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Stereoselective Synthesis of Enantiopure Cyclic α-Aminophosphonic Acids: Direct Observation of Inversion at Phosphorus in Phosphonate Ester Silyldealkylation by Bromotrimethylsilane

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ABSTRACT: *The paper describes a simple, direct synthesis of enantiopure cyclic α-aminophosphonic acids on the basis of silyldealkylation and followed by hydrolysis of the parent diastereoisomeric cyclic 1,4,2-oxazaphosphorines, which have been obtained by intramolecular stereospecific nucleophilic addition of phosphites to imines. In this approach, the high diastereoselectivity of the stereocontrolling penultimate step is preserved by conversion of the intermediate ester to the final phosphonic acid under very mild, nonracemizing conditions.* © 2008 Wiley Periodicals, Inc. Heteroatom Chem 19:575–582, 2008; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20480

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INTRODUCTION

α-Aminophosphonic acids constitute an important class of biologically active compounds with wide-ranging applications in medicine and agriculture [1] and also have potential as enantioselective organocatalysts [2]. Accordingly, the synthesis of chiral α-aminophosphonic acids is of continuing [3] interest. α-Aminophosphonates may be regarded as peptidomimetic transition state analogs of natural amino acid amides (or esters), undergoing enzymatic hydrolysis or similar nucleophilic addition-elimination cleavage chemistry [4–7]. Tetrahedral phosphorus is considered to be isosteric and isopolar with the peptide carboxy carbon after attack by the nucleophile. In contrast to labile phosphate derivatives, α-aminophosphonates are stabile in vivo, owing to the relatively metabolism-resistant phosphonate P—C bond.

Most of previous methods devised for the synthesis of aminophosphonates [2–7] entail acyclic compounds. Thus, isostructural analogues of many natural and unnatural amino acids have been prepared. In contrast, the synthesis of enantiopure

cyclic α-aminophosphonic acids in which the entire aminophosphonate fragment is incorporated into a ring has been little explored, although the resulting increased conformational rigidity could potentially afford a "constrained conformation" effect [8], enhancing binding to a targeted enzyme active site.

Recently, we reported a new, efficient way to synthesize cyclic aminophosphonate esters by the reaction of dialkyl chlorophosphites with β-aldiminoalcohols [9–11]. The reaction was shown to proceed by intramolecular cyclization, leading to the formation of 1,4,2-oxazaphosphorine derivatives. When starting imines are derived from asymmetric β-aminoalcohols, a new chiral center at C-3 of the oxazaphosphorine ring is generated with very high stereoselectivity (more than 98%). The products were unequal mixtures of two diastereomeric phosphonate esters, differing only in configuration at phosphorus.

These diastereomeric ester products derived from enantiopure β-aldiminoalcohols in principle should afford enantiopure cyclic aminophosphonic acids even when chirality at the phosphorus atom in the oxazaphosphorine ring is lost due to hydrolysis, provided that the conditions are sufficiently mild to avoid racemization elsewhere in the molecule. The silyldealkylation reaction [12,13], with bromotrimethylsilane (BTMS) followed by hydrolysis in water, aqueous buffer, or an alcohol, is a facile, very mild route from phosphonate esters to the corresponding acids.

RESULTS AND DISCUSSION

To evaluate this route to cyclic aminophosphonic acids, we began with achiral *N*-benzylidene-2-amino-2-methylpropanol-1 (**1**), then tried chiral racemic (±)-(**2**) and enantiopure (R)-(+)-*N*-benzylidene-2-aminobutanol-1 (**3**), as well as racemic (±)-*N*-*p*-nitrobenzylidene-2-aminobutanol-1 (**4**) and achiral *N*-*p*-chlorobenzylidene-2-amino-2-methylpropanol-1 (**5**), with diethyl chlorophosphite being chosen as phosphorus-containing reaction component (Scheme 1).

In the general procedure used, the starting materials in dry chloroform at 0–20°C were first reacted to form the 2-ethoxy-2-oxo-1,4,2-oxazaphosphorine diastereomers **6–9**. The reaction progress and phosphonate ester diastereomer ratios were determined by ^{31}P and ^{1}H NMR. In all cases, we obtained the two diastereomers **A** and **B** (Scheme 1). The predominant diastereomer was identified, based on our previous work, as that one exhibiting ^{1}H NMR signals at relatively higher field [9–11] (isomer having a cis-oriented alkoxy group, relative to the aryl substituent at the ring C-3 atom). After the solvent was removed in vacuo, the residue was dissolved in methylene chloride and about a twofold excess of BTMS was added. The mixture was stirred for 3 h, then treated with methanol.

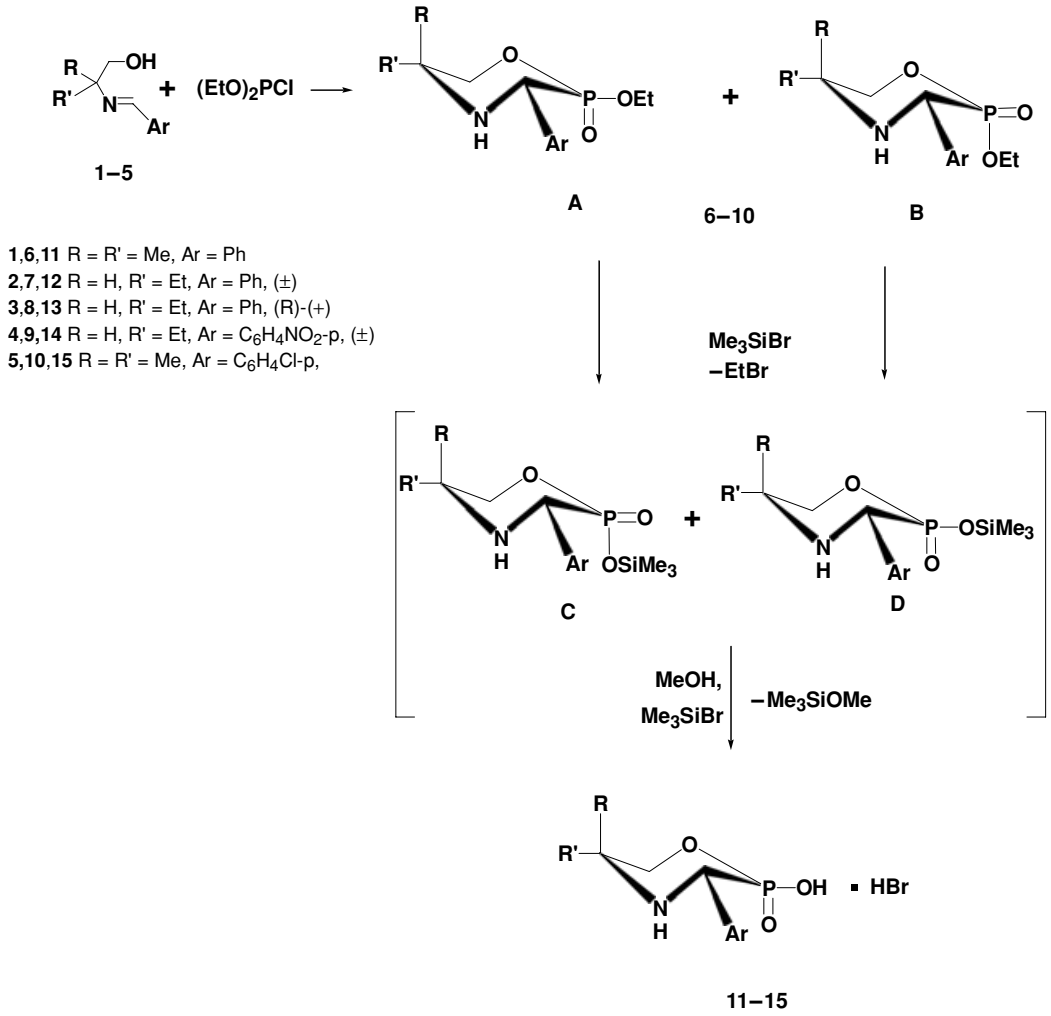
Intriguingly, the intensities of the low and high field diastereomer signals reversed upon addition of BTMS to form the intermediate trimethylsilyl phosphonate ester. Normally, replacement of the ethyl group by trimethylsilyl would result in an upfield shift of 8–9 ppm in the ^{31}P NMR resonance [12], thus both resonances should have been displaced by about the same amount, with their relative intensities maintained. For example, the ^{31}P NMR spectra of the crude products from reaction of **3** with diethyl chlorophosphite in chloroform revealed the presence of two phosphorus-containing products, **A** (higher field signal, δ_P 14.7 ppm) and **B** (lower field signal, δ_P 16.6 ppm) with **A**:**B** ratio ~2:1. Previously, we established by structural studies that products **A** and **B** are diastereomers of (3*R*,5*R*)-2-ethoxy-2-oxo-3-phenyl-5-ethyl-1,4,2-oxazaphosphorine **7**, epimeric at the phosphorus atom [10].

After adding BTMS and aging the reaction mixture for 2.5 h, these signals were replaced by two new signals—a minor peak at high field (δ_P 0.4 ppm) and a major peak at low field (δ_P 3.6 ppm). The ratio of ~2:1 was preserved, but the intensities of the high and low field signals were reversed. Most probably, inversion of configuration at the phosphorus atom took place upon the silylation reaction (Scheme 2).

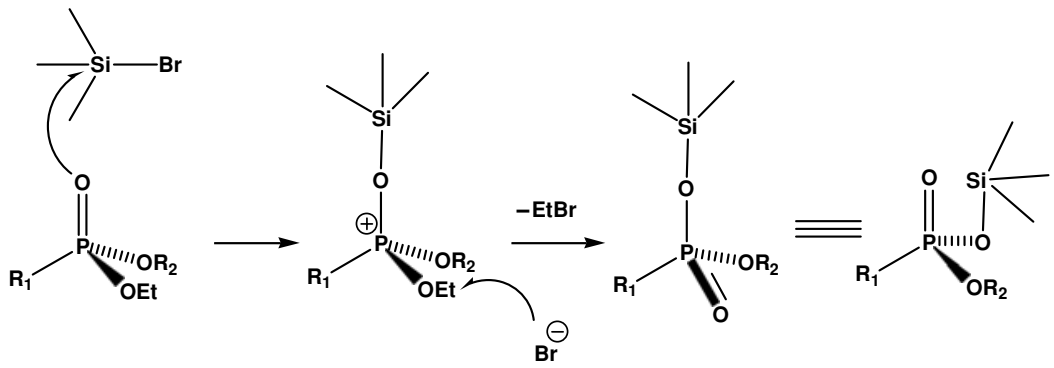
As a result, we obtained two new epimeric silyl esters of the 1,4,2-oxazaphosphorine with inverted configuration at P atom—minor highfield **C** and major lowfield **D** isomers (Scheme 1).

It is not necessary to remove the solvent from the reaction mixture before adding BTMS. The same results are obtained when this reagent is added immediately after the reaction of the iminoalcohol with diethylchlorophosphite is completed. The subsequent addition of excess of methanol to the reaction mixture gives rise to a solid product in good yield, identified as the hydrobromide of 2-hydroxy-1,4,2-oxazaphosphorine **11–15**. As in the silylation reaction, an excess BTMS was used and the addition of methanol resulted in the formation of hydrogen bromide, which was bound by cyclic aminophosphonic acids. The overall synthesis is outlined in Scheme 1.

A diastereoselective synthesis of similar 1,4,2-oxazaphosphorines starting from (*R*)-(–)-phenylglycinol via the reaction of corresponding oxazolidines with trimethyl phosphite in the presence of $SnCl_4$ has been reported by Royer and coworkers [14]. The reaction proceeds with high to



SCHEME 1



SCHEME 2

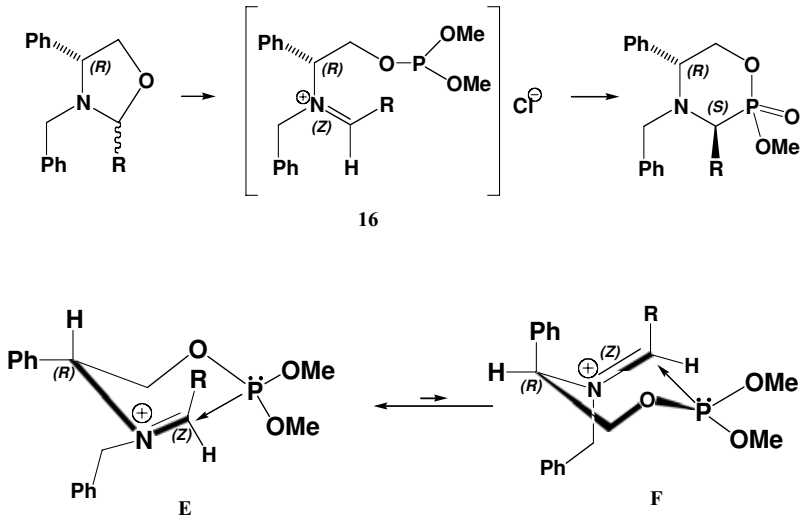
total diastereoselectivity, leading to predominant formation of the phosphorine derivative having an *S* configuration at the ring C3 atom. These authors considered that the Lewis acid (Sn IV) mediates opening of the oxazolidine ring to generate a much more reactive iminium salt. They proposed formation of the (*Z*)-iminium salt **16** resulting from simultaneous transesterification of

trimethyl phosphite and the opening of oxazolidine (Scheme 3). The geometry of the double bond of this intermediate depends on the configuration of the starting oxazolidine. The major oxazolidine has the *N*-benzyl group trans relative to both the phenyl and alkyl groups at C2 and C4. The formation of the iminium salt occurred through a trans-antiperiplanar process to give the (*Z*)-salt **14**. In the minor component, the nitrogen lone-pair configuration underwent rapid inversion, and both iminium geometries could be formed a priori. Diastereofacial selectivity to give the *S* isomer as the major product could be explained by a less constrained transition state **E** compared with **F**, which has all substituents in axial positions. It should be noted that the absolute *S* configuration of the new chiral center at C3 was established by an indirect method, namely by measurement of the rotation angle of well-known free amino acids obtained from phosphorines [14].

In our case, a mirror process is realized with the formation of the *R* configuration of the new chiral center at C3 position in compounds **8**, the absolute (*R*)-(–)-configuration of the chiral center of the parent aminoalcohol being the same. Earlier, we established the absolute configuration by single crystal X-ray diffraction [9]. Stereoisomers of compound **8**, purified by column chromatography, are obtained as stable, colorless crystals. It was found that products **A** and **B** are two diastereoisomeric forms of (3*R*,5*R*)-2-ethoxy-2-oxo-3-phenyl-5-ethyl-1,4,2-oxazaphosphorine, distinguished from each other only by the P atom configuration. The major isomer has the *R* configuration at the P atom, and minor isomer, the *S* configuration. In both diastereomers, the configuration at C3 is *R* (Fig. 1).

A probable mechanism for the formation of the P-epimeric 1,4,2-oxazaphophorines **6–10** in the reaction of the corresponding imino alcohols with diethyl chlorophosphite (Scheme 4) consists of the initial nucleophilic substitution of the P(III) chlorine atom by the iminoalkoxy group to form of phosphite **17** and HCl, with subsequent formation of the iminium salt **18**. Salt **18** then undergoes cyclization to give the quasi-phosphonium salt **19**, which is transformed into the products **6–10** (**A** and **B**). The preferred formation of the epimers having an axial alkoxy group can be explained by the greater exposure of the equatorial alkoxy group in intermediate **19** to nucleophilic attack by chlorine anion. This reaction pathway is supported by NMR spectral data, which confirm the formation of the two proposed intermediates: phosphite **17** and iminium salt **18** [9].

When optically pure chiral (*R*)-(+)-iminoalcohols **3** is used in this reaction, the same *R* configuration at the heterocycle C3-atom of epimers **8A** and **8B** is retained, showing that the intramolecular cyclization of the iminium salt **18** to give the quasiphosphonium salt **19** via the nucleophilic attack by the phosphite P atom on the iminium carbon is a stereospecific process, involving only one of the two diastereotopic faces (*re*) of the imine double bond. In this case, the possible factors influencing the stereochemistry are the trans-geometry of the C=N iminium fragment, the more favorable equatorial position of C5-atom



SCHEME 3

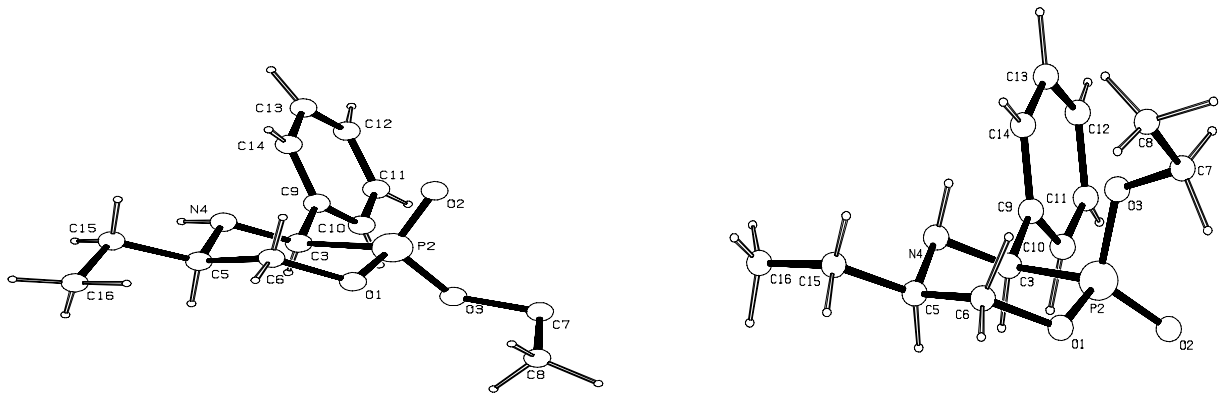
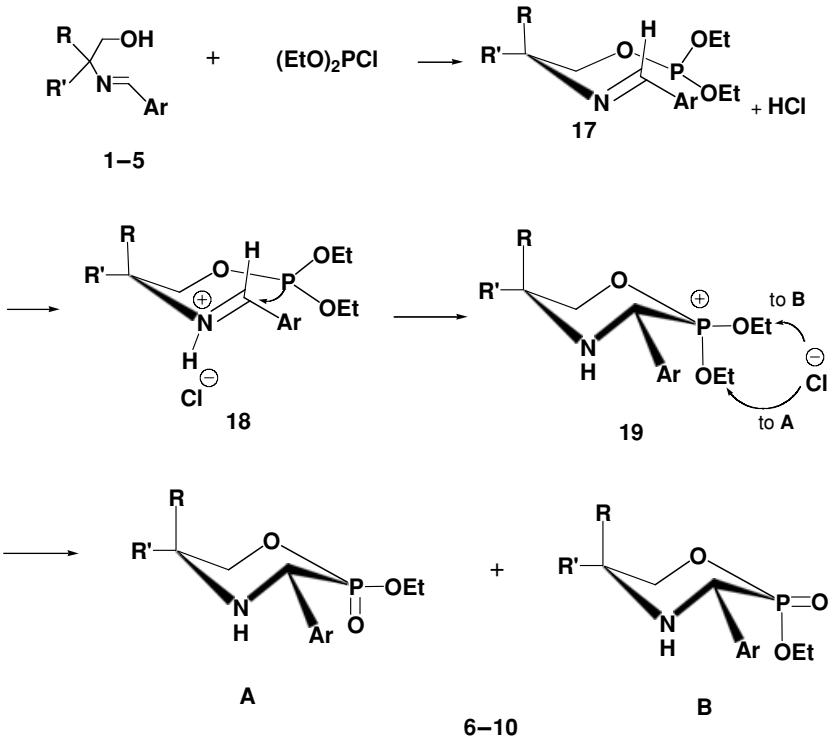


FIGURE 1 Molecular structure of epimers **8A** and **8B** [9].



SCHEME 4

the Et group and the preequatorial position of the C3-atom Ph group in the six-membered ring forming in the transition state (Scheme 5).

This stereodeterminant (the most bulky groups are equatorial) is possible only in the absence of substituents at the nitrogen atom, and appears to be the key feature that distinguishes the stereochemistry of our reactions from those studied by Royer and coworkers. Subsequent attack by the chlorine anion on the two phosphorus ester alkoxy groups in intermediate **19** is only partially stereoselective, leading to an unequal mixture of both phosphorus epimers **A** and **B**.

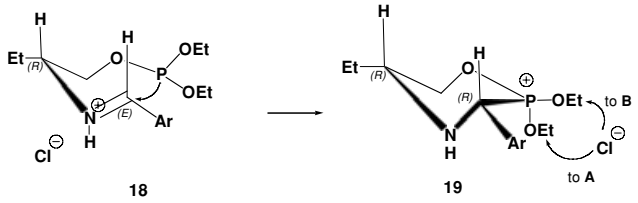
CONCLUSION

Thus, the method described in this paper and that of Royer and coworkers [14] are complementary to each other, providing α-aminophosphonic acid enantiomers and their 1,4,2-oxazaphosphorine heterocycle precursors with a choice of configuration.

EXPERIMENTAL

Materials and Spectroscopy

All syntheses were performed under an atmosphere of dry argon. All solvents and starting



SCHEME 5

reagents were distilled immediately prior to use. Commercial (R)-(–)-2-aminobutanol-1 was obtained from Lancaster, (95%). (R)-(+)-*N*-benzylidene-2-aminobutanol-1 (**3**), derived from benzaldehyde and (R)-(–)-2-aminobutanol-1, had $[\alpha]_D^{20} = +36.6$ (C, 13.25, CH_3OH), (lit. +39.3). (±)-*N*-benzylidene-2-aminobutanol-1 (**2**), (±)-*N*-*p*-nitrobenzylidene-2-aminobutanol-1 (**4**), and *N*-*p*-chlorobenzylidene-2-aminopropanol-1 (**5**) derived from benzaldehyde, substituted benzaldehyde, and (±)-2-aminobutanol and 2-amino-2-methylpropanol-1, respectively, were prepared by literature procedures [15–17].

$^{31}P\{1H\}$ NMR spectra were recorded on a CXP 100 or Bruker MSL-400 spectrometer with 85% H_3PO_4 as the external standard. ^1H NMR spectra were measured on an AVANCE 600 instrument. The ^{13}C NMR spectra were recorded on a Bruker MSL 400. All chemical shifts are ppm downfield from the reference peak, and *J* values are in hertz. IR spectra were measured on a Vector 22 Fourier Transform IR spectrometer (Bruker). Optical rotations were measured using a Perkin–Elmer 341 polarimeter.

General Procedure for the Reaction of Diethyl Chlorophosphite with β-Aldiminoalcohols **1–5**

To a stirred solution of the chlorophosphite (10–20 mmol) in dry chloroform (10 mL), a solution of equimolar amount of **1–5** in chloroform (5–10 mL) was added dropwise at 10–15°C. Stirring was continued for 2 h. The solvent was evaporated in vacuo, and the oily residue was analyzed by NMR and elemental analysis.

2-Ethoxy-2-oxo-3-phenyl-5,5-dimethyl-1,4,2-oxazaphosphorine **6**. Yield 90.3%, ^{31}P NMR (CXP 100, $CDCl_3$) δp: 12.6, 17.9, 4.3:1 ratio. Found (%): C 58.28; H 7.40; N 5.40; P 11.19. Calcd. for $C_{13}H_{20}NO_3P$ (%):C, 57.98; H, 7.49; N, 5.20; P, 11.50 ^1H NMR (AVANCE 600, 600 MHz, $CDCl_3$) δ: 1.44, 1.40 (two s, 6H, $(CH_3)_2C$), 1.06, 1.31 (two t, 3H, CH_3CO, $^3J_{HH} = 7.0$ Hz), 3.85–4.12 (m, 4H, C^6-H^{ax}, C^6-H^{eq}, CH_2O), 4.53, 4.33 (two d, 1H, HCP, $^2J_{HP} = 12.6$ and 10.6 Hz), 7.24–7.84 (m, 5H, C_6H_5).

Racemic 2-Ethoxy-2-oxo-3-phenyl-5-ethyl-1,4,2-oxazaphosphorine **7**. Yield 95.0%, ^{31}P NMR (CXP 100, CDCl3) δp: 13.2, 17.3, 3.5:1 ratio. Found (%): C 57.48; H 7.18; N 5.36; P 11.20. Calcd. for $C_{13}H_{20}NO_3P$ (%): C, 57.98; H, 7.49; N, 5.20; P, 11.50. ^1H NMR (AVANCE 600, 600 MHz, CD_3OD) δ: 1.02, 1,21 (two t, 3H, CH_3CC, $^3J_{HH} = 7.3$ and 7.0 Hz), 1.16, 1.36 (two t, 3H, CH_3CO, $^3J_{HH} = 7.0$ and 7.0 Hz), 1.50–1.60 (m, 2H, CCH_2C), 3.21, 3.29 (two m, 1H, C^5-H^{ax}), 3.77–4.43 (eight m, 4H, $CH_3C\underline{H}O$, $CH_3C\underline{H}'O$, C^6-H^{ax}, C^6-H^{eq}), 4.46, 4.47 (two d, 1H, HCP, $^2J_{HP} = 12.1$ and 11.5 Hz), 7.35–7.56 (m, 5H, C_6H_5).

(3R,5R)-2-Ethoxy-2-oxo-3-phenyl-5-ethyl-1,4,2-oxazaphosphorine **8**. Yield 93.2%, $[\alpha]_D^{20} = +61.0$ (c, 3.11, CH_3OH), ^{31}P NMR (CXP 100, $CDCl_3$) δp: 13.4, 17.5, 3.5:1 ratio. Found (%): C 57.91; H 7.28; N 5.25; P 11.45. Calcd for $C_{13}H_{20}NO_3P$ (%): C, 57.98; H, 7.49; N, 5.20; P, 11.50. ^1H NMR (AVANCE 600, 600 MHz, CD_3CN) δ: 0.97, 1,18 (two t, 3H, CH_3CC, $^3J_{HH} = 7.5$ and 7.0 Hz), 1.10, 1.32 (two t, 3H, CH_3CO, $^3J_{HH} = 7.0$ and 7.0 Hz), 1.41–1.49 (m, 2H, CCH_2C), 3.06–3.13 (m, 1H, C^5-H^{ax}), 3.66–4.29 (eight m, 4H, $CH_3C\underline{H}O$, $CH_3C\underline{H}'O$, C^6-H^{ax}, C^6-H^{eq}), 4.31, (two d, 1H, HCP, $^2J_{HP} = 13.0$ and 11.5 Hz), 7.33–7.52 (m, 5H, C_6H_5).

Racemic 2-Ethoxy-2-oxo-3-(4′-nitrophenyl)-5-ethyl-1,4,2-oxazaphosphorine **9**. ^{31}P NMR (CXP 100, $CHCl_3$ + $CDCl_3$) δp: 12.0, 16.2, and 5.5:1 ratio. BTMS and then methanol was added to the reaction mixture without evaporation of solvent, the reaction being monitored by NMR.

Racemic 2-Ethoxy-2-oxo-3-(4′-chlorophenyl)-5-ethyl-1,4,2-oxazaphosphorine **10**. ^{31}P NMR (CXP 100, $CHCl_3$ + $CDCl_3$) δp: 12.0, 16.2, 5.5:1 ratio. BTMS and methanol were added as mentioned above with NMR monitoring.

General Procedure for the Reaction of 2-Ethoxy-2-oxo-3-aryl-1,4,2-oxazaphosphorines **6–10** *with BTMS and then Methanol*

To a stirred solution of the 1,4,2-oxazaphosphorine (**6–10)** (6 mmol) in dry dichloromethane (40 mL) at room temperature, BTMS (14 mmol) was added. Stirring was continued for 2.5 h. After evaporation of solvent, the solid residue was washed with 15 mL dry methanol, leaving a white or yellow powder upon drying.

2-Hydroxy-2-oxo-3-phenyl-5,5-dimethyl-1,4,2-oxazaphosphorine Hydrobromide **11**. mp 229°C, yield 94.7%. ^{31}P NMR (CXP 100 , D_2O, K_2CO_3)

δp: 11.28. ^{1}H NMR (AVANCE 600, 600 MHz, D_2O, K_2CO_3) δ: 1.12, 1.35 (two s, 6H, CH_3C, CH'_3C), 3.93 (dd, 1H, C^6-H, $^3J_{HP} = 16.8$, $^2J_{HH} = -11.8$), 4.22 (dd, 1H, C^6-H′, $^3J_{HP} = 2.6$, $^2J_{HH} = -11.8$), 4.23, (d, 1H, HCP, $^2J_{HP} = 13.1$ Hz), 7.35–7.43 (m, 5H, C_6H_5). ^{13}C NMR (D_2O, K_2CO_3) δ: 21.71, 25.68 (two s, CH_3); 52.25 (d, CN, $^3J_{CP} = 2.9$); 55.14 (d, CP, $J_{CP} = 130$); 78.89 (d, COP, $^2J_{CP} = 5.8$); 128.28–137.43 (m, C_{ar}). IR (Nujol, ν, cm^{-1}): 1044,1085 (P—O—C), 1227 (P=O), 2227–2725 (NH). Found (%): C 40.91; H 5.24; Br 24.80; N 4.35; P 9.53. Calcd. for $C_{11}H_{17}BrNO_3P$ (%): C, 41.01; H, 5.32; Br, 24.80; N, 4.35; P, 9.62.

Racemic 2-Hydroxy-2-oxo-3-phenyl-5-ethyl-1,4,2-oxazaphosphorine Hydrobromide **12**. mp 298–300°C, yield 91.0%. ^{31}P NMR (CXP 100 , D_2O, K_2CO_3) δp: 13.23 ^{1}H NMR, (AVANCE 600, 600 MHz, D_2O, K_2CO_3) δ: 0.92 (t, 3H, CH_3CC, $^3J_{HH} = 7.4$ Hz), 1.39–1.49 (m, 2H, CCH_2C), 3.00 (ddd, 1H, C^5-H, $^3J_{HH} = 3.1$, $^3J_{HH} = 11.2$), 4.06 (ddd, 1H, C^6-H, $^3J_{HP} = 2.3$, $^2J_{HH} = -11.2$), 4.20 (ddd, 1H, C^6-H′, $^3J_{HP} = 17.8$, $^2J_{HH} = -11.8$), 4.19, (d, 1H, HCP, $^2J_{HP} = 13.0$), 7.34–7.40 (m, 5H, C_6H_5). ^{13}C NMR (D_2O, K_2CO_3) δ: 10.66 (s, CH_3); 24.37 (s, CH_2); 58.47 (br. s, CN); 61,57 (d, CP, $J_{CP} = 132$); 76.24 (d, COP, $^2J_{CP} = 5.9$); 128.22–137.37 (m, C_{ar}). IR (Nujol, ν (cm^{-1})): 1047, 1085 (P—O—C), 1226 (P=O), 2211–2725 (NH). Found (%): C 40.90; H 5.20; Br 24.60; N 4.31; P 9.60. Calcd for $C_{11}H_{17}BrNO_3P$ (%):C, 41.01; H, 5.32; Br, 24.80; N, 4.35; P, 9.62.

(R,R)-(+)-2-Hydroxy-2-oxo-3-phenyl-5-ethyl-1,4,2-oxazaphosphorine Hydrobromide **13**. mp 299°C, yield 91.5%. ^{31}P NMR (CXP 100, D_2O, K_2CO_3) δp: 13.23. ^{1}H NMR, (AVANCE 600, 600 MHz, D_2O, K_2CO_3) δ: 0.94 (t, 3H, CH_3CC, $^3J_{HH} = 7.4$ Hz), 1.39–1.49 (m, 2H, CCH_2C), 3.03 (ddd, 1H, C^5-H, $^3J_{HH}$ 3.1, $^3J_{HH}$ 11.2), 4.07 (ddd, 1H, C^6-H, $^3J_{HP} = 2.3$, $^2J_{HH} = -11.2$), 4.21 (ddd, 1H, C^6-H′, $^3J_{HP} = 17.8$, $^2J_{HH} = -11.8$), 4.23, (d, 1H, HCP, $^2J_{HP} = 13.0$), 7.34–7.40 (m, 5H, C_6H_5). Found (%): C 40.89; H 5.24; Br 24.80; N 4.34; P 9.60. Calcd. for $C_{11}H_{17}BrNO_3P$ (%):C, 41.01; H, 5.32; Br, 24.80; N, 4.35; P, 9.62.

Racemic 2-Hydroxy-2-oxo-3-(p-nitrophenyl)-5-ethyl-1,4,2-oxazaphosphorine Hydrobromide **14**. mp 310°C, yield 95.5%. ^{31}P NMR (CXP 100, $CDCl_3$) δp: 11.28. ^{1}H NMR (AVANCE 600, 600 MHz, D_2O, K_2CO_3) δ: 0.94 (t, 3H, CH_3CC, $^3J_{HH} = 7.4$ Hz), 1.39–1.51 (m, 2H, CCH_2C), 3.03 (ddd, 1H, C^5-H, $^3J_{HH} = 3.1$, $^3J_{HH} = 11.2$), 4.07 (ddd, 1H, C^6-H, $^3J_{HP} = 2.3$, $^2J_{HH} = -11.2$), 4.21 (ddd, 1H, C^6-H′, $^3J_{HP} = 17.8$, $^2J_{HH} = -11.8$), 4.23, (d, 1H, HCP, $^2J_{HP} = 13.0$), 7.61, 8.23 (two m, 4H, $C_6H_4NO_2$). ^{13}C NMR, (D_2O, K_2CO_3) δ : 10.61 (s, CH_3); 24.32 (s, CH_2); 58.49 (br. s, CN); 60,89 (d, CP, $J_{CP} = 129.0$); 74.23 (d, COP, $^2J_{CP} = 4.3$); 124.33–147.45 (m, C_{ar}). IR (Nujol, ν (cm^{-1})): 1047, 1085 (P—O—C), 1226 (P=O), 2210–2700 (NH). Found (%): C 35.94; H 4.31; Br 21.74; N 7.60; P 8.43. Calcd. for $C_{11}H_{16}BrN_2O_5P$ (%): C, 35.99; H, 4.39; Br, 21.76; N, 7.63; P, 8.44.

Racemic 2-Hydroxy-2-oxo-3-(p-chlorophenyl)-5,5-dimethyl-1,4,2-oxazaphosphorine Hydrobromide **15**. mp 301–302°C, yield 96.7%. ^{31}P NMR (CXP 100, $CDCl_3$) δp: 11.86. ^{1}H NMR (AVANCE 600, 600 MHz, D_2O, K_2CO_3) δ: 1.09, 1.32 (two s, 6H, CH_3C, CH'_3C), 3.89 (dd, 1H, C^6-H, $^3J_{HP} = 12.0$, $^2J_{HH} = -11.8$), 4.22 (dd, 1H, C^6-H′, $^3J_{HP} = 2.4$, $^2J_{HH} = -11.8$), 4.23, (d, 1H, HCP, $^2J_{HP} = 13.1$), 7.36, 7.41 (two d 4H, C_6H_4Cl). ^{13}C NMR (D_2O, K_2CO_3) δ: 21.42, 25,36 (two s, CH_3); 52.20 (d, CN, $^3J_{CP} = 4.4$); 54.50 (d, CP, $J_{CP} = 129.0$); 78.73 (d, COP, $^2J_{CP} = 5.8$); 129.15–135.84 (m, C_{ar}). IR (Nujol, ν, (cm^{-1})): 1038, 1089 (P—O—C), 1228 (P=O), 2240–2727 (NH). Found (%): C 37.00; H 4.47; Cl 9.90; Br 22.40; N 3.92; P 8.60. Calcd. for $C_{11}H_{16}BrClNO_3P$ (%): C, 37.05; H, 4.52; Br, 22.41; Cl, 9.94; N, 3.93; P, 8.69.

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