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Design of β-Amino Alcohols as Chiral Auxiliaries in the Electrophilic Amination of 1,3,2-Oxazaphospholanes

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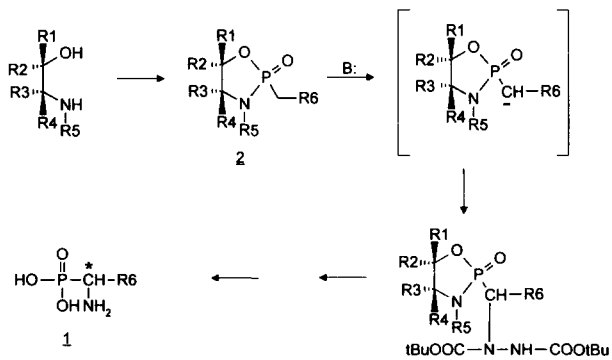
Abstract: Theoretical studies to predict the diastereoselectivity of the electrophilic amination of chiral 1,3,2-oxazaphospholanes led to the design of (1R), (2S)-1,3-diphenyl-2- (N-isopropylamino)-1-propanol 7 as a powerful chiral auxiliary. The experimental results are in good agreement with the calculations. An efficient synthesis of enantiomerically pure 7 is also reported.

INTRODUCTION

In recent years the asymmetric synthesis of α-aminophosphonic acids 1 has attracted much attention, considering that the biological activity of these compounds depends on their absolute stereochemistry[1]. Among the various reported methods[2], our research group focused on the use of enantiomerically pure β-amino alcohols as chiral auxiliaries in the electrophilic amination of 1,3,2-oxazaphospholanes (Scheme 1).[3]



Scheme 1

In a previous paper[3] we reported the realisation of a theoretical model capable of predicting the diastereoselectivity of the amination step of compounds 2, which could be obtained by condensing ephedrine or pseudo ephedrine derivatives with ethyl phosphonic acid dichloride.

Considering the good agreement between the prediction and the experimental results, we decided to further investigate this field with the aim of designing more powerful chiral auxiliaries.

In this paper we report the results of the theoretical analysis which led to a major improvement of the diastereomer excess in the amination step, employing (1R),(2S)-1,3-diphenyl-2(N-isopropylamino)-1-propanol.

THEORETICAL STUDIES

In exploiting the capacities of the model we developed, we extended our theoretical analysis by submitting new compounds to the model with the aim of designing very good auxiliaries. Because the model highlighted the higher potential of the pseudo ephedrine derivatives, carrying both the ring substituents on the same side, we directed our attention to new derivatives comparable to the prototype. (Figure 1)

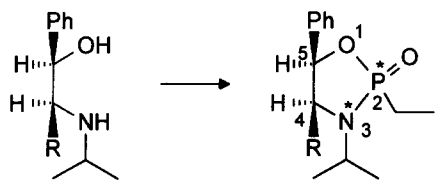


Fig. 1

In the preceding study[3] we focused on, as guiding factors of the diastereoselectivity, the effects of steric compression and hindrance caused by the substituents on the oxazaphospholane ring. In particular the restriction of the rotational freedom of the ethyl group at P(2) was held to be as the determining factor; this freedom is dependent on the relative position of the isopropyl group at N(3) that, in its turn, is influenced by the neighbouring groups. We chose to fix the phenyl group and vary the methyl group, increasing the sterical demand by selecting a phenyl or benzyl substituent. Consequently we analysed 12 compounds deriving from the combination of three substituents (R = Me, Ph, CH_2Ph) at C(4) with the configurations of the two stereocentres at P(2) and N(3) (Figure 2).

The methodology used was that reported in the previous paper[3] and is, briefly: a) a search of the rotational space[4]; b) a semiempirical quantomechanics minimisation of the most stable rotamer[5]; c) the analysis of the rotational freedom of the ethyl group at P(2)[6].

Table 1. Energy of Conformers of Compounds A, B, and C, Calculated by AM1 Program.

Compound[b]	Energy (eV) iPr *cis* to Et	Energy(eV) iPr *trans* to Et	Δ E (eV)
A1	-3098.13326	-3098.27247	-0.13921
A2	-3098.16709	-3098.29841	-0.13132
B1	-3739.87861	-3739.89535	-0.01674
B2	-3739.77398	-3740.00660	-0.23262
C1	-3895.72731	-3895.61003	+0.11728
C2	-3896.06406	-3895.75636	+0.30770

[a] Energy is in eV. [b] Compound structures are reported in Figure 2.

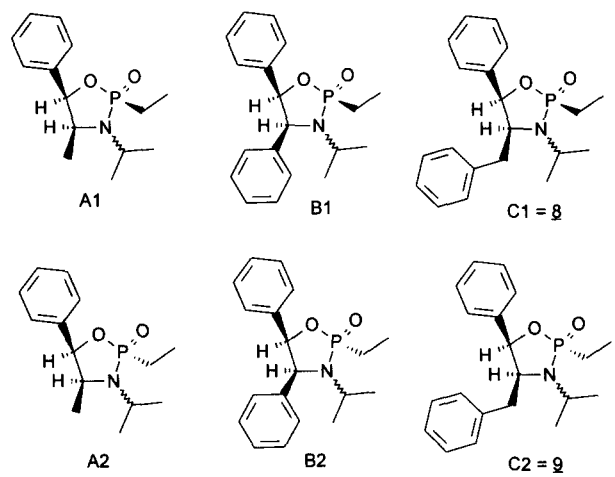


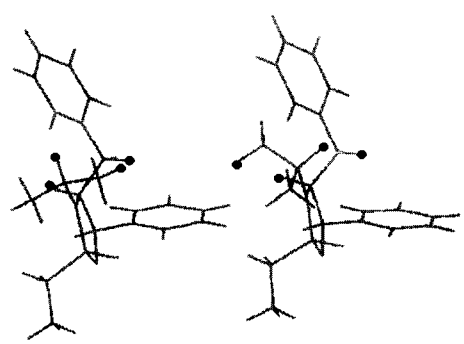
Fig. 2. Analysed structures

Compounds A and B showed a greater stability for the isomers with the isopropyl at N(3) *trans* positioned with respect to the ethyl at P(2). This result was expected for compounds A; in fact A2 placed the isopropyl group on the same side of the methyl at C(4), whereas A1 placed the isopropyl group *trans* to both the methyl at C(4) and the ethyl at P(2). Also B1 presented a *trans-trans* disposition in agreement with minimal steric interactions (the phenyl at C(4) *trans* to the isopropyl at N(3) and the isopropyl at N(3) *trans* to the ethyl at P(2)); on the contrary, B2 preferred a *cis* disposition between the phenyl at C(4) and the isopropyl at N(3), that moved from its initial position to a quasi-planar position with respect to the ring. Compounds C behaved differently; in fact compound C2 placed the isopropyl at N(3) *trans* with respect to the benzyl at C(4), highlighting its greater stereochemical demand. This disposition sited the isopropyl group on the same side as

the ethyl at P(2) thus suggesting a greater interaction between the two. Compound C1 starting from a structure with all the substituents in a relative *cis* position, had the best configuration when the isopropyl at N(3) moved to a *trans* position with respect to all the other substituents. This minimised structure was obviously different and more stable than that obtained from C1 with the isopropyl positioned *trans* from the beginning of the calculation.

The above reported results clearly show that the benzyl substituent should, in principle, have given the best diastereoselection. We could also hypothesise that the best result would derive from the diastereoisomer carrying the ethyl at P(2) *trans* to the benzyl and phenyl substituents and *cis* to the isopropyl at N(3). The experimental results, obtained using both the diastereoisomers of the benzyl derivative, showed very good agreement with the calculations. In fact, compound C2 was experimentally more stable than compound C1, in agreement with the values calculated by all the programs (MM[4], AM[5], Lilith[7]); when using C2 in the amination step a major improvement of the diastereomer excess was obtained (see Table 3).

In order to have confirmation of our considered structures, we ran NOESY experiments to assess the relative positions of the hydrogen atoms of compounds 8-9 (see Scheme 3). Initially, the result was disappointing as the conformations deduced from the spectra were not in agreement with the model. Our minimised structure could not explain the presence of the NOE effect between the hydrogen atoms C<u>H</u>$(CH_3)_2$ and C<u>H</u>$_2$Ph of compound C2 and the absence of a NOE effect between the hydrogen atoms C<u>H</u>$(CH_3)_2$ and H-4 (Figure 3). To account for this result we reproduced, by rotating the isopropyl at N(3), the structure deduced by NOE experiment (NOE structure) and calculated the energies and accessibility of this new compound. The energy result showed that the difference between the best and the NOE conformers was very small, and, when using the AM1 program, the NOE conformer is more stable.[8] To further confirm this result we also performed a conformational search by rotating the angle between the isopropyl group and the nitrogen atom showing an



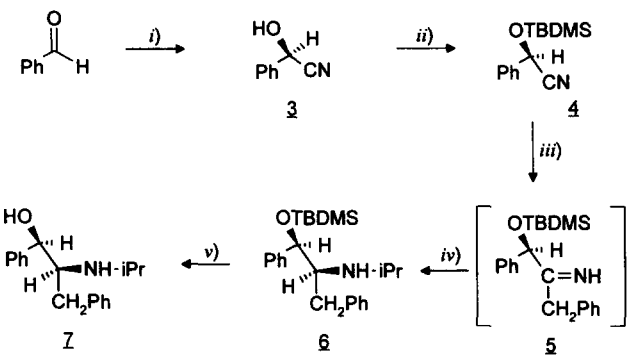
C2M **C2N**

Fig. 3. Minimised (C2M) and NOE (C2N) conformers of compound 9; the dots refer to the hydrogen atoms giving raise to NOE.

easy, in terms of energy (3.28 to 4.12 Kcal), passage between the two conformers at room temperature, i.e. at NMR temperature. With regard to the accessibility of the methylene of the ethyl at P(2), we repeated the rotational analysis around the C-P bond for the NOE structure; the result was in complete agreement with the previous calculation showing a free rotation of ≈ 250 degrees for both isomers (ΔE = ± 30 Kcal). However, from the accessibility of the two protons P-CH_2CH_3 we were able to respectively determine a range of 110 and 30 degrees for compound C2 and 90 and 80 degrees for compound C1.

EXPERIMENTAL RESULTS

The enantiomerically pure (1R), (2S)-1,3-diphenyl-2-(N-isopropylamino)-1-propanol 7 was prepared according to Scheme 2



Reagents: i) oxynitrilase, KCN/HOAc; *ii*)TBDMSCl, imidazole; *iii*) $PhCH_2MgBr$, then MeOH; *iv*) $(iPr)_2NH$, then $NaBH_4$; *v*) 40% aq. HF

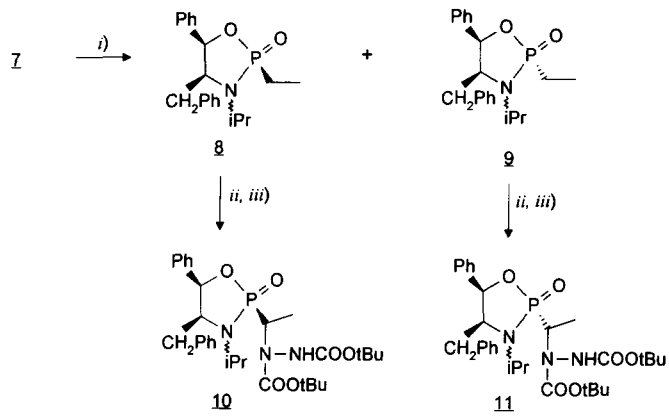
Scheme 2

R-(+)-mandelonitrile, obtained from benzaldehyde and potassium cyanide-acetic acid buffer in the presence of the enzyme oxynitrilase, was converted into the known (R)-t-butyl dimethylsilyl cyanohydrin 4.[9] Compound 4 was treated with benzylmagnesium bromide; by quenching the reaction mixture with methanol the imine 5 was obtained, which was not isolated but reacted *in situ* with di-isopropylamine and sodium borohydride.

The coordination of the magnesium (II) ions[10] by the imine nitrogen and oxygen atoms was invoked to justify the high level of diastereoselectivity observed in the reduction pathway of similar compounds . In our case only the erythro diastereoisomer 6 was obtained from 4 in 80% yield, as detected by ^{1}H-NMR and ^{13}C-NMR spectra. Hydrolysis of 6 with aqueous hydrofluoric acid afforded (1R), (2S)-1,3-diphenyl-2-(N-isopropylamino)-1-propanol 7 in quantitative yield. The optical purity of the erythro aminoalcohol 7 was

determined by comparison of the ^{1}H-NMR spectra of 7 and a racemic sample run in the presence of a chiral shift reagent [Eu(hfc)$_3$]. The enantiomeric excess of 7 was at least 99%.

The subsequent cyclization of compound 7 with ethyl phosphonic acid dichloride afforded the two diastereoisomeric 2-ethyl-2-oxo-1,3,2-oxazaphospholanes 8 and 9 in good yield (Scheme 3).



Reagents: i) $EtPOCl_2$, Et_3N; *ii)* LDA; *iii)* tBuOOC-N=N-COOtBu

Scheme 3

The diastereomer excess depends on the reaction temperature and is reported in Table 2.

Table 2. Temperature Dependence of the Diastereomer Excess of Compounds 8 and 9

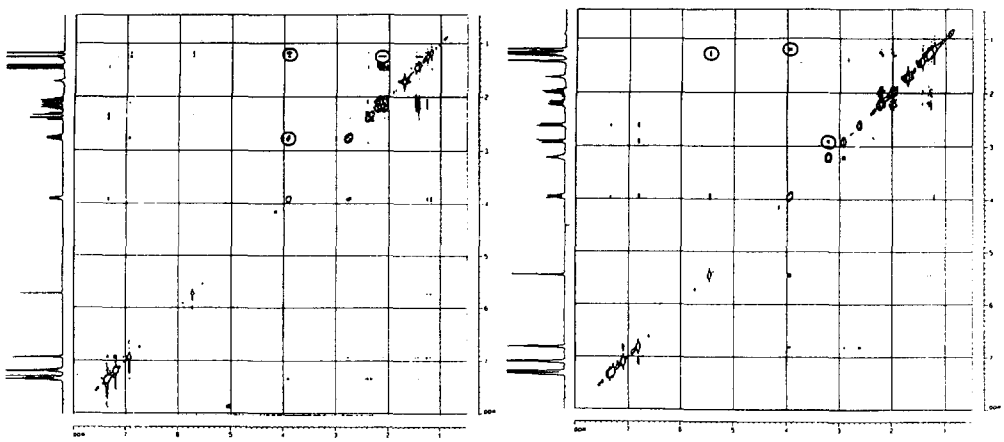
Temperature °C	-35	-20	+20	+110
8:9	12.6 : 1	11.2 : 1	5.3 : 1	1 : 1.3

The absolute stereochemistry of the phosphorus stereocenter was determined by the ^{1}H-NMR spectra of the two diasteroisomers 8 and 9 considering that the proton *cis* to the phosphoryl oxygen is deshielded as already reported.[3] In the ^{1}H-NMR spectra of 8 and 9, the benzylic proton resonates as a doublet at 5.72 and 5.30 δ, thus allowing the assessment of the absolute stereochemistry and the diastereomer excess in the crude reaction mixture.

In order to define the proximity of the hydrogen atoms of compounds 8 and 9 and to confirm the theoretical data, we performed NOESY experiments. The spectra were registered at different temperatures (ranging from -40°C to +25°C) and with different mixing times (ranging from 100 ms to 800 ms) with no appreciable differences, suggesting good conformational stability of the conformers at various temperatures.

For compound 8 the NOESY data demonstrate that the hydrogen atoms $CH(CH_3)_2$ and H-4 are very close, supporting the theoretical results. Moreover, the cross-peaks between the signals of H-4 and both the isopropyl methyl groups suggest an appreciable rotational freedom around the $N\text{-}CH(CH_3)_2$ bond.

For compound 9 the NOESY data revealed a spatial proximity between the hydrogen atoms $CH(CH_3)_2$ and one of CH_2Ph, together with correlation peaks between H-5 and the ethyl methyl group and H-4 and one of the isopropyl methyl groups.



8 9

Fig. 4. NOESY spectra of compounds 8-9; circled atoms corresponds to NOE signals

The strong correlation between H-5 and the methyl ethyl group and between H-4 and one of the isopropyl methyl groups support the high conformational stability of compound 9, and indicate restricted rotation around $N\text{-}CH(CH_3)_2$ bond.

The electrophilic amination reaction on the two oxazaphospholanes 8 and 9, after deprotonation with lithium diisopropylamide (deep red colour), was run with di-tert-butyl azodicarboxylate at -65 and -30 °C, without any difference in the diastereomer excess.

The diastereomer excesses of compounds 10 and 11 were determined by analysis of the ^{1}H-NMR and /or ^{31}P-NMR spectra and are reported in Table 3.

Table 3. Diastereomer Excess of Compounds 10 and 11

Compound	10	11
de	52.4 %	83.3 %

The experimental results obtained in the amination step of compounds 8 and 9 are in full agreement with the calculations. In fact, the restriction of the rotational freedom of the ethyl group at P(2) that is present in compound 9 as a consequence of the relative stereochemistry of the 1,3,2-oxazaphospholane ring substituents may justify the high diastereomer excess of compound 11.

EXPERIMENTAL

^{1}H-NMR and ^{13}C-NMR spectra were measured in deuterochloroform with a Bruker AC 200 (200 MHz and 50.3 MHz, respectively) and ^{31}P-NMR spectra with a Varian XL-200 (81.0 MHz); NOESY spectra were measured on a Bruker AMX-400, in phase sensitive mode, with mixing time of 800 ms for 8 and 500 ms for 9. Mass spectra were obtained with a VG 7070 EQ spectrometer. Optical rotations were measured at 25 °C using a 1 dm 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 diethylether were distilled under nitrogen from lithium aluminum hydride, toluene from sodium. Melting points (mp) were determined with a hot plate microscope and are uncorrected.

(1R),(2S)-1,3-diphenyl-2(N-isopropylamino)-1-(t-butyldimethylsilyloxy)-propane 6

A solution of benzyl magnesium bromide (26.0 mmol) in anhydrous diethyl ether (90 ml) was slowly dropped into a solution of 4 (2.60 g, 10.5 mmol) in anhydrous diethylether (30 ml) under nitrogen atmosphere. The mixture was refluxed for 5 h; after cooling to room temperature the reaction was quenched with anhydrous methanol (20 ml). Isopropylamine (1.81 ml, 21.1 mmol) in anhydrous methanol (10 ml) was then added and the reaction was stirred overnight at room temperature. Solid sodium borohydride (0.78 g, 20.6 mmol) was slowly added in three portions at 0°C. After stirring for 8 h at room temperature, the mixture was poured into water (100 ml) and extracted with diethyl ether (3 x 100 ml). The combined organic extracts were washed with brine (2 x 100 ml), dried over anhydrous potassium carbonate and evaporated under vacuum. After purification by silica gel flash chromatography, pure product 6 (3.22 g, 80% yield) was obtained as an oil. Compound 6: $[\alpha]_D^{20}$ -37.6 (c = 1, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 200 Mhz) δ: 7.40-7.10 (10H, m, aromatic protons), 4.65 (1H, d, J = 4.5 Hz, H-1), 2.95-2.89 (2H, m, H-2 and C$\underline{H}_2$Ph), 2.40-2.35 (2H, m, C$\underline{H}_2$Ph and C$\underline{H}$(CH$_3$)$_2$), 0.91 (9H, s, (C$\underline{H}_3$)$_3$C-Si), 0.75 (3H, d, J = 6.3 Hz, C$\underline{H}_3$-CH-N), 0.59 (3H, d, J = 6.3 Hz, C$\underline{H}_3$-CH-N), 0.40 (3H, s, C$\underline{H}_3$-Si), -0.19 (3H, s, C$\underline{H}_3$-Si); ^{13}C-NMR ($CDCl_3$, 50.3 MHz) δ: - 5.0 (C$\underline{H}_3$Si), -4.6 (C$\underline{H}_3$Si), 18.2 (SiC(CH$_3$)$_3$), 22.3 (C$\underline{H}_3$-CH-N), 23.4 (C$\underline{H}_3$-CH-N), 25.9 (SiC(C$\underline{H}_3$)$_3$), 37.3 (C$\underline{H}_2$Ph), 46.3 (C$\underline{H}$(CH$_3$)$_2$), 63.7 (CH$_2$C$\underline{H}$NH), 77.4 (C$\underline{H}$OSi), 125.7 (CH), 126.9 (CH), 127.8 (CH), 129.3 (CH), 140.5 (C), 143,2 (C); MS

(70 eV): 384 (M^+ + 1), 368, 326, 292, 252, 221, 162, 120, 91. Anal. Calcd. for $C_{24}H_{37}NOSi$: C, 75.18; H, 9.66; N, 3.65. Found: C, 75.24; H, 9.58; N, 3.60.

(1R),(2S)-1,3-diphenyl-2(N-isopropylamino)-1-propanol 7

A 40% hydrofluoric acid aqueous solution (1 ml) was dropped into a solution of compound 6 (1.50 g, 3.9 mmol) in acetonitrile (5 ml) and the reaction was stirred for 5 h at 50°C. After cooling to room temperature, water (20 ml) was added; the mixture was alkalinised with 5 N NaOH aqueous solution until pH = 12 and then extracted with dichloromethane (3 x 20 ml). The combined organic extracts were washed with brine, dried over K_2CO_3 and evaporated under vacuum affording pure compound 7 as a white solid (1.04 g, 99% yield) which was crystallised from diisopropylether.

Compound 7: m.p. 66°C; $[\alpha]_D^{20}$ -34.1 (c = 1, $CHCl_3$); >99.9% e.e. by ^{1}H-NMR in the presence of [Eu(hfc)$_3$]; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 0.81 (3H, d, J = 6.2 Hz, C$\underline{H}_3$-CH-N), 1.04 (3H, d, J = 6.3 Hz, C$\underline{H}_3$-CH-N), 2.28-2.49 (2H, m, C$\underline{H}_2$-Ph), 2.71-2.87 (1H, m, C$\underline{H}$(CH$_3$)$_2$), 3.11-3.20 (1H, m, H-2), 4.85 (1H, d, J = 3.7 Hz, H-1), 7.00-7.50 (10 H, m, aromatic protons); ^{13}C-NMR ($CDCl_3$, 50.3 MHz) δ: 22.3 (C$\underline{H}_3$-CH-N), 24.2 (C$\underline{H}_3$-CH-N), 34.8 (C$\underline{H}_2$-Ph), 46.1 (C$\underline{H}$(CH$_3$)$_2$); 61.7 (CH$_2$-C$\underline{H}$-NH), 72.0 (C$\underline{H}$OH), 125.9 (C$\underline{H}$), 126.2 (C$\underline{H}$), 126.9 (C$\underline{H}$), 128.1 (C$\underline{H}$), 128.4 (C$\underline{H}$), 128.9 (C$\underline{H}$), 139.0 (C$\underline{}$), 141.1 (C$\underline{}$); MS (70 eV): 270 (M^+ + 1), 252, 178, 162, 120, 107, 91.

Anal. Calcd. for $C_{18}H_{23}NO$: C, 80.30; H, 8.55; N, 5.20. Found: C, 80.25; H, 8.60; N, 5.24

(2S,4S,5R)-2-ethyl-2-oxo-3-isopropyl-4-phenylmethyl-5-phenyl-1,3,2-oxazaphospholane 8

Triethylamine (0.75 ml, 5.4 mmol) and a solution of ethyl phosphonic acid dichloride (0.27 ml, 2.5 mmol) in anhydrous toluene (12 ml) were added to stirred a solution of the aminoalcohol 7 (0.59 g, 2.2 mmol) in anhydrous toluene (8 ml) at -35°C under nitrogen atmosphere. After 3 h at -35°C, the reaction was left to reach room temperature and stirred overnight. The triethylamine hydrochloride was filtered over celite, the precipitate washed with dichloromethane (2 x 10 ml) and the solvent evaporated under vacuum. Water (8 ml) and dichloromethane (12 ml) were added to the residue; the organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 12 ml). The combined organic extracts were washed with brine (12 ml), dried over K_2CO_3, filtered and evaporated under vacuum.

Analysis of the ^{1}H-NMR spectrum of the crude product revealed a 8:9 diastereoisomeric ratio 12.6:1. Pure compound 8 (0.60 g, 80% yield) was obtained by silica gel flash chromatography (ethylacetate/n-hexane 9:1).

Compound 8: m.p. 147°C; $[\alpha]_D^{20}$ + 98.3 (c = 1, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.15 (3H, d, J = 6.5 Hz, C$\underline{H}_3$-CH-N), 1.22 (3H, d, J = 6.9 Hz, C$\underline{H}_3$-CH-N), 1.42 (3H, dt, J = 7.7 Hz, $J_{H\text{-}P}$ = 20.0 Hz, C$\underline{H}_3$CH$_2$P), 1.90-2.45 (4H, m, CH$_3$-C$\underline{H}_2$P and C$\underline{H}_2$Ph), 2.60-2.83 (1H, m, C$\underline{H}$(CH$_3$)$_2$), 3.81-3.87 (1H, m, H-4), 5.70 (1H, d, J = 5.5 Hz, H-5), 6.85-7.43 (10H, m, aromatic protons); ^{13}C-NMR ($CDCl_3$, 50.3 MHz) δ: 7.90 (C$\underline{H}_3$-CH$_2$P, J_C.

$_P$ = 6.6 Hz), 21.6 ($\underline{C}H_3$-CHN), 22.1 ($\underline{C}H_3$-CHN), 23.8 (CH_3-$\underline{C}H_2$-P, $J_{C\text{-}P}$ = 130.9 Hz), 37.6 ($\underline{C}H_2$-Ph), 48.7 ($\underline{C}H(CH_3)_2$, $J_{C\text{-}P}$ = 3.2 Hz), 64.6 (C-4, $J_{C\text{-}P}$ = 6.5 Hz), 79.7 (C-5), 125.6 (CH), 126.1 (CH), 128.0 (CH), 128.2 (CH), 128.4 (CH), 128.9 (CH), 135.9 (C, $J_{C\text{-}P}$ = 11.0 Hz), 138.2 (C); MS (70 eV): 344 (M^+ + 1), 252, 210, 162, 118, 91. Anal. Calcd. for $C_{20}H_{26}NO_2P$: C, 69.97; H, 7.58; N, 4.08. Found: C, 69.90; H, 7.63; N, 4.11.

(2R,4S,5R)-2-ethyl-2-oxo-3-isopropyl-4-phenylmethyl-5-phenyl-1,3,2-oxazaphospholane 9

A solution of the aminoalcohol 7 (0.59 g, 2.2 mmol) and triethylamine (0.75 ml, 5.4 mmol) in anhydrous toluene (8 ml) was heated to reflux under nitrogen atmosphere. A solution of ethyl phosphonic acid dichloride (0.27 ml, 2.5 mmol) in anhydrous toluene (12 ml) was added dropwise. After refluxing for 30', the mixture was cooled to room temperature and stirred overnight. The work-up was as described for compound 8. Analysis of the ^{1}H-NMR spectrum of the crude mixture revealed a 8:9 diastereoisomeric ratio 1:1.3. Purification by silica gel flash chromatography afforded pure compound 8 (0.20 g, 26% yield) and pure compound 9 (0.24 g, 32% yield).

Compound 9: m.p. 122-124 °C; $[\alpha]_D^{20}$ - 19.4 (c = 1, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.18 (3H, d, J = 6.3 Hz, $C\underline{H}_3$-CHN), 1.25 (3H, dt, J = 7.6 Hz, $J_{H\text{-}P}$ = 20.1 Hz, $C\underline{H}_3$-CH_2P), 1.41 (3H, d, J = 6.8 Hz, $C\underline{H}_3$-CHN), 1.86-2.30 (2H, m, CH_3-$C\underline{H}_2$P), 2.58 (1H, dd, J = 14.4 Hz, J = 7.1 Hz, $C\underline{H}_2$Ph), 2.88 (1H, dd, J = 14.4 Hz, J = 5.9 Hz, $C\underline{H}_2$Ph), 3.12-3.25 (1H, m, $C\underline{H}(CH_3)_2$), 3.84-4.08 (1H, m, H-4), 5.43 (1H, d, J = 5.4 Hz, H-5), 6.76-7.41 (10H, m, aromatic protons); ^{13}C-NMR ($CDCl_3$, 50.3 MHz) δ: 7.7 ($\underline{C}H_3$-CH_2P, $J_{C\text{-}P}$ = 5.8 Hz), 21.8 ($\underline{C}H_3$-CHN), 22.7 ($\underline{C}H_3$-CHN), 23.4 (CH_3-$\underline{C}H_2$P, $J_{C\text{-}P}$ = 124.4 Hz), 36.1 (CH_2Ph), 45.5 ($\underline{C}H(CH_3)_2$, $J_{C\text{-}P}$ = 4.7 Hz), 62.5 (C-4, $J_{C\text{-}P}$ = 9.0 Hz), 82.3 (C-5), 125.6 (CH), 125.9 (CH), 128.0 (CH), 128.2 (CH), 128.6 (CH), 135.6 (C, $J_{C\text{-}P}$ = 7.1 Hz), 138.4 (C); MS (70 eV): 344 (M^+ + 1), 252, 210, 162, 118, 91.

Anal. Calcd. for $C_{20}H_{26}NO_2P$: C, 69.97; H, 7.58; N, 4.08. Found: C, 69.92; H, 7.53; N, 4.12.

Electrophilic amination of compounds 8-9

A precooled (-30°C) solution of lithium diisopropyl amide (1.3 mmol) in anhydrous tetrahydrofuran (2.6 ml) was added via cannula to a solution of the appropriate 2-ethyl-2-oxo-1,3,2-oxazaphospholane 8-9 (1 mmol) in anhydrous tetrahydrofuran (8 ml) at -30°C and under nitrogen atmosphere (deep red colour). The reaction was stirred for 5' at -30°C. After this period, a precooled (-30°C) solution of di-tert-butyl azodicarboxilate (1.2 mmol) in tetrahydrofuran (6 ml) was added via cannula. The reaction mixture was kept at -30°C for 5', quenched with glacial acetic acid (3 mmol) and allowed to reach room temperature. The mixture was partitioned between ethylacetate (25 ml) and pH 7 phosphate buffer; the aqueous phase was extracted with ethylacetate (3 x 15 ml). The combined organic extracts were washed with water, dried over Na_2SO_4 and evaporated under vacuum. The residue was purified by silica gel flash chromatography (ethyl acetate/n-hexane) 3:7 (as eluant) in order to remove the starting material and di-tert-butyl azodicarboxilate.

The spectroscopic data refer to the mixture of diastereoisomers. The diastereomer excesses were determined by analysis of ^{1}H-NMR or ^{31}P-NMR spectra.

From 8: yield 41%; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.00-1.88 (27H, m, two $C(CH_3)_3$, CH_3-CH-N, CH_3-CH-N, CH_3-CHP), 2.20-2.55 (2H m, CH_2Ph), 2.65-2.90 (1H, m, $CH(CH_3)_2$), 3.80-4.02 (1H, m, H-4), 4.90-5.15 (1H, m, CH_3-CH-N-COOtBu), 5.60-5.71 (1H, 2d, J = 5.6 Hz, H-5), 6.75-7.45 (10H, m, aromatic protons); ^{31}P-NMR ($CDCl_3$, 81.0 MHz) δ:40.15, 41.78 (ratio 3:1); MS (CI, isobutane): 574 (M^+ + 1); MS (70 eV): 473, 373, 224, 160, 118, 91.

From 9: yield 46%; ^{1}H-NMR ($CDCl_3$, 200MHz) δ: 1.22 (3H, d, J = 6.5 Hz, CH_3-CHN), 1.42 (3H, d, J = 6.4 Hz, CH_3-CH-N), 1.45-1.53 (21H, 2s + m, two $C(CH_3)_3$, CH_3-CHP), 2.55 (1H, dd, J = 6.8 Hz, J = 13.8 Hz, CH_2Ph), 2.87 (1H, dd, J = 5.7 Hz, J = 13.8 Hz), 3.08-3.29 (1H, m, $CH(CH_3)_2$), 3.83-4.05 (1H, m, H-4), 4.95-5.15 (1H, m, CH_3-CH-N-COOtBu), 5.41 and 5.48 (1H, 2d, J = 5.0 Hz, H-5, ratio 10.8:1), 6.68-7.42 (10H, m, aromatic protons); ^{31}P-NMR ($CDCl_3$, 81.0 MHz) δ: 37.44, 38.25 (ratio 11.2:1); MS (CI, isobutane): 574 (M^+ + 1); MS (70 eV): 473, 373, 224, 160, 118, 91.

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