Tetrahedron Vol. 48, No. 35, pp. 7275-7288, 1992
Printed in Great Britain

0040-4020/92 $5.00+.00

Studies Toward a Model for Predicting the Diastereoselectivity in the Electrophilic Amination of Chiral 1,3,2-oxazaphospholanes

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(*Received in UK* 11 *June* 1992)

Abstract. A model has been developed for predicting the diastereoselectivity in the electrophilic amination of chiral 1,3,2-oxazaphospholanes derived from ephedrine and pseudoephedrine derivatives. The influence of the five-membered ring conformations and of the bulkiness of the ring substituents has been deeply analyzed both for reactivity prediction and for ^{1}H-NMR data interpretation. The theoretical and experimental results are in good agreement.

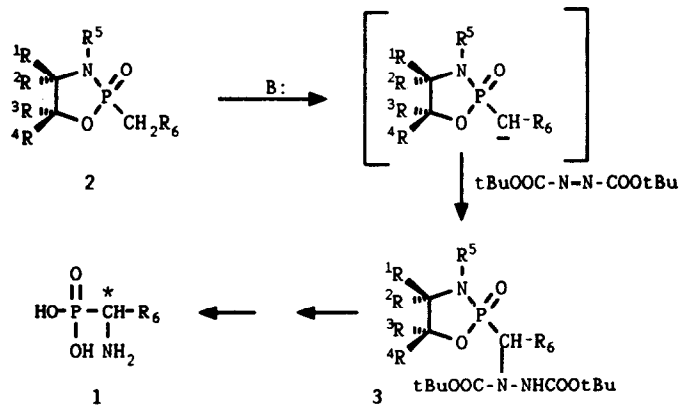
INTRODUCTION

Chiral 1,3,2-oxazaphospholane derivatives have received considerable attention for the determination of enantiomeric purities[1], for physical organic studies[2] and for application in asymmetric organic synthesis[3]. As our research group is interested in the asymmetric synthesis of α-aminophosphonic acids 1[4], this last application attracted our attention.

The strategy we envisioned consisted in electrophilic amination of a chiral 2-alkyl-2-oxo-1,3,2-oxazaphospholane 2 according to Scheme 1.

As far as we know[5], this field has not been investigated and in this communication we report our studies on the prediction of the diastereoselectivity of the amination step (2-3, Scheme 1), our experimental results and a detailed discussion of the structure of 1,3,2-oxazaphospholanes by means of ^{1}H-nmr spectra, X-ray analysis and modelling techniques.

We analyzed some molecules in great detail so as to have a theoretical model available for explaining and, if possible, predicting the reaction behaviour of the compounds under study. In the analyzed molecules, two main structure features were varied: the relative stereochemistry of ring substituents and the geometrical hindrance of the nitrogen substituents. Besides the advantages illustrated later, the two



2 3 1

Scheme n. 1

series derived from ephedrine and pseudo-ephedrine offer the possibility of studying a complementary arrangement of the ring groups. Eight molecules were considered for the realization of the model : they were derived from the two diastereoisomeric amino-alcohols ephedrine and pseudo-ephedrine, two different nitrogen substituents (R5=methyl, iso-propyl) and the new stereogenic centre on the phosporous atom.

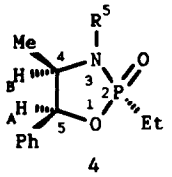
METHODOLOGY

A first requirement to study molecular reactivity is the determination of the most stable conformation of all the molecules. No methods are yet available for the search of the conformational absolute minima; moreover the studies on isolated molecules (e.g. neglecting solvent interactions) can furnish unreliable results. In our case three considerations can simplify the analysis: a) the electrophilic amination is experimentally performed at low temperatures, assuring the population of only the low energy states; b) solvent interactions can be thought to give a similar contribution in homologous structure series; c) the conformational space can be divided into sections, the first relative to the five-membered ring mobility, the second relative to the rotation of the substituents attached to the ring. This first aspect was the principal goal of our studies and, as will be shown, it was successfully solved by the used program; on the other hand the second problem was solved using a statistical approach, where the reliability can be considered adequate considering the rigidity of the present substituents (phenyl, methyl, iso-propyl, ethyl groups).

The chosen procedure was therefore based on three main steps: 1) the building of the starting molecules including both isomers at the nitrogen atom; 2) the search for the most probable structure inside the substituent rotational space, utilizing a Montecarlo-Metropolis approach (a procedure of the MAD[6] program); 3) the minimization of the obtained structures employing a semiempirical program (AM1[7]) where the validity of the calculated values depends on the molecular orbitals; this

semiempirical approach is preferable with respect to classical mechanics (unreliable for molecules containing non-standard atoms like phosphorous) and ab-initio programs (too time-consuming because of the high number of studied structures and not presenting advantages for sets of similar molecules).

The location of the conformational minima is not sufficient for the diastereoselectivity prediction. We had to hypothesize the possible factors influencing the electrophilic amination, i.e. step 2-3. The reaction can be schematized in two main steps: an acid-base reaction consisting in removing of a proton from the CH2-P moiety (Scheme 1) with a carbanion formation; a subsequent electrophilic addition by di-tert-butyl-azodicarboxylate. In the reaction conditions employed (low temperature, kinetic base) the main geometrical controlling factor is the accessibility of the proton during its removal and/or the accessibility of the formed carbanion. In both cases, the structural intervening features can be considered similar and therefore their "a priori" analysis is reliable enough. A partial rigidity of the anionic intermediate is assured by the presence of polar groups[8]. The quantitative correlation of the accessibility to the reaction centre with the molecular geometry is not yet feasible: on the other hand it is possible to make a qualitative analysis and to predict the most promising structure.



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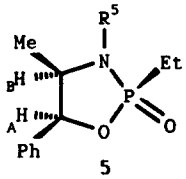
SET B1

a: R^5 = Me

b: R^5 = iPr



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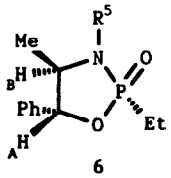
SET B2

a: R^5 = Me

b: R^5 = iPr



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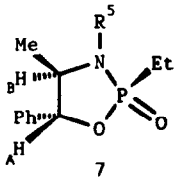
SET A1

a: R^5 = Me

b: R^5 = iPr



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SET A2

a: R^5 = Me

b: R^5 = iPr

Scheme n. 2

MODELLING RESULTS

Scheme 2 depicts the eight compounds analyzed. To make the discussion

easier we have defined four structure sets: sets A1 and A2 are composed by pseudo-ephedrine derivatives with the ethyl group on phosphorous atom trans (6a and 6b) and cis (7a and 7b) to the ring methyl; sets B1 and B2 are composed by ephedrine derivatives with the ethyl group on phosphorous atom trans (4a and 4b) and cis (5a and 5b) to the ring methyl. First of all, the relative stabilities of the isomeric molecules were examined (Table 1). The most stable molecules have a trans relationship between the nitrogen substituent and the ethyl group. This is in full agreement with the alternating substituent disposition of the A2 and B2 sets; whereas a clear preference for a cis relationship of the nitrogen substituent and the ring methyl group is observed for A1 and B1 sets, the ethyl moiety being trans. These last results cannot be simply explained by steric effects because of the similarity of methyl and ethyl groups; but the results of the calculations are acceptable considering that the most stable dispositions always have dipole-dipole stabilizing interactions between P-O and C-N bonds. We used only the most stable isomers for the modelling analysis.

Table 1. Energies Calculated for the Analyzed Molecules.

Molecule	Energy[a] R^5 cis to Et	Energy[a] R^5 trans to Et	Difference
4a	-2786.82188	-2786.92999	-0.10811
4b	-3098.16709	-3098.29841	-0.13132
5a	-2786.76893	-2786.88645	-0.11752
5b	-3098.13326	-3098.27247	-0.13921
6a	-2786.84404	-2787.05161	-0.20757
6b	-3098.22671	-3098.47547	-0.24876
7a	-2786.91002	-2786.99599	-0.08597
7b	-3098.23544	-3098.40437	-0.16893
8	-3297.91822	-3297.99640	-0.07818
9	-3297.85056	-3298.01345	-0.16289
10	-3297.75823	-3297.91465	-0.15642
11	-3297.80842	-3297.88731	-0.07889

[a] Energies are in Ev.

The interactions between the ethyl and the other ring groups probably determine the accessibility to the reaction centre. It is possible to try to estimate the differences between compounds 4-7 by utilizing the distances between the methylene carbon of the ethyl group and the carbon atoms of the other substituents, considering that: 1) the methyl has an isotropic hindrance independent of the rotation; 2) the phenyl cannot be positioned parallel to the ring-average plane because of the interactions with the methyl or the adjacent hydrogen atom; 3) the iso-propyl, even if non-rotationally isotropic, can be considered as being so because positions perpendicular to the ring are clearly very unlikely.

The distances between ring α-carbons are reported in Table 2. By

separately analyzing sets A and B it is possible to observe that set A1 has the nitrogen substituent further from the ethyl group than set A2, but, on the other hand, the phenyl group exerts a compression on the ethyl itself. The results of these two contrasting effects is the lack of differentiation between the two sets when R=CH_3; whereas when R=$CH(CH_3)_2$ the nitrogen substituent plays a determinant role (the diastereoselectivity augments for the set A2). The set B1 has only the nitrogen substituent near the ethyl group, thus allowing this group greater mobility; the predicted selectivity is therefore quite low, even if by increasing the hindrance on the nitrogen atom it could be improved. On the other hand, the set B2 has the highest compression of all the substituents, suggesting a good selectivity that could become very good by using more sterically demanding groups on the nitrogen atom. In conclusion the analysis suggests an increase in diastero- selectivity for the sequence B1(N-Me) < B1(N-iPr) < A1(N-Me) < A2(N-Me) < B2(N-Me) < A1(N-iPr) < A2(N-iPr) < B2(N-iPr). As illustrated in the following section the two diastereoisomers 4b and 5b could not be separated by chromatographic systems, so we could verify the prediction for six compounds.

Table 2. Distances Between the Carbons of Ring Substituents[a]

Molecule	Dist. Et-R[b]	Dist. Et-R^5	Dist. R^5-R'[c]	DS ratio[d]
4a (B1)	5.05(Ph)	3.78		1 : 1
4b (B1)	5.05(Ph)	3.53	4.97	-
5a (B2)	3.87(Ph)	3.82		2 : 1
5b (B2)	3.97(Ph)	3.77	4.75	-
6a (A1)	4.52(Ph)	3.96		1.5 : 1
6b (A1)	4.51(Ph)	4.18	4.90	3 : 1
7a (A2)	4.75(Me)	3.86		1.5 : 1
7b (A2)	4.54(Me)	3.83	5.17	4 : 1

[a] Radical numbers refer to Scheme 1. [b] R is methyl or phenyl depending on which is nearer. [c] R' is the methyl of the isopropyl nearest to R^5. [d] Diastereoisomeric ratio of compounds 3.

EXPERIMENTAL RESULTS

For our studies optically active (+)-ephedrine and (-)-pseudoephedrine were chosen as the chiral amino-alcohols also on the basis of their availability at relatively low cost and the excellent diastereoselectivity obtained in the asymmetric synthesis of α-aminoacids[9]; (1S,2R)-2-isopropylamino-1-phenyl-1-propanol and (1R,2R)-2-isopropylamino-1-phenyl-1-propanol were prepared from (+)-Norephedrine and (-)-Norpseudoephedrine respectively according to literature methods[10].

The 1,3,2-oxazaphospholane 4-7 were obtained in good yields, as a

mixture of diastereoisomers, by reacting the appropriate chiral amino-alcohol with the commercially available ethyl phosphonic acid dichloride in anhydrous toluene and in the presence of triethylamine. Except for 4b and 5b, the diastereoisomers could be cleanly separated by flash chromatography on silica gel. Attempts were made to synthesize 1,3,2-oxazaphospholanes bearing an electron- withdrawing group on the nitrogen atom so as to investigate the role of the substituent on the stereochemical outcome of the amination step.

N-tert-butoxycarbonyl-nor-ephedrine, N-benzyloxycarbonyl-nor-ephedrine, N-tosyl-nor-ephedrine[11] were synthesized but the subsequent cyclization with ethyl phosphonic acid dichloride was unsuccessful. Evidently, the nucleophilicity of the nitrogen atom is too depressed by linkage with an electron-withdrawing group in the amino-alcohol to allow a reaction.

The 2-ethyl-2-oxo-1,3,2-oxaza-phospholanes 4-7 were deprotonated at -78°C with lithium diisopropylamide in anhydrous tetrahydrofurane according to the Evans procedure[12]: the carbanion was treated with di-tert-butyl-aza-dicarboxylate at the same temperature and the reaction mixture quenched with glacial acetic acid. No effect, neither on the reaction yields nor on the diastereoselectivity, was observed on varying the reaction times with the electrophile from 3' to 30'.

Table 3. Numerical and Literal Description of Five Membered Rings Obtained by Using the RICON Program (v. 4.06).

Molecule	S(2)[a]	Psi(2)[b]	Ring Conformation
4a	0.460	10.47	TWIST-ENVELOPE
4b	0.517	6.37	TWIST-ENVELOPE
5a	0.461	15.17	TWIST
5b	0.411	15.62	TWIST
6a	0.344	15.28	TWIST
6b	0.419	8.18	TWIST-ENVELOPE
7a	0.383	14.83	DISTORTED TWIST
7b	0.289	4.99	DISTORTED ENVELOPE
8	0.308	9.94	TWIST-ENVELOPE
9	0.338	7.95	TWIST-ENVELOPE
10	0.408	13.38	DISTORTED TWIST
11	0.424	7.28	TWIST-ENVELOPE
RX[c]	0.470	9.06	TWIST-ENVELOPE

[a] S(2) is the Total Puckering Amplitude. [b] Psi(2) is the reduced initial angle. [c] RX is the structure derived from the X-ray analysis.

The diastereoisomeric ratios are reported in Table 2 and were determined by analysis of ^{1}H-NMR and/or ^{31}P-NMR spectra.

By using a program by Zefirov et al.[13] (RICON) it is possible to quantify the conformations of the five-membered rings in compounds 4-7.

The results show marked differences, varying from an envelope-like conformation (7b) to twist-like ones (5a (and 5b)). It is interesting to observe that the best diastereoselectivity is obtained with molecules possessing envelope-like or twist-like conformations, whereas it drastically diminishes for molecules with intermediate conformations (Table 3). The reaction behaviour of these compounds is not so easily rationalizable; it seems that extreme conformations, being more rigid, amplify the effects of the substituents on the molecules. By analyzing the data reported in Table 2, it is possible to verify that, through the model we developed, the prediction of diastereoselectivity and the experimental results are in good agreement.

^{1}H-NMR SPECTRA OF COMPOUNDS 4-7

The two diastereoisomers derived from cyclization of (+)-ephedrine with ethyl phosphonic acid dichloride could be readily distinguished by the chemical shift of the benzylic proton HA: the proton cis to phosphoryl oxygen is deshielded as already reported by other authors[14]. We confirmed this assignment by X-ray analysis on derivative 4a[15] (figure 1).

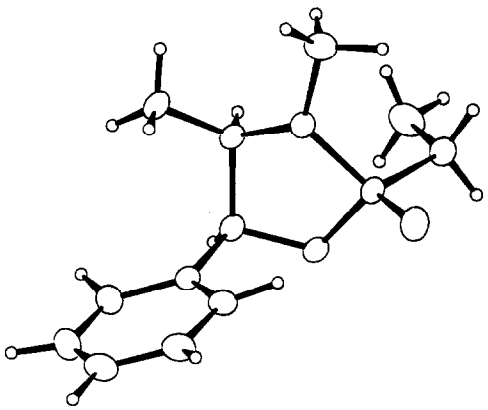


Figure n. 1. X-ray Derived Structure for Compound 4a.

The compounds 4a and 5a were obtained in the ratio 1:1 and 4b and 5b in the ratio 1:1.4, as evaluated by integration of the resonances of the proton HA in the corresponding reaction mixtures. In compound 4a the proton HA resonates as a double doublet at 5.45δ with a coupling

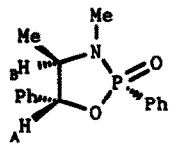
constant of 6.2Hz with HB and a coupling constant of 3.8Hz with the phosphorous atom; the coupling constant of the proton HB (ddq) with the phosphorous atom is 15.6 Hz. In the diastereoisomer 5a there is no coupling between HA and the phosphorous atom and the proton HA displays a doublet at 5.77δ (^{3}JHA-HB=6.1Hz); the proton HB displays a coupling constant ^{3}JHB-P of 10.9 Hz.

Clearly distinguishable in the ^{1}H-NMR spectra of the mixture 4b and 5b are two doublets at 5.38δ (^{3}JHA-HB=5.9Hz) and 5.70δ (^{3}JHA-HB=5.9Hz), two complex systems (ddq) at 3.91-3.70δ (^{3}JHA-HB=5.9Hz, ^{3}JHB-Me=6.3Hz, ^{3}JHB-P=12.7Hz) and at 3.63-3.40δ (^{3}JHA-HB=5.9Hz, ^{3}JHB-Me=6.1Hz, ^{3}JHB-P=12.7Hz), and two doublets at 0.86δ (^{3}JMe-HB=6.3Hz) and 0.70δ (^{3}JMe-HB=6.1Hz).

By flash chromatography it was possible to separate the two diastereoisomers derived from the cyclization both with R=Me (ratio 6a:7a=1:1) and with R=i-Pr (ratio 6b:7b=1:3). The evaluation of the relative percentages of compounds 6 and 7 was calculated assuming that, also in this case, the proton HA cis to the phosphoryl oxygen is deshielded. In compounds 6a and 6b, the proton HA has a multiplicity of a doublet (^{3}JHA-P=0Hz) at 4.97δ (^{3}JHA-HB=9.0Hz) and 4.90δ (^{3}JHA-HB=8.8Hz) respectively; the value of the ^{3}JHB-P is zero. A common pattern is exhibited by compounds 7a and 7b in their ^{1}H-NMR spectra: the proton HA resonates at 4.72δ (dd, ^{3}JHA-HB=9.0Hz, ^{3}JHA-P=2.4Hz) in 7a and at 4.69δ (dd, ^{3}JHA-HB=7.7Hz, ^{3}JHA-P=4.1Hz) in 6b; the value of ^{3}JHB-P is again approximately zero in both compounds.

The ^{1}H-NMR resonances were assigned by analysis of the resolution enhanced spectra of compounds 4-7 by proton-proton and proton-phosphorous decoupling experiments.

The model developed for the reactivity prediction has also been applied to discuss the spectroscopic data (Table 4). For this, we have also introduced compounds 8, 9, 10, 11, already synthesized by Seltzer et al.[14], into our discussion. (See Scheme 3)



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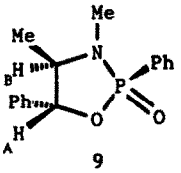

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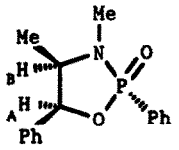

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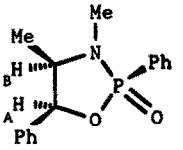

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Scheme n. 3

The difficulty in correlating the coupling constant JH-P with the

substituents position and nature is well known[16]; moreover problems can also be envisaged for JH-H because the phosphorous atom effect cannot be considered like that of the usual substituents, nor can it be discussed utilizing the Hasnoot equation[17]. However the results for all compounds are in good qualitative agreement with experimental data and, in the case of our compounds, they even give semiquantitative correlations. We first considered the values of the JHA-HB and found, as a common trend, that the pseudo-ephedrine derivatives display a greater JHA-HB than the ephedrine ones; it must be emphasized that in 7b the JHA-HB is 7.7Hz (Tables 4 and 5). If we directly compare the dihedral angles HA-C-C-HB with the experimental JHA-HB, there is better agreement than by applying the Hasnoot equation, observing values of ~9Hz for dihedral angles of ~155° and values of ~6Hz for dihedral angles of ~30°. Compound 7b is still an exception (J=7.7Hz, HA-C-C-HB=143.5°), but, as has been illustrated, it is the only one possessing an envelope-like conformation.

Table 4. Calculated Dihedral Angles Compared with Measured Coupling Constants.

Molecule	Angle HA-HB (^{3}J AB)	Angle HA-P (^{3}J AP)	Angle HB-P (^{3}J BP)
4a	-32.47	-93.11	143.11
	(6.2)	(3.8)	(15.6)
4b	-35.94	-92.69	147.97
	(5.9)	(0.0)	(12.7)
5a	-31.41	-87.91	141.02
	(6.1)	(0.0)	(10.9)
5b	-27.41	-90.75	137.69
	(5.9)	(0.0)	(12.7)
6a	-155.27	-100.29	-94.22
	(9.0)	(0.0)	(0.0)
6b	-161.58	-98.19	-86.77
	(8.8)	(0.0)	(0.0)
7a	-152.47	-94.83	-97.27
	(9.0)	(2.4)	(0.0)
7b	-143.50	-99.52	-105.32
	(7.7)	(4.1)	(0.0)
8	-146.07	-102.74	-99.04
	(8.6)	(2.8)	(0.0)
9	-161.04	-96.09	-88.88
	(8.9)	(0.0)	(0.0)
10	-32.70	-94.96	141.22
	(6.5)	(0.0)	(10.7)
11	-28.25	-96.61	141.14
	(6.3)	(4.7)	(14.4)

The only report that, as far as we know, concerns the correlation between JH-P with the structure introduces some interesting, but, in our

opinion, not exhaustive concepts[14]. We think it unnecessary to consider dynamic conformational equilibria whilst we suggest that the location of the most stable conformation could be sufficient to infer the values of the JH-P (our results are in good agreement with the experimental data but they are not a general solution to the very difficult problem of correlating structure and JH-P). The phosphoryl oxygen exerts an amplification effect on the JH-P when it is positioned trans to the observed hydrogen. We can observe that values of JH-P ~0 (oxygen atom cis) or JH-P 4.7-2.4Hz (oxygen atom trans) correspond to dihedral angles of ~90°; values of JH-P ~11Hz (oxygen atom cis) and JH-P ~15Hz (oxygen atom trans) are indicative of a dihedral angle of ~150°. Moreover small variations in the dihedral angles strongly affect the absolute values of the JH-P if the oxygen is trans positioned (e.g. 7a and 7b) (Table 4)

EXPERIMENTAL

^{1}H-NMR spectra were measured in deuterochloroform with a Bruker AC 200 (200MHz) and ^{31}P-NMR with a Varian XL-200 (81.0 MHz). Mass spectra were obtained with a VG 7070 EQ spectrometer. Optical rotations were measured at 25°C using a 1dm cell on a Perkin -Elmer 241 polarimeter. Microanalyses were carried out in the microanalytical laboratory of our Department using a Perkin-Elmer 240 instrument. Analytical thin-layer chromatography was carried out on Merck Kieselgel 60 F254. Tetrahydrofuran and toluene were distilled under nitrogen from lithium aluminum hydride and sodium respectively. Melting points (mp) were determined with a hot plate microscope and are uncorrected.

General procedure for the preparation of 2-ethyl-2-oxo-1,3,2-oxazaphospholanes 4-7. To a stirred solution of the appropriate amino-alcohol (4.2mmol) in anhydrous toluene (10ml) triethylamine (9.6mmol, 1.34ml) and ethylphosphonic acid dichloride (4.8mmol, 0.52ml) were added at -20°C under nitrogen atmosphere. After 3h at -20°C the reaction mixture was left to reach room temperature and stirred overnight. The triethylamine hydrochloride was filtered off and the solvent removed in vacuo. Water (15ml) and methylene chloride (20ml) were added to the residue. The organic layer was separated and the aqueous layer extracted with methylene chloride (3X20ml). The combined organic layers were washed with water (20ml), dried over K_2CO_3, filtered and concentrated in vacuo. The diastereoisomers at the phosphorous stereocentre were separated by flash chromatography (ethyl acetate as eluant). The ^{1}H-NMR data of compounds 4-7 are reported in Table 5.

(2S,4R,5S)-2-ethyl-2-oxo-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholane **4a**: mp=163-165°C; $[\alpha]_D^{20}$ =+47.1 (c=6.2, $CHCl_3$); MS(70eV)239 (M^+),224, 133, 104. Anal.Calcd for $C_{12}H_{18}NO_2P$: C, 60.25; H, 7.53; N, 5.86. Found: C, 59.90; H, 7.35; N,5.68.

(2R,4R,5S)-2-ethyl-2-oxo-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholane **5a**: mp=57-60°C; $[\alpha]_D^{20}$ =+74.84 (c=10.3, $CHCl_3$); MS(70eV) 239 (M^+), 224, 133, 104. Anal.Calcd for $C_{12}H_{18}NO_2P$: C, 60.25; H, 7.53; N, 5.86. Found: C, 60.16; H, 7.28; N, 5.60.

Table 5. ^{1}H-NMR data of compounds 4-7

	HA	HB	Harom.	CH_3CH_BN	R-N	CH_2-P	CH_3-CH_2P
4a	5.45 δ (dd) ($^3J_{HA-HB}$ = 6.2Hz, $^3J_{HA-P}$ = 3.8Hz)	3.75-3.54 δ (ddd) ($^3J_{HA-HB}$ = 6.2Hz, $^3J_{HB-P}$ = 15.6Hz, $^3J_{HB-CH3}$ = 6.6Hz,	7.40-7.30 δ (m)	0.85 δ (d) ($^3J_{CH3-HB}$ = 6.6Hz)	2.72 δ (d) ($^3J_{Me-P}$ = 9.8Hz)	2.20-1.85 δ (m)	1.23 δ (dt) ($^3J_{CH3-CH2}$ = 7.6Hz,
4b	5.38 δ (d) ($^3J_{HA-HB}$ = 5.9Hz)	3.91-3.70 δ (ddq) ($^3J_{HA-HB}$ = 5.9Hz, $^3J_{HB-Me}$ = 6.3Hz, $^3J_{HB-P}$ = 12.7Hz)		0.86 δ (d) ($^3J_{HB-Me}$ = 6.3Hz)			
5a	5.77 δ (d) ($^3J_{HA-HB}$ = 6.1Hz)	3.78-3.50 δ (ddq) ($^3J_{HA-HB}$ = 6.1Hz, $^3J_{HB-Me}$ = 6.6Hz, $^3J_{HB-P}$ = 10.9Hz)	7.45-7.20 δ (m)	0.71 δ (d) ($^3J_{CH3-CH3}$ = 6.6Hz)	2.82 δ (d) ($^3J_{CH3-P}$ = 9.0Hz)	2.20-2.81 δ (m)	1.32 δ (dt) ($^3J_{CH3-CH2}$ = 7.7Hz,
5b	5.70 δ (d) ($^3J_{HA-HB}$ = 5.9Hz)	3.63-3.40 δ ($^3J_{HB-HA}$ = 5.9Hz, $^3J_{HB-Me}$ = 6.1Hz, $^3J_{HB-P}$ = 12.7Hz)		0.70 δ (d) ($^3J_{CH3-HB}$ = 6.1Hz)			
6a	4.97 δ (d) ($^3J_{HA-HB}$ = 9.0Hz)	3.42-3.28 δ (dq) ($^3J_{HA-HB}$ = 9.0Hz, $^3J_{HB-Me}$ = 6.1Hz)	7.42-7.30 δ (m)	1.21 δ (d) ($^3J_{CH3-HB}$ = 6.1Hz)	2.72 δ (d) ($^3J_{CH3-P}$ = 9.8Hz)	2.22-1.85 δ (m)	1.27 δ (dt) ($^3J_{CH3-CH2}$ = 7.6Hz, $^3J_{CH3-P}$ = 19.8Hz)
6b	4.90 δ (d) ($^3J_{HA-HB}$ = 8.8Hz)	3.59-3.45 δ (dq) ($^3J_{HA-HB}$ = 8.8Hz, $^3J_{HB-Me}$ = 6.6Hz)	7.40-7.35 δ (m)	1.20 δ (d) ($^3J_{CH3-HB}$ = 6.6Hz)	CH-N: 3.61-3.40 δ (m) CH_3-CH: 1.44 δ (d) ($^3J_{CH3-CH}$ = 6.9Hz) CH_3CH: 1.20 δ (d) $^3J_{CH3CH}$ = 6.6Hz)	2.27-1.78 δ (m)	1.27 δ (dt) ($^3J_{CH3-CH2}$ = 7.8Hz, $^3J_{CH3-P}$ = 19.8Hz)
7a	4.72 δ (dd) ($^3J_{HA-HB}$ = 9.0Hz, $^3J_{HA-P}$ = 2.4 Hz)	3.73-3.24 δ (dq) ($^3J_{HA-HB}$ = 9.0Hz, $^3J_{HB-Me}$ = 6.2Hz)	7.50-7.30 δ (m)	1.17 δ (d) ($^3J_{CH3-HB}$ = 6.2Hz)	2.66 δ (d) ($^3J_{CH3-P}$ = 10.8Hz)	2.10-1.83 δ (m)	1.20 δ (dt) ($^3J_{CH3-CH2}$ = 7.6Hz, $^3J_{CH3-P}$ = 20.9Hz)
7b	4.69 δ (dd) ($^3J_{HA-HB}$ = 7.7Hz, $^3J_{HA-P}$ = 4.1Hz)	3.63-3.50 δ (dq) ($^3J_{HA-HB}$ = 7.7Hz, $^3J_{CH3-HB}$ = 6.5Hz)	7.50-7.30 δ (m)	1.18 δ (d) ($^3J_{CH3-HB}$ = 6.5Hz)	CH-N: 3.55-3.30 δ (m) CH_3: 1.37 δ (d) ($^3J_{CH3-CH}$ = 6.9 Hz CH_3: 1.25 δ (d) ($^3J_{CH3-CH}$ = 6.8Hz)	2.20-1.75 δ (m)	1.19 δ (dt) ($^3J_{CH3-CH2}$ = 7.8Hz, $^3J_{CH3-P}$ = 20.4Hz)

Yields (4a+5a):90%.

(2S,4R,5R)-2-ethyl-2-oxo-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholane 4a : oil; $[\alpha]_D^{20}$ = -25.90 (c=7,4, $CHCl_3$); MS(70eV) 239 (M^+), 224, 133, 104. Anal.Calcd for $C_{12}H_{18}NO_2P$: C, 60.25; H, 7.53; N, 5.86. Found :C, 60.10; H, 7.38; N, 5.62.

(2R,4R,5R)-2-ethyl-2-oxo-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholane 5a: mp=83-84°C; $[\alpha]_D^{20}$ =-50.40 (c=6.2, $CHCl_3$); MS 239 (M^+), 224, 133, 104. Anal.Calcd for $C_{12}H_{18}NO_2P$: C, 60.25; H, 7.53; N, 5.86. Found :C, 60.12; H, 7.30; N, 5.60.

Yields(6a+7a): 80%.

(2S,4R,5R)-2-ethyl-2-oxo-3-isopropyl-4-methyl-5-phenyl-1,3,2-oxazaphospholane 6b: mp= 185-187°C; $[\alpha]_D^{20}$ =-55.71 (c=2.5, $CHCl_3$); MS (70eV) 267 (M^+), 252, 210, 160, 132, 105. Anal.Calcd for $C_{14}H_{22}NO_2P$: C, 62.92; H, 8.24; N, 5.24. Found : C, 62.75; H, 8.15 N, 5.10.

(2R,4R,5R)-2-ethyl-2-oxo-3-isopropyl-4-methyl-5-phenyl-1,3,2-oxazaphospholane 7b: mp=227-230°C; $[\alpha]_D^{20}$ =-49.57 (c=10.6, $CHCl_3$); MS (70eV) 267 (M^+), 252, 210, 160, 132, 105. Anal.Calcd for $C_{14}H_{22}NO_2P$: C, 62.92; H, 8.24; N, 5.24. Found: C, 62.70; H, 8.11; N, 5.14.

Yields (6b+7b): 90%.

General procedure for the electrophilic amination of compounds 4-7. **To a stirred solution of lithium diisopropylamide (1.1mmol) in anhydrous tetrahydrofuran (4ml) a solution of the appropriate 2-ethyl-2-oxo-1,3,2-oxazaphospholane (1mmol) in anhydrous tetrahydrofuran (3ml) was added at -78°C and under nitrogen atmosphere. After 30' at -78°C, a precooled (-78°C) solution of di-tert-butyl azodicarboxylate (1.1mmol) in tetrahydrofuran (3ml) was added via cannula. The reaction mixture was kept at -78°C for 30', quenched with glacial acetic acid (2.6mmol) and allowed to reach room temperature. The mixture was partitioned between ethylacetate (20ml) and pH 7 phosphate buffer; the aqueous phase was extracted with ethyl acetate (3X10ml). The combined organic layers were washed with saturated aqueous $NaHCO_3$, water, dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by flash chromatography on silica gel (ethyl acetate/light petroleum 3:7) in order to remove the starting material and di-tert-butyl azodicarboxylate. The reported spectroscopic data refer to the mixture of diastereoisomers. The diastereoisomeric excesses were determined by analysis of ^{1}H-NMR or ^{31}P-NMR spectra.**

From 4a: yield 50%; ^{1}H-NMR δ 7.40-7.28 (m, 5H), 5.48-5.35 (m, 1H), 5.05-4.65 (m, 1H), 3.80-3.55 (m, 1H), 2.70 (d, ^{3}JMe-P=9.0Hz, 3H), 1.62-1.38 (m+s, 21H), 0.85-0.75 (2d, ^{3}JMe-HBb=6.2Hz for the major diastereoisomer, ^{3}JMe-HB=6.0Hz for the minor diastereoisomer, 3H); ^{31}P-NMR 41.33, 40.02 (ratio 1:1); MS (70eV) 470 (M^++1), 469 (M^+), 413, 369, 340, 313, 269, 253, 211, 147, 105.

From 5a: yield 55%; ^{1}H-NMR δ 7.42-7.25 (m, 5H), 5.82-5.70 (m, 1H), 4.95-4.65 (m, 1H), 3.80-3.58 (m, 1H), 2.86-2.74 (2d, ^{3}JMe-P=8.7Hz for both diastereoisomers, ratio 2:1, 3H), 1.60-1.38 (m+s, 21H), 0.77-0.67 (2d, ^{3}JMe-HB=6.0Hz for both diastereoisomers, 3H); MS (70eV) 470 (M^++1), 469 (M^+), 414, 369, 340, 313, 269, 253, 211, 148, 105.

From 6a: yield 54%; ^{1}H-NMR δ 7.44-7.28 (m, 5H), 4.98-4.72 (m+2d, ^{3}JHA-HB=8.8Hz for both diastereoisomers, 2H), 3.50-3.30 (m, 1H), 2.78-2.65 (2d, ^{3}JMe-P=9.0Hz for both diastereoisomers, ratio 1.5:1, 3H), 1.63-1.40 (m+2s, 21H), 1.66-1.22 (2d, ^{3}JMe-HB=6.2Hz for both diastereoisomers, 3H); MS(70eV) 470 (M^++1), 469 (M^+), 414, 369, 340, 313, 269, 253, 211, 148, 105.

From 7a: yield 58%; ^{1}H-NMR δ 7.48-7.30 (m, 5H), 4.98-4.60 (m, 2H), 3.40-3.20 (m, 1H), 2.70-2.61 (2d, ^{3}JMe-P=10.5Hz for both diastereoisomers, ratio 1.5:1, 3H), 1.65-1.35 (m+s, 21H), 1.22-1.15 (2d, ^{3}JMe-HB=6.1Hz for the major diastereoisomer, ^{3}JMe-HB=6.0Hz for the minor diasteroisomer, 3H); MS (70eV) 470 (M^++1), 468, 414, 369, 340, 313, 269, 253, 211, 148, 105.

From 6b: yield 62%; ^{1}H-NMR δ 7.40 (m, 5H), 5.15-4.90 (m+2d, ^{3}JHA-HB=8.8Hz for the minor diasteroisomer, ^{3}JHA-HB=9.5Hz for the major diasteroisomer, ratio 1:3, 2H), 3.78-3.48(m, 2H), 1.52-1.20 (m, 30H); ^{31}P-NMR 37.05, 35.01 (ratio 1:3); MS (70eV) 498 (M^++1), 497 (M^+), 397, 368, 297, 239, 133, 103.

From 7b: yield 65%; ^{1}H-NMR δ 7.50-7.30 (m, 5H), 5.05-4.40 (m, 2H), 3.70-3.40 (m, 2H), 1.65-1.10 (m, 30H); ^{31}P-NMR 43.83, 42.00 (ratio 1:4); MS (70eV) 498 (M^++1), 497 (M^+), 397, 368, 297, 239, 133, 103.

Acknowledgment: We would like to thank Drs. Alberto and Giorgio Ripa for their contribution to the work during their stay in our Department and Dr. Tullio Pilati (Dipartimento di Chimica Fisica ed Elettrochimica, University of Milan) for performing the X-ray analysis. We are grateful to Prof. Nikolai Zefirov for having made his program available to us. Financial support was provided by the Consiglio Nazionale delle Ricerche (CNR, Roma) through Progetto Finalizzato "Chimica Fine II".

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