc} = = 1.30 g cm^{-3}, μ(Cu) = 17.79 cm^{-1}, F(000) = 576; crystals of $C_{13}H_{20}NO_3P$ (**6B**) are orthorhombic, space group $P2_12_12_1$, a = 9.178(6) Å, b = = 9.457(4) Å, c = 16.282(4) Å, V = 1413(1) Å^3, Z = 4, M = 269.28, d_{calc} = = 1.27 g cm^{-3}, μ(Cu) = 17.34 cm^{-1}, F(000) = 576. Intensities of 1682 reflections for **6A** and 2757 reflections for **6B** were measured with an Enraf Nonius CAD-4 diffractometer at 20 °C [λ(CuKα) radiation, $\omega/2\theta$ scan technique, $2\theta_{max}$ < 148°] of which 1611 and 2188 were with $I > 3\sigma$ for **6A** and **6B**, respectively. The structures were determined by direct methods and difference Fourier syntheses using the SIR program[7] and the MolEN package.[8] All non-hydrogen atoms were refined anisotropically. Atom C(7) of the ethoxy group of **6B** is disordered by two positions with occupancies of 0.6 and 0.4. Hydrogen atoms, excluding hydrogens of the disordered ethoxy group of **6B**, located in ΔF maps, were refined isotropically. The absolute structures of crystals and the absolute configurations of molecules **6A** and **6B** were found from the Hamilton test ratio[9] with a probability of 95%. The final agreement factors are R = 0.046, R_w = 0.061 based on 1597 reflections with $F^2 \geq 3\sigma$ for **6A** and R = 0.038, R_w = 0.048 based on 2042 reflections with $F^2 \geq 3\sigma$ for **6B**. Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2001. Any request to the CCDC for data should quote the full literature citation and the reference number 1135/102.



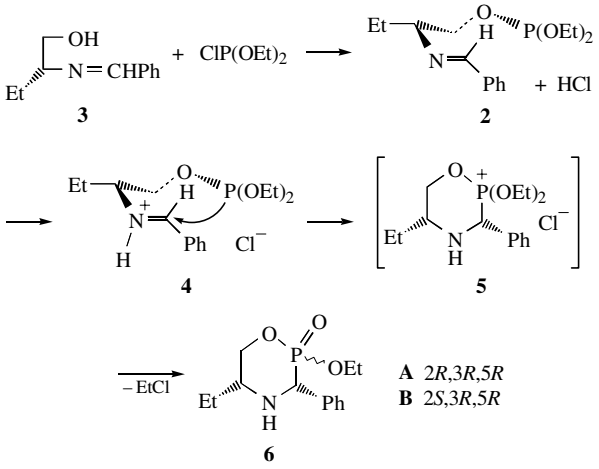
Epimer **A**



Epimer **B**

Figure 1 Molecular structures of epimers **6A** and **6B**. Selected bond lengths (Å) for **6A**: P(2)–O(1) 1.589(2), P(2)–O(2) 1.471(2), P(2)–O(3) 1.571(2), P(2)–C(3) 1.826(2), N(4)–C(3) 1.467(3), N(4)–C(5) 1.470(3), C(5)–C(6) 1.525(4), O(1)–C(6) 1.459(4), C(3)–C(9) 1.509(3), C(5)–C(15) 1.534(4); selected bond angles (°): O(1)–P(2)–O(2) 108.8(1), O(1)–P(2)–O(3) 107.0(1), O(1)–P(2)–C(3) 103.4(1), O(2)–P(2)–O(3) 116.8(1), O(2)–P(2)–C(3) 117.9(1), O(3)–P(2)–C(3) 101.67(9), P(2)–O(1)–C(6) 119.0(2), P(2)–O(3)–C(7) 123.1(2), P(2)–C(3)–N(4) 111.5(1), P(2)–C(3)–C(9) 110.9(1), C(3)–N(4)–C(5) 112.8(2), N(4)–C(3)–C(9) 113.9(2), N(4)–C(5)–C(6) 112.6(2), N(4)–C(5)–C(15) 110.2(2), O(1)–C(6)–C(5) 111.5(2), C(6)–C(5)–C(15) 109.1(2).
Selected bond lengths (Å) for **6B**: P(2)–O(1) 1.585(2), P(2)–O(2) 1.449(2), P(2)–O(3) 1.559(2), P(2)–C(3) 1.810(2), N(4)–C(3) 1.459(3), N(4)–C(5) 1.467(3), C(5)–C(6) 1.500(4), O(1)–C(6) 1.446(3), C(3)–C(9) 1.513(3), C(5)–C(15) 1.508(3); selected bond angles (°): O(1)–P(2)–O(2) 114.3(1), O(1)–P(2)–O(3) 102.71(9), O(1)–P(2)–C(3) 103.06(9), O(2)–P(2)–O(3) 115.4(1), O(2)–P(2)–C(3) 115.3(1), O(3)–P(2)–C(3) 104.4(1), P(2)–O(1)–C(6) 116.8(1), P(2)–O(3)–C(7) 121.1(3), P(2)–C(3)–N(4) 107.1(2), P(2)–C(3)–C(9) 112.5(2), C(3)–N(4)–C(5) 114.9(2), N(4)–C(3)–C(9) 112.5(2), N(4)–C(5)–C(6) 108.1(2), N(4)–C(5)–C(15) 109.5(2), O(1)–C(6)–C(5) 110.4(2), C(6)–C(5)–C(15) 111.7(2).

HCl resulted in the precipitation of unstable immonium salt **4**. In the IR spectrum of imine **2** the C=N band (ν 1645 cm^{-1}) is shifted towards higher frequencies (ν 1690 cm^{-1}),[5] assigned to the immonium group of **4**. Furthermore, in a chloroform solution, salt **4** converted rapidly into an epimeric mixture of **6A** and **6B** in the same **A**:**B** ratio as in the reaction illustrated in Scheme 1.



Scheme 1

The same *R* configuration at the C^3-atom of heterocyclic epimers **6A** and **6B** illustrates that the step of immonium salt **4** intermolecular cyclization into quasiphosphonium salt **5** *via* nucleophilic attack of an electrophilic C atom on the imonium group by a P^{III} atom results in 1,4,2-oxazaphosphorinane-type heterocycle formation, which is a stereospecific process involving only one of two diastereotopic faces (*re*) of the imine double bond. In this case, the most probable stereocontrolled factors are the *trans*-geometry of the C=N imonium fragment and the more preferable equatorial position of the Et group at the C^5-atom and the Ph group at the C^3-atom in the transition six-membered cycle at the step of cyclization of imonium salt **4**.

Thus, it is reasonable to assume that the interaction between chiral β-iminoalcohols and monohalophosphites in the absence of a base is promising for the stereoselective synthesis of 1,4,2-oxazaphosphorinanes as precursors of nonracemic (enantiopure) α-aminophosphonic acids. This approach based on the intramolecular stereocontrolled version of an addition reaction of P^{III} derivatives to compounds containing the C=N bond can be considered as a new strategy for the stereoselective synthesis of α-aminophosphonates.

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§ *Spectroscopic data for* **2**. ^{1}H NMR ($CDCl_3$) δ: 0.82 (t, 3H, MeCC, $^3J_{HH}$ 7.5 Hz), 1.26 (t, 6H, 2MeCO, $^3J_{HH}$ 7.0 Hz), 1.58 (m, 2H, CH_2CN), 3.20 (m, 1H, CH–N), 3.55–4.28 (m, 6H, 3CH_2O), 7.10–7.70 (m, 5H, Ph), 8.19 (s, 1H, CH=N). ^{31}P NMR ($CDCl_3$) δ: 138.9. IR (UR-20, neat, ν/cm^{-1}): 1035, 1045 (P–O–C), 1645 (C=N).