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NMR and X-ray crystallographic studies of axial and equatorial 2-ethoxy-2-oxo-1,4,2-oxazaphosphinane

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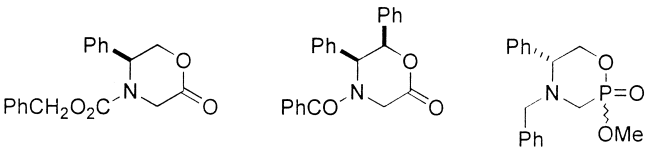
Abstract—Condensation of (*S*)-(*N*-benzyl)-phenylglycinol with formaldehyde in the presence of diethylphosphite afforded hydroxy-aminophosphonate (*S*)-**3**, which upon treatment with KH yielded a 97:3 mixture of the interesting, phosphorus-containing 2-ethoxy-2-oxo-1,4,2-oxazaphosphinanes (2*S*,5*S*)-**1** and (2*R*,5*S*)-**1**. Suitable crystals of both diastereomers were used in X-ray crystallographic studies that permitted unequivocal configurational assignment, as well as examination of the consequences of $n_O \rightarrow \sigma^*_{P-O}$ stereoelectronic interactions on structural properties.

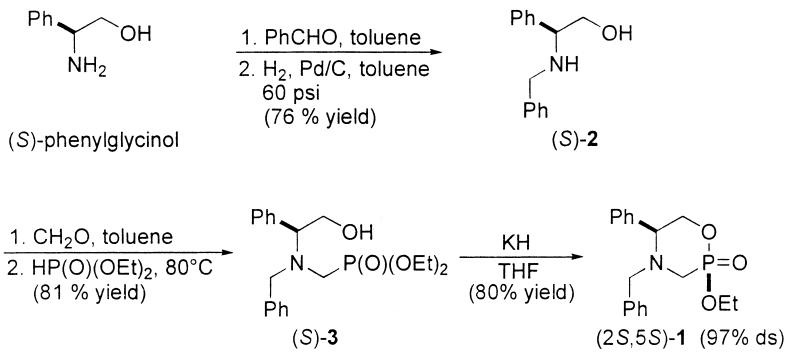
1. Introduction

Some years ago, Dellaria, Williams, and co-workers[1] developed chiral glycine derivatives **A** and **B** as convenient precursors in the enantioselective synthesis of α-substituted α-amino acids. Inspired by this work, and motivated by the large range of biological activities presented by the analogous α-phosphonic acids,[2,3] Royer et al. recently reported the preparation of oxazaphosphinane derivative **C**.[4] Nevertheless, compounds **C** were obtained as a 4:1 diastereomeric mixture of epimers at phosphorus, that was not separated into the pure epimers.



A **B** **C**

In this paper, we describe a highly diastereoselective synthetic procedure for the preparation of enantiopure (2*S*,5*S*)-4-benzyl-2-ethoxy-2-oxo-5-phenyl-1,4,2-oxaza-phosphinane [(2*S*,5*S*)-**1**] from (*S*)-phenylglycinol (Scheme 1).



Scheme 1.

Keywords: phosphorus heterocycles; diastereoselection; NMR; stereoelectronic effects.

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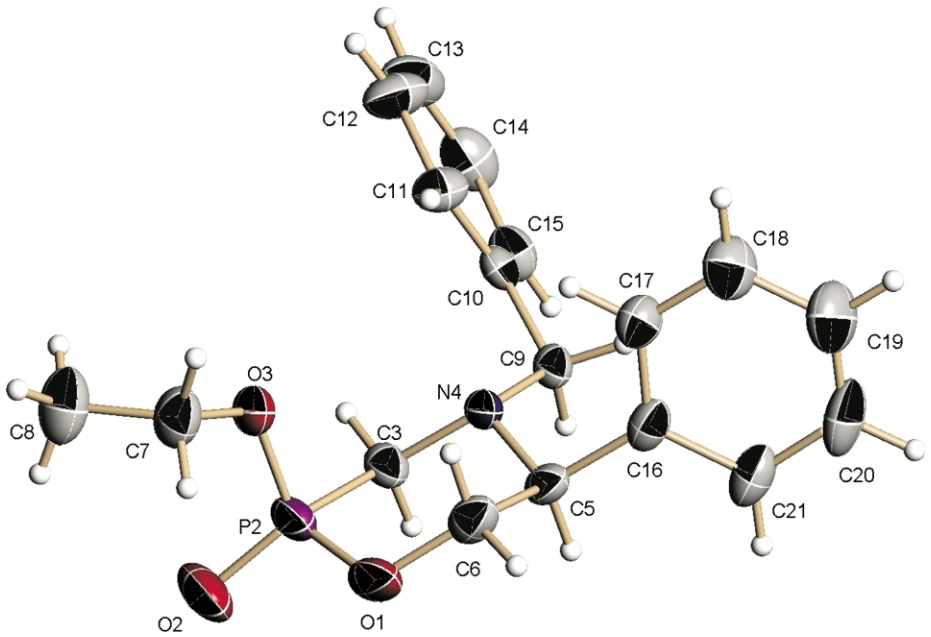


Figure 1. X-Ray cystallographic structure and solid-state conformation of (2*S*,5*S*)-4-benzyl-2-ethoxy-2-oxo-5-phenyl-1,4,2-oxazaphosphinane, (2*S*,5*S*)-**1**.[9]

In addition, isolation of the pure (2*R*,5*S*) epimer permitted comparison of ^{1}H, ^{13}C, and ^{31}P NMR data of both isomers. Finally, suitable crystals of both (2*S*,5*S*)-**1** and (2*R*,5*S*)-**1** were subjected to X-ray crystallographic analysis. This study not only secured the assignment of configuration based on infrared and NMR data, but afforded relevant information on the stereoelectronic interactions that may account for the increased stability of (2*S*,5*S*)-**1** (axial *P*-ethoxy group).

2. Results and discussion

2.1. Preparation of oxazaphosphinane 2-oxides (2*S*,5*S*)-1 and (2*R*,5*S*)-1

N-Benzylation of (*S*)-phenylglycinol was achieved by condensation with benzaldehyde followed by palladium-catalyzed hydrogenation.[5] *N*-Benzyl-(*S*)-phenylglycinol, (*S*)-**2**, was then condensed with formaldehyde (toluene

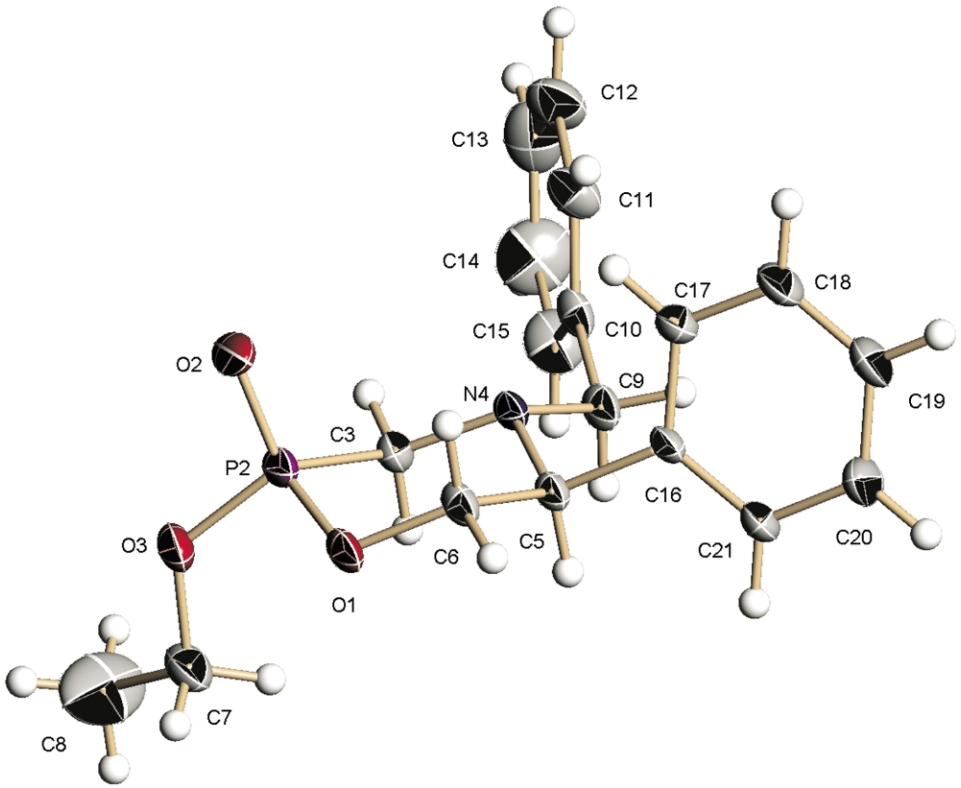


Figure 2. X-Ray crystallographic structure and solid-state conformation of (2*R*,5*S*)-4-benzyl-2-ethoxy-2-oxo-5-phenyl-1,4,2-oxazaphosphinane, (2*R*,5*S*)-**1**.[9]

solvent) and the resulting imminium salt was immediately treated with diethyl phosphite to afford Mannich product (*S*)-**3** in 81% isolated yield.[6]

Treatment of carbinol (*S*)-**3** with KH in THF solution afforded in good yield and high diastereoselectivity the cyclization products 1,4,2-oxazaphosphinanes (2*S*,5*S*)-**1** and (2*R*,5*S*)-**1**, in a 97:3 ratio (Scheme 1). Separation of these diastereomeric phosphorus-containing heterocycles was feasible by means of flash column chromatography, and unequivocal assignment of configuration was achieved by X-ray diffraction structural determination.

That the 97:3 ratio of cyclized derivatives (2*S*,5*S*)-**1** and (2*R*,5*S*)-**1** is the result of kinetic rather than thermodynamic control is inferred by the fact that treatment of either diastereomer with KH in THF for two hours and at −75°C (i.e. the same conditions employed for the cyclization reaction) afforded no epimerized product.

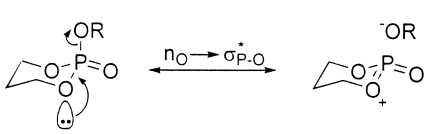
The crystallographic data of (2*S*,5*S*)-**1** and (2*R*,5*S*)-**1** were also of significant interest with regard the possible manifestation of stereoelectronic interactions in O–P=O and O–P–OEt segments.[7,8] Furthermore, the availability of both diastereomeric oxazaphosphinanes in pure form permitted evaluation of the spectroscopic criteria that are usually examined for the configurational assignment at phosphorus.[8]

2.2. X-Ray crystallographic structural analysis of (2*S*,5*S*)-1 and (2*R*,5*S*)-1

Figs. 1 and 2 present the solid-state conformations that were determined by X-ray diffraction analysis of suitable crystals of (2*S*,5*S*)-**1** and (2*R*,5*S*)-**1**, respectively.

Salient features in the crystallographic structures (Figs. 1 and 2) are the chair conformation of the six-membered heterocyclic rings and the anchoring effect of the phenyl substituent at C(5),[10,11] that is reflected in an axial or equatorial orientation of the P=O phosphoryl group in (2*R*,5*S*)-**1** and (2*S*,5*S*)-**1**, respectively. Of course, since the absolute configuration at C(5) is (*S*), then determination of the relative configuration at phosphorus establishes the absolute configuration of this center of chirality as well.

X-Ray crystallography has proved to be a powerful tool to reveal the effect of substituent orientation on phosphorus in 1,3,2-dioxaphosphorinanes on critical bond lengths and angles about phosphorus.[12] In particular, hyperconjugative stereoelectronic $n_O \rightarrow \sigma^*_{P-OEt}$ interaction is expected to be reflected in longer P–OEt bond length when the ethoxy group is axial, relative to equatorial P–OEt. The double bond–no bond canonical structure that results from $n_O \rightarrow \sigma^*_{P-OEt}$ hyperconjugation (Scheme 2) is also consistent with the shorter O_{ring}–P bond that is usually observed in the



Scheme 2.

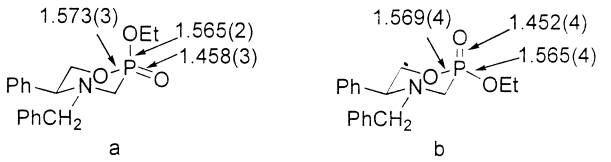
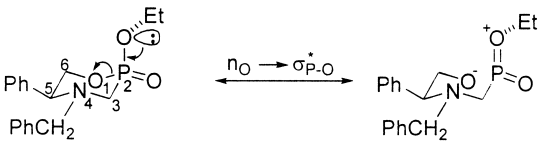


Figure 3. P–O bond lengths Å in diastereomeric (a) (2*S*,5*S*)-**1** and (b) (2*R*,5*S*)-**1**.

isomer presenting the axial P–OR substituent (Scheme 2).[8,12–14]

Unexpectedly, all three relevant P–O bond lengths present in diastereomeric (2*S*,5*S*)-**1** and (2*R*,5*S*)-**1** are identical, within the experimental margin of error (Fig. 3).

We initially considered the possibility that a dominant *exo* anomeric interaction[13] in (2*S*,5*S*)-**1** relative to (2*R*,5*S*)-**1** could be responsible for elongation of the endocyclic P–O bond in the former, as consequence of $n_{OEt} \rightarrow \sigma^*_{P-O(1)}$ hyperconjugation (Eq. (1)).



(1)

Nevertheless, examination of the X-ray crystallographic structures (Figs. 1 and 2) helps discard this hypothesis, since it is the O–Et bond in (2*S*,5*S*)-**1** rather than the lone pair at oxygen that is more closely antiperiplanar to P–O(1): τ=140.8° (Fig. 4(a)). By contrast, one of the lone electron pairs at oxygen in the equatorial O–Et isomer (2*R*,5*S*)-**1** can be located at τ=170.7°, i.e. an almost ideal orientation for the anticipated $n_{OEt} \rightarrow \sigma^*_{P-O(1)}$ stereoelectronic interaction (Fig. 4(b)).

It can be appreciated in Fig. 4, that one of the oxygen lone pairs in (2*S*,2*S*)-**1** (axial P–OEt) should be nearly eclipsed with the long P–O(1) endocyclic bond (estimated dihedral angle between the exocyclic sp^3-hybridized lone pair and the endocyclic P–O(1) bond is equal to 20.8°). It could be argued that *syn*-periplanar $n_{OEt} \rightarrow \sigma^*_{P-O(1)}$ hyperconjugation in the nearly *syn* arrangement leads to the observed lengthening in the acceptor orbital.[13] (Eq. (2)), counterbalancing the normal

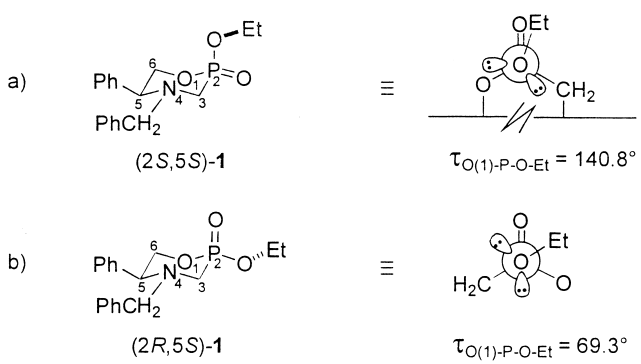
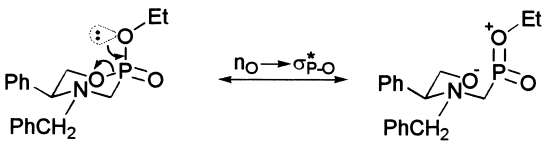


Figure 4. Dihedral angles for the O(1)–P–O–Et segments in epimeric oxazaphosphinanes (2*S*,2*S*)-**1** and (2*R*,2*S*)-**1**, as determined from the X-ray crystallographic structures (Figs. 1 and 2).

antiperiplanar $n_{O(1)} \rightarrow \sigma^*_{P-OEt}$ hyperconjugative interaction.



(2)

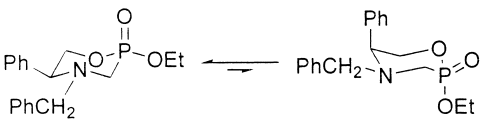
2.3. Infrared and multinuclear NMR analysis of (2*S*,5*S*)-1 and (2*R*,5*S*)-1

The most useful criteria for assigning configuration at phosphorus in individual diastereomers of 1,3,2-dioxaphosphorinanes include infrared frequencies for the P═O stretch and relative ^{31}P chemical shifts.[8] For the P═O stretch one finds ν(P═O_{eq})>ν(P═O_{ax}),[15] and this trend is also evident in diastereomeric (2*S*,5*S*)-**1** with ν=1261 cm^{-1} (equatorial phosphoryl), and (2*R*,5*S*)-**1** with ν=1225 and 1256 cm^{-1} (axial phosphoryl).[16]

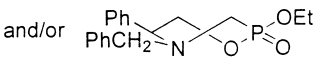
With regard ^{31}P NMR chemical shifts, an extensive list of data for 1,3,2-diheterophosphorinanes has been compiled in Ref. 17, showing that $\delta\,^{31}$P(P═O_{ax})>$\delta\,^{31}$P(P═O_{eq}).[17] This trend is also found in epimeric 2-oxo-1,4,2-oxazaphosphinane (2*S*,5*S*)-**1** and (2*R*,5*S*)-**1**, where $\delta\,^{31}$P(P═O_{ax})=20.3 ppm and $\delta\,^{31}$P(P═O_{eq})=19.4 ppm.

Finally, a remarkable similarity in ^{1}H and ^{13}C NMR data for (2*S*,5*S*)-**1** and (2*R*,5*S*)-**1** is evident. (Figs. 5 and 6). As noted by Royer and co-workers,[4] perhaps the most distinctive feature for the proton NMR spectra is the smaller $^3J_{P/H(6ax)}$ (2.5 vs. 7.2 Hz) and larger $^3J_{P/H(6eq)}$ (21.9 vs. 17.4 Hz) coupling constants in the major (2*S*,5*S*) isomer.

A salient observation from Fig. 5 is that, whereas $^3J_{anti}$ for H(6) in (2*S*,5*S*)-**1**, i.e. axial P–OEt isomer is a normal 11.1 Hz, in the equatorial (2*R*,5*S*)-**1** compound is only 8.4 Hz. This suggest a possible conformational equilibrium in the latter, with appreciable amounts of either an inverted chair (axial P–OEt and axial phenyl group) or a twist-boat conformation (Eq. (3)).



(3)



Comparison of the ^{13}C NMR data for (2*S*,5*S*)-**1** and (2*R*,5*S*)-**1** (Fig. 6) indicates an absence of the γ-*gauche* upfield shift[18] at C(3) in the latter isomer. This finding, together with evidence of a deformed chair in the X-ray crystallographic structure of (2*S*,5*S*)-**1** (Fig. 2; for example, the ring torsion angle N(4)–C(3)–P(2)–O(1)=52.9(4)° in (2*R*,5*S*)-**1** is significantly larger than $\tau_{N(4)-C(3)-P(2)-O(1)}$=46.8(2)° for (2*S*,5*S*)-**1**). Thus it is apparent that the absence of the $n_{O(1)} \rightarrow \sigma^*_{P-OEt}$ anomeric effect in chair-shaped (2*R*,5*S*)-**1** causes a destabilization,

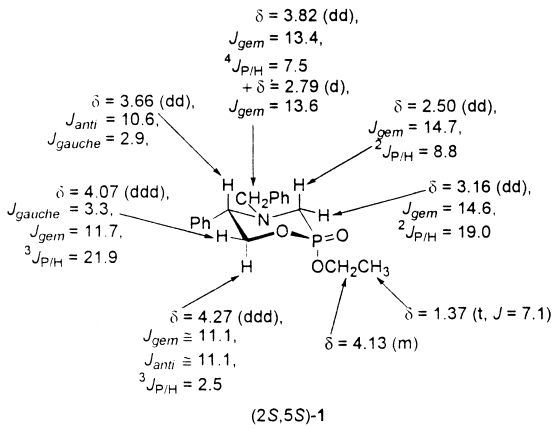


Figure 5. Relevant ^{1}H NMR chemical shifts (ppm) and coupling contants (Hz) in (2*S*,5*S*)-**1** and (2*R*,5*S*)-**1**, at 400 MHz.

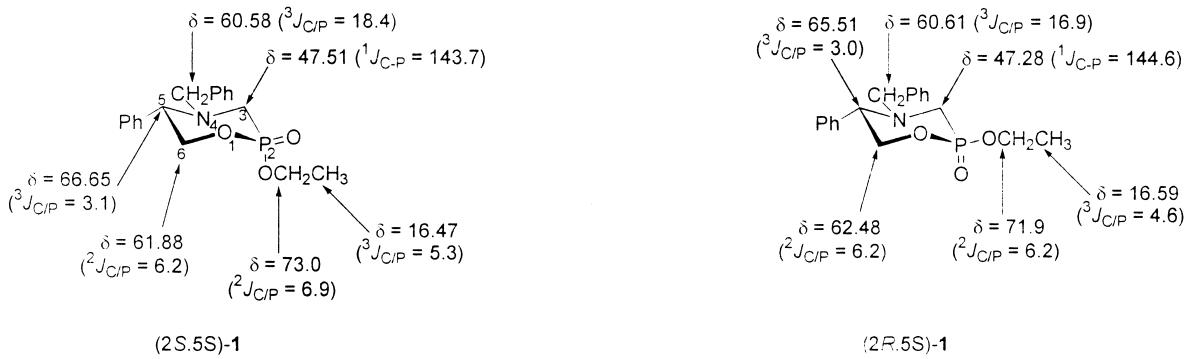


Figure 6. Relevant ^{13}C NMR chemical shifts (ppm) and coupling contants (Hz) in (2*S*,5*S*)-**1** and (2*R*,5*S*)-**1**, at 100 MHz.

which pushes the ring in the direction of a twist-boat conformation.

3. Concluding remarks

As evidenced by Royer's observations,[4] the method of synthesis presented in this report should be applicable when other aldehydes are employed in place of formaldehyde, providing ready access to alkylated analogs of phosphonic acids. Furthermore, given the availability of both isomers of **1**, it should be possible to find conditions to deprotonate and alkylate either isomer to gain access to the analogs noted above. We are currently pursuing these objectives.

4. Experimental

4.1. General

Flasks, stirring bars, and hypodermic needles used for the generation and reactions of organolithiums were dried for about 12 h at 120°C. Anhydrous THF was obtained by distillation from benzophenone ketyl. The butyllithium employed was titrated according to the method of Juaristi et al. (4-biphenylmethanol indicator).[19] TLC, F_{254} silica gel plates; detection by UV light or iodine vapor. Flash column chromatography: silica gel (230–400 mesh). All melting points are uncorrected. ^{1}H NMR spectra: JEOL FX-90Q (90 MHz), JEOL GSX-270 (270 MHz), and JEOL Eclipse-400 (400 MHz) spectrometers. ^{13}C NMR spectra: JEOL FX-90Q (22.5 MHz), JEOL GSX-270 (67.8 MHz), and JEOL Eclipse-400 (100 MHz) spectrometers. Optical rotations were measured in a Perkin–Elmer Model 241 polarimeter, using the sodium D-line (589 nm). Elemental analyses were performed by Galbraith Laboratories, Inc., TN. The purity of new compounds, for which elemental analyses are not provided, was judged to be >97%, as evidenced by ^{1}H and ^{13}C NMR spectra.

4.1.1. (*S*)-2-(Benzylamino)-2-phenylethanol, (*S*)-2. (*S*)-Phenylglycinol (1.9 g, 13.8 mmol) was placed in a 50-mL three-neck round-bottom flask fitted with a magnetic stirbar, a Dean–Stark trap, and a reflux condenser. Toluene (20 mL) and 1.46 g (13.7 mmol) of benzaldehyde were added to the flask, and the reaction mixture was heated to reflux for 30 min and then allowed to cool to room temperature. The resulting imine mixture was immediately treated with 0.31 g of 10% palladium on charcoal and shaken in a Parr apparatus during 2.5 h under 60 psi of hydrogen pressure. After removal of the catalyst by filtration over celite and evaporation of the solvent, the crude product was recrystallized from methylene chloride–hexane (1:9) to give 2.4 g (76% yield) of the desired product as a white solid: mp 86–87°C (lit.[4] mp 88°C). $[\alpha]_D^{28}$=+83.2 (*c*=1.6, EtOH) lit.[4] $[\alpha]_D$=−82.5 (*c*=1, $CHCl_3$) for the (*R*) enantiomer.

4.1.2. {[Benzyl-(2-hydroxy-1*S*-phenyl-ethyl)-amino]-methyl}-phosphonic acid diethyl ester, (*S*)-3. *N*-Benzylated (*S*)-phenylglycinol, (*S*)-**2**, (2.29 g, 10.0 mmol) was placed in a 50-mL round-bottom flask and dissolved in 25 mL of toluene before the addition of 0.82 mL of an aqueous 37% solution of formaldehyde (0.03 g, 10 mmol). The flask was fitted with a Dean–Stark trap and the reaction mixture was heated to reflux for 30 min with removal of water. The flask was allowed to cool to ambient temperature before the addition of 1.39 g (10 mmol) of diethyl phosphite, and the reaction mixture was heated to 80°C for 4 h. The solvent was removed in a rotary evaporator and the residue was purified by flash chromatography (ethyl acetate–hexane, 8:2→6:4) to give 2.75 g (81% yield) of aminophosphonate (*S*)-**3** as a colorless liquid: $[\alpha]_D^{28}$=+66.6 (*c*=1.42, $CHCl_3$). IR (cm^{-1}) ν 3397, 1663, 1217, 1027. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.29 and 1.34 (2×t, 6H, J_{vic}=7.0 Hz), 2.68 (dd, 1H, J_{gem}=15.7 Hz, $^2J_{H/P}$=3.3 Hz), 3.26 (dd, 1H, J_{gem}=16.1 Hz, $^2J_{H/P}$=17.2 Hz), 3.46 (d, 1H, J_{gem}=13.8 Hz), 3.65 (dd, 1H, J_{gem}=11.0 Hz, $^4J_{H/P}$=18.7 Hz), 4.0 (s, 1H), 4.06 (masked, 1H), ca. 4.1 (masked, 1H), 4.14 (masked, 4H), 7.18–7.44 (m, 10H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.5 (d, $^3J_{C/P}$=5.4 Hz), 45.0 (d, $^1J_{C/P}$=167.6 Hz), 56.7 (d, $^4J_{C/P}$=5.4 Hz), 61.75, 62.2 (d, *J*=6.9 Hz), 64.3, 127.3, 127.9, 128.5, 128.5, 128.8, 128.9, 135.9, 138.5. ^{31}P NMR ($CDCl_3$, 161.8 MHz) δ 27.9. HRMS calcd for $C_{20}H_{28}NO_4P$ (M^++1): 378.1834. Found: 378.1831.

4.1.3. (2*R*,5*S*)- and (2*S*,5*S*)-4-Benzyl-2-ethoxy-2-oxo-5-phenyl-1,4,2,-oxazaphos-phinane, (2*R*,5*S*)-1 and (2*S*,5*S*)-1. In a 50-mL round-bottom flask fitted with rubber septa and under nitrogen atmosphere, potassium hydride (65.7 mg, 1.64 mmol) was suspended in 15 mL of dry THF. The flask was cooled to −75°C in a dry ice-acetone bath before the addition of 619 mg (1.64 mmol) of aminophosphonate (*S*)-**3** in 9 mL of dry THF. The reaction mixture was allowed to react at −75°C for 2 h before quenching with 20 mL of brine solution. The organic product was extracted with three 15-mL portions of ethyl acetate; dried over anh. sodium sulfate, and evaporated in a rotary evaporator. ^{31}P NMR analysis of the crude product showed a 97:3 mixture of the expected diastereomeric products (431 mg, 79% yield), which were separated by flash chromatography (hexane–ethyl acetate, 75:25). Recrystallization from hexane–CH_2Cl_2 (4:1) afforded crystals suitable for X-ray diffraction analysis.

(2*R*,5*S*)-**1**: mp 138–140°C; $[\alpha]_D^{28}$=−33.9 (*c*=1.09, $CHCl_3$). IR (cm^{-1}) ν 1256, 1047. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.34 (t, 3H, J_{vic}=7.0 Hz), 2.54 (dd, 1H, J_{gem}=14.1 Hz, $^2J_{H/P}$=12.6 Hz), 3.14 (dd, 1H, J_{gem}=14.1 Hz, $^2J_{H/P}$=15.6 Hz), 3.18 (d, 1H, J_{gem}=13.6 Hz), 3.70 (dd, 1H, J_{anti}=8.4 Hz, J_{gauche}=3.3 Hz), 3.78 (dd, 1H, J_{gem}=13.3 Hz, $^4J_{H/P}$=6.1 Hz), 4.20 (m, 2H), 4.26 (ddd, 1H, J_{gem}=11.9 Hz, J_{gauche}=3.2 Hz, $^3J_{H/P}$=17.4 Hz), 4.52 (ddd, 1H, J_{gem}=11.7 Hz, J_{anti}=8.4 Hz, $^3J_{H/P}$=7.2 Hz), 7.22–7.50 (m, 10H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.6 (d, $^3J_{C/P}$=4.6 Hz), 47.3 (d, $^1J_{C/P}$=144.6 Hz), 60.6 (d, $^3J_{C/P}$=16.9 Hz), 62.48 (d, $^2J_{C/P}$=6.2 Hz), 65.5 (d, $^3J_{C/P}$=3.0 Hz), 71.9 (d, $^2J_{C/P}$=6.2 Hz), 127.4, 128.5, 128.7, 129.0, 136.7, 137.0; ^{31}P NMR ($CDCl_3$, 161.8 MHz) δ 20.3. X-Ray crystallographic structure in Fig. 2.[9] Anal. calcd for $C_{18}H_{22}NO_3P$: C, 65.24; H, 6.69; N, 4.22. Found: C, 65.58; H, 5.92; N, 3.95.

(2*S*,5*S*)-**1**: mp 92–94°C. $[\alpha]_D^{28}$=+31.0 (*c*=1.03, $CHCl_3$). IR (cm^{-1}) ν 1261, 1039. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.37 (t, 3H, J_{vic}=7.1 Hz), 2.50 (dd, 1H, J_{gem}=14.7 Hz, $^2J_{H/P}$=8.8 Hz), 2.93 (d, 1H, J_{gem}=13.6 Hz), 3.16 (dd, 1H,

J_{gem}=14.6 Hz, $^{2}J_{H/P}$=19.0 Hz), 3.66 (dd, 1H, J_{anti}=10.6 Hz, J_{gauche}=2.9 Hz), 3.82 (dd, 1H, J_{gem}=13.4 Hz, $^{4}J_{H/P}$=7.5 Hz), 4.07 (ddd, 1H, J_{gem}=11.7 Hz, J_{gauche}=3.3 Hz, $^{3}J_{H/P}$=21.9 Hz), 4.13 (m, 2H), 4.27 (ddd, $J_{gem}\cong$11.1 Hz, $J_{anti}\cong$11.1 Hz, $^{3}J_{H/P}$=2.5 Hz), 7.20–7.46 (m, 10H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.5 (d, $^{3}J_{C/P}$=5.3 Hz), 47.5 (d, $^{1}J_{C/P}$=143.7 Hz), 60.6 (d, $^{3}J_{C/P}$=18.4 Hz), 61.9 (d, $^{2}J_{C/P}$=6.2 Hz), 66.7 (d, $^{3}J_{C/P}$=3.1 Hz), 73.0 (d, $^{2}J_{C/P}$=6.9 Hz), 127.5, 128.3, 128.5, 128.7, 128.7, 129.1, 136.9, 137.0. ^{31}P NMR ($CDCl_3$, 161.8 MHz) δ 19.4. X-Ray crystallographic structure in Fig. 1.[9] Anal. calcd for $C_{18}H_{22}NO_3P$: C, 65.24; H, 6.69; N, 4.22. Found: C, 65.04; H, 6.71; N, 4.17.

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