Tetrahedron Asymmetry Vol. 2, No. 12, pp. 1371-1378, 1991
Printed in Great Britain

0957-4166/91 $3.00+.00
Pergamon Press plc

Nitrone Cycloadditions to 2,3-Dihydro-1-phenyl-1*H*-phosphole 1-Oxide. Double Asymmetric Induction and Kinetic Resolution by a Chiral Nitrone

Andrea Goti, Stefano Cicchi, Alberto Brandi*
Dipartimento di Chimica organica "U. Schiff" and Centro dei Composti Eterociclici C.N.R., Università di Firenze, via G. Capponi 9, I-50121 Firenze, Italy

K. Michal Pietrusiewicz*
Polish Academy of Sciences, Centre of Molecular and Macromolecular Studies, Sienkiewicza 112, 90-363 Lodz, Poland

(*Received* 1 *October* 1991)

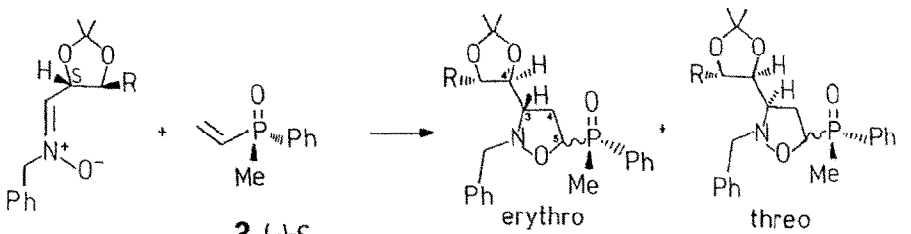
Abstract: *The cycloadditions of nitrones with 2,3-dihydro-1-phenyl-1H-phosphole 1-oxide give a single cycloadduct deriving from a highly diastereoselective approach of the nitrone anti to the phenyl ring of phospholene oxide. When the chiral gliceraldehyde derived nitrone is used, only two diastereoisomers are produced in 1.7:1 ratio. The structural assignment based on NMR data and X-ray analysis of the major isomer established a trans C3-C4 stereochemistry (derived from endo TS with respect to nitrone) and a C3-C4' relative stereochemistry of threo type in the major isomer and erythro in the minor one. Therefore, each enantiomer of phospholene oxide* **6** *gives exclusively one cycloadduct with five contiguous stereogenic centres in an established and predictable absolute configuration. The difference of reactivity of the two enantiomers allowed a partial kinetic resolution of the racemic phospholene oxide, affording (+)-(S) enantiomer with 90% enantiomeric excess.*

The cycloaddition of nitrones to vinylphosphine derivatives has provided recently access to attractively functionalized isoxazolidines, and has proven to be very broad in scope.[1,2]

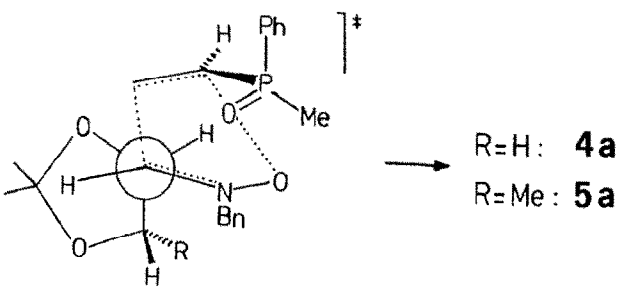
The availability of optically active vinylphosphine oxides[3] and nitrones has driven our attention to the study of the structural factors that allow the stereocontrol in the reaction. With *P*-chiral vinylphosphine derivatives the facial selectivity can be effectively controlled by the phosphorus stereocentre up to a 25:1 ratio[4] by means of a generalized "inside heteroatom" transition state model[4,5] analogous to the Houk's "inside alkoxy" model.[6]

By matching interactions with optically active nitrones the selectivity could be raised up to 40:1 for an *endo* approach.[7] In particular, when optically active nitrones such as (*S*)-(*Z*)-*N*-(2,2-dimethyl-1,3-dioxolan-4-yl)methylenebenzylamine *N*-oxide (**1**) or its 5-(*S*) methyl homologue **2** were reacted with enantiomerically pure (–)-(*S*)-methylphenylvinylphosphine oxide (**3**),[3a] high diastereoisomeric ratios have been obtained in the formation of 5-phosphinylisoxazolidines **4** and **5**.[7] The major products **4a** and **5a** were found to have the C3-C4' *erythro* and C3-C5 *trans* relative stereochemistry (Scheme 1).[7] They likely derive from a favoured *endo* approach in the transition state with the dipolarophile preferred conformation having the largest group *anti* to the incoming dipole and the oxygen inside (Scheme 2).[4,7] Therefore, nitrones (*S*) **1** and (*S,S*) **2** constitute with vinylphosphine oxide (*S*) **3** matched pairs of reagents for the highly selective synthesis of 5-phosphinylisoxazolidines.

Scheme 1



Scheme 2



Cycloaddition to the chiral racemic 2,3-dihydro-1-phenyl-1*H*-phosphole 1-oxide (**6**),[8] reported in this paper, allows us now to establish the degree of asymmetric induction that can be achieved in the formation of 4-phosphinylisoxazolidines.

RESULTS AND DISCUSSION

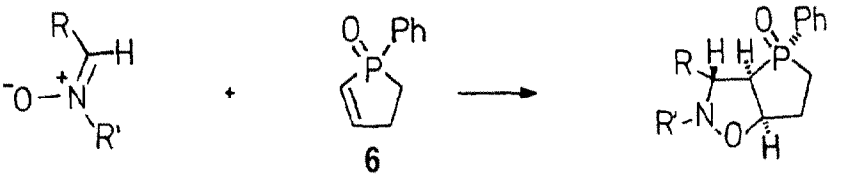
The cycloaddition reactions of phospholene oxide **6** with three model achiral nitrones **7-9** were carried out (Scheme 3). They gave regiospecifically the 4-phosphinyl adducts **10-12** in good isolated yields (65-72%).

The regiochemical assignment came straightforwardly from the observation of diagnostic signals of carbons coupled to phosphorus in the ^{13}C NMR spectra. C4 carbon atoms (δ 48-54 ppm) showed a significantly higher coupling constant ($^1J_{PC} = 68$ Hz) than C5 ones ($J_{PC} = 10$-12 Hz, δ 80-82 ppm).

The cycloadditions occurred with complete stereoselectivity giving only one diastereoisomer for each reaction. Structures **10-12** were assigned unambiguously to the cycloadducts on the basis of their ^1H NMR data and their comparison with previous results.[1] The *trans* C3-C4 relationship in compounds

10-12 is well documented by the diagnostic coupling constant between the H3 and H4 protons (5 Hz, 5.5 Hz and 7.4 Hz for **10**,[1] **11** and **12**, respectively). The relative stereochemistry is confirmed by the high values of H3-P coupling constants (14.1 Hz, 16.6 Hz and 15.7 Hz, for **10**,[1] **11** and **12** respectively), in accord with a *cis* relationship between the H3 proton and the phosphorus atom.[1] Coupling constants for a *trans* relationship typically range 7-9 Hz.[1] The preference for a C3-C4 *trans* relationship in isoxazolidines containing substituents at the C4 position has been recently proven also by a single-crystal X-ray diffraction analysis.[9]

Scheme 3



7 R-R'=-$CH_2CH_2C(CH_3)_2$-	65%	**10**
8 R= COOMe R=Me	65%	**11**
9 R= Ph R=Me	72%	**12**

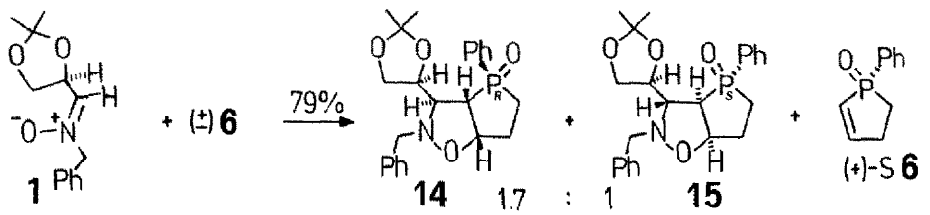
The assigned stereochemistry at the phosphorus atom (Scheme 3) has been unequivocally proven by the observation of the chemical shifts of H3 and H4 protons (isoxazolidine numbering). Values of δ 2.79, 2.96, and 3.32 ppm for H4 protons in **10**, **11** and **12**, respectively, denote the presence of a shielding effect by the *cis* phenyl ring on phosphorus. On the other hand, H3 proton (δ 4.42, 4.07, and 4.31 ppm for **10**, **11** and **12**, respectively), experiences a deshielding effect due to the proximity of the phosphinyl oxygen, if compared to other 4-phosphinylisoxazolidines from the same nitrones.[1]

The cycloaddition products **10-12**, as apparent from their structure, likely derive from a highly selective approach of the dipole on the less hindered face of the cyclic phospholene oxide, opposite to the phenyl ring. The cycloadditions allow, therefore, the complete control of four contiguous stereogenic centres in the final isoxazolidines.

The extremely high diastereoselectivity found prompted us to study the possible asymmetric induction with an optically active chiral nitrone, as (–)-(*S*) **1**. The asymmetric induction of α,β-dialkoxy nitrones to disubstituted olefins has been only little investigated.[10] DeShong and coworkers[10b] obtained with vinylene carbonate predominantly C3-C4' *erythro* cycloaddition products with moderate to good diastereofacial selectivity (up to 9:1), depending on the substitution at nitrogen and at the dioxolane ring. Thomas and coworkers[10c] obtained by cycloaddition of nitrone **1** to *E*-methylcrotonate all the four possible adducts with little selectivity.[11]

The reaction between (–)-(*S*) **1** and racemic **6**[13] could in principle furnish eight diastereomeric 4-phosphinylisoxazolidines. The ^{31}P NMR spectrum of the crude reaction mixture (2 h in refluxing toluene, with a two-fold excess of nitrone[14]) showed on the contrary only two peaks at δ 57.22 and 57.70 ppm in 1.7:1 ratio, together with some unreacted phospholene oxide **6**.[15] The two products **14** and **15** (Scheme 4) could be separated by flash column chromatography and were isolated in 79% overall yield.

Scheme 4



The two adducts were assigned the structures **14** and **15** on the basis of their ^{1}H and ^{13}C NMR spectra. The regiochemistry of the adducts derived from their ^{13}C NMR spectra that showed the signals of C4 carbons (isoxazolidine numbering) with the greater coupling constant ($^{1}J_{PC} = 68$ Hz) shifted more upfield than the corresponding C5 carbons (δ 47.56 and 46.08 ppm vs δ 81.20 and 81.08 ppm in **14** and **15**, respectively) that present a smaller coupling constant ($J_{PC} = 10$ Hz).

Both the adducts have been assigned the same C3-C4 and C4-P relative stereochemistry on the basis of their ^{1}H NMR spectra, as above. The protons on C3 show a small coupling constant with the hydrogen on C4 (J = 5-6 Hz) and a large one with phosphorus (J = 16 Hz), thus assessing the *trans* C3-C4 stereochemistry. The stereochemistry at phosphorus rests on the shielding of the proton on C4 (δ 2.61 and 3.06 ppm in **14** and **15**, respectively) and on the deshielding of the proton on C3 (δ 3.87 and 3.77 ppm), with respect to the corresponding protons in compound **13**[12] (δ 3.52 and 3.50 ppm, respectively) or in the 4-phosphinylisoxazolidine obtained[7] among the minor components from the cycloaddition of nitrone **2** with diphenylvinylphosphine oxide (δ 3.71 and 3.49 ppm, respectively).

Finally, the C3-C4' relative stereochemistry has been assigned on the basis of the coupling constants between the protons attached on those atoms, since the *threo* compounds showed regularly higher J values than the *erythro* ones in 3-dioxolanylisoxazolidines substituted at C4 with bulky groups.[10c,7] Therefore, the major product **14** was ascribed the *threo* stereochemistry and the minor **15** the *erythro* one based on $J_{H3\text{-}H4'}$ of 6.5 Hz and 4 Hz, respectively. This is also the main difference displayed by the NMR spectra of **14** and **15**, attesting that the only change of relative stereochemistry between two adjacent stereocentres in the two products occurs between C3 and C4' carbons.

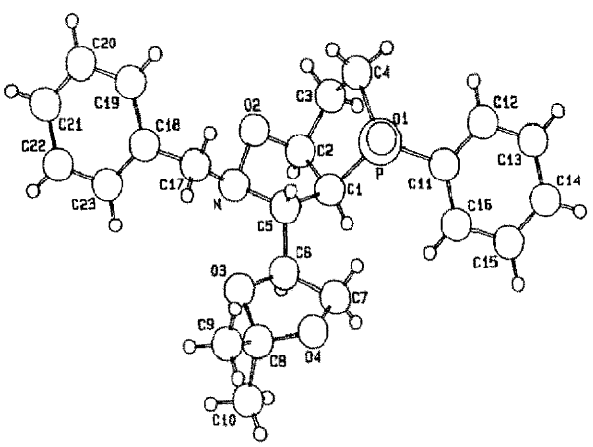


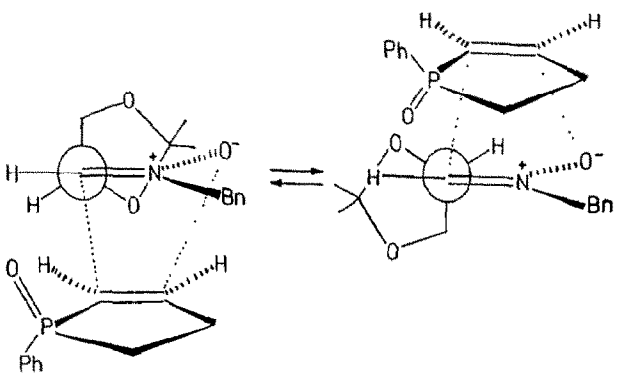
Figure 1. A perspective view of compound **14** with arbitrary atom labelling.

A single-crystal X-ray diffraction analysis[16] of the major product **14** (Figure 1) furnished the definitive proof of the correct structural assignment for that product and, indirectly, constituted a stronger support to the assignment made for the minor isomer **15**.

This structural assignment implies that the adduct **14** derived from (*R*) phospholene oxide **6** and **15** from the enantiomer (*S*) **6**, thus proving that nitrone **1** gives completely selective interactions (>99% d.e.) with both the enantiomers of **6**.

An explanation for this complete selectivity can be ascribed to highly preferred approaches of **1** to **6**, depicted in Scheme 5, to give the two products. It is reasonable that both attacks proceed *via* less encumbered *endo* (with respect to nitrone) transition states and in an antiperiplanar manner with respect to the largest methylene group of the dioxolane ring. Moreover, since as already established the phospholene oxide should attack with the oxygen *syn* and the phenyl *anti* to the nitrone, (*R*) **6** must attack the *re-re* face of **1** to give **14** and (*S*) **6** the opposite *si-si* face to give **15**.

Scheme 5



These transition state models can also account for the observed difference in reactivity between the enantiomers of **6**. In fact, the more pronounced steric hindrance present in the approach leading to compound **15** might explain the experimental 1.7:1 ratio. As a consequence of these observations it resulted that the residual unreacted phospholene oxide, that could be isolated as well although in poor yield (6%), should be highly enriched in the enantiomer with the *S* absolute configuration at the phosphorus stereogenic centre. Indeed, polarimetric measurements gave for the recovered *S*-phospholene oxide **6** a high value of specific optical rotation ($[\alpha]_D^{25} = +91.2$) that confirms its optical activity. A ^{31}P NMR experiment by employing an equimolar ratio of phospholene oxide **6** and a chiral shift reagent allowed a partial resolution of the signals of the two enantiomers of **6** and gave an estimate of 90% e.e. for the recovered phospholene oxide **6**.

Further experiments run using a 1:1 ratio of the reagents or an excess of phospholene oxide, checked by ^{31}P NMR spectroscopy at low conversions showed that the maximum ratio for the two products is 2.3:1, that should correspond to the ratio of the reaction rates of the two enantiomers of **6** towards nitrone **1**.

It is worthy of noting that the studied cycloaddition represents, to our knowledge, the first example of kinetic resolution by means of a 1,3-dipolar cycloaddition reaction. Moreover, from the organophosphorus chemistry viewpoint, it constitutes an effective resolution of the phosphorus stereogenic centre in a C-P heterocycle.[17,18] Further studies along this line are in progress in our laboratories.

EXPERIMENTAL

All reactions were carried out under nitrogen in dry and deoxygenated solvents. R_f values refer to TLC, carried out on 0.25 mm silica gel plates (Merck F_{254}). Melting points (uncorrected) were measured with a Kofler apparatus. NMR spectra in $CDCl_3$ solutions were recorded on Varian FT-80 A (^{13}C, 20 MHz; ^{31}P, 32.203 MHz) and on Varian Gemini 200 (^1H NMR, 200 MHz; ^{13}C NMR, 50 MHz) spectrometers: the chemical shifts for ^1H and ^{13}C NMR spectra are given in ppm from TMS; for ^{31}P NMR spectra in ppm from H_3PO_4 85%. Ratios of diastereomeric products were obtained by integration of the corresponding ^{31}P NMR signals of the crude mixtures. The assignment to the more significant H3, H4, H5 (isoxazolidine numbering), and H4' (dioxolanyl ring) protons are reported in the ^1H NMR spectra. IR spectra were recorded on a Perkin-Elmer 881 spectrophotometer. Optical rotation measurements were carried out on a Perkin-Elmer 241 polarimeter. Combustion analyses were carried out with a Perkin-Elmer 240 C elemental analyzer. Nitrone **1** was synthesized according to ref. 10b starting from 1,2:5,6-di-O-isopropylidene-D-mannitol. Racemic phospholene oxide **6** was synthesized according to ref. 13.

***Cycloaddition of 3,4-Dihydro-2,2-dimethyl-2H-pyrrole 1-Oxide* (7) *to 2,3-Dihydro-1-phenyl-1H-phosphole 1-Oxide* (6).**

See reference 1.[19] *6,6-Dimethyl-1-phenyl-octahydro-1H-pyrrolo[1,2-b]phospholo[2,3-d]isoxazole 1-oxide* (**10**): mp = 142-143 °C (ligroin). ^1H NMR: δ 7.75-7.60 (m, 2H), 7.55-7.40 (m, 3H), 4.77 (dddd, J = 17.6, 7.1, 4.9, 2.3 Hz, 1H, H5), 4.42 (dddd, J = 14.1, 9.0, 5.0, 1.8 Hz, 1H, H3), 2.79 (br d, J = 7.4 Hz, 1H, H4), 2.47-1.93 (m, 4H), 1.84 (m, 2H), 1.63 (m, 2H), 1.29 (s, 3H), 1.09 (s, 3H).

***Cycloaddition of C-Methoxycarbonyl-N-methyl Nitrone* (8) *to 2,3-Dihydro-1-phenyl-1H-phosphole 1-Oxide* (6).**

A solution of 107 mg (0.6 mmoles) of **6** and 140 mg (1.2 mmoles) of nitrone **8** in 1.5 ml of toluene was refluxed under stirring for two hours. The crude reaction mixture was checked by ^{31}P NMR spectroscopy. Purification by flash column chromatography (eluent ethyl acetate) and crystallization gave 115 mg of the adduct **11** (65% yield).

3-Methoxycarbonyl-2-methyl-4-phenyl-hexahydro-4H-phospholo[2,3-d]isoxazole 4-oxide (**11**): mp = 94-95 °C (diisopropylether). Anal. calcd for $C_{14}H_{18}NO_4P$: C, 56.95 ; H, 6.15 ; N, 4.74%; found C, 57.26; H, 6.35; N, 4.90%. R_f = 0.25 (ethyl acetate). ^{31}P NMR: δ 57.36; ^1H NMR: δ 7.65-7.23 (m, 5H), 4.78 (dddd, J = 21.9, 5.9, 4.3, 1.2 Hz, 1H, H5), 4.07 (dd, J = 16.6, 5.5 Hz, 1H, H3), 3.72 (s, 3H), 3.32 (dt, J = 3.6, 5.8 Hz, 1H, H4), 2.93 (s, 3H), 2.65-2.10 (m, 3H), 1.90-1.65 (m, 1H); ^{13}C NMR: δ 169.70 (d, J_{PC} = 6.9 Hz) (s), 132.46 (d, J_{PC} = 93.3 Hz) (s), 132.09 (d, J_{PC} = 2.7 Hz) (d), 129.47 (d, J_{PC} = 9.5 Hz) (d, 2C), 128.84 (d, J_{PC} = 11.4 Hz) (d, 2C), 81.13 (d, J_{PC} = 9.9 Hz) (d), 69.63 (d), 52.58 (q), 48.20 (d, J_{PC} = 68.6 Hz) (d), 44.77 (q), 24.69 (d, J_{PC} = 8.1 Hz) (t), 24.62 (d, J_{PC} = 66.7 Hz) (t); IR (CCl_4): 3062, 2955, 1750, 1438, 1222, 1197 cm^{-1}.

***Cycloaddition of C-Phenyl-N-methyl Nitrone* (9) *to 2,3-Dihydro-1-phenyl-1H-phosphole 1-Oxide* (6).**

A solution of 107 mg (0.6 mmoles) of **6** and 81 mg (0.6 mmoles) of nitrone **9** in 1.5 ml of toluene was refluxed under stirring for two hours. The crude reaction mixture was checked by ^{31}P NMR

spectroscopy. Purification by flash column chromatography (eluent ethyl acetate) and crystallization gave 135 mg of the adduct **12** (72% yield).

2-Methyl-3,4-diphenyl-hexahydro-4H-phospholo[2,3-d]isoxazole 4-oxide (**12**): mp = 129-130 °C (diisopropylether). Anal. calcd for $C_{18}H_{20}NO_2P$: C, 69.00; H, 6.43 ; N, 4.47%; found C, 69.08; H, 6.70; N, 4.49%. R_f = 0.30 (ethyl acetate). ^{31}P NMR: δ 58.00; ^1H NMR: δ 7.65-7.23 (m, 10H), 4.93 (ddd, J = 21.4, 6.8, 4.4 Hz, 1H, H5), 4.31 (dd, J = 15.7, 7.4 Hz, 1H, H3), 2.96 (dt, J = 3.0, 7.0 Hz, 1H, H4), 2.70 (s, 3H), 2.55-2.05 (m, 3H), 1.90-1.65 (m, 1H); ^{13}C NMR: δ 138.75 (d, J_{PC} = 2.7 Hz) (s), 132.67 (d, J_{PC} = 91.8 Hz) (s), 131.95 (d, J_{PC} = 2.7 Hz) (d), 129.62 (d, J_{PC} = 9.2 Hz) (d, 2C), 128.79 (d, J_{PC} = 9.9 Hz) (d, 2C), 128.69 (d, 2C), 127.78 (d), 127.66 (d, 2C), 80.82 (d, J_{PC} = 11.0 Hz) (d), 73.47 (d), 53.47 (d, J_{PC} = 67.5 Hz) (d), 42.70 (q), 24.41 (d, J_{PC} = 9.3 Hz) (t), 24.40 (d, J_{PC} = 66.1 Hz) (t); IR (CCl_4): 3061, 2970, 1438, 1254, 1197, 1159 cm^{-1}.

***Cycloaddition of 4(S)-(Z)-N-(2,2-Dimethyl-1,3-dioxolan-4-yl)methylenebenzylamine N-oxide* (1) *to 2,3-Dihydro-1-phenyl-1H-phosphole 1-Oxide* (6).**

A solution of 107 mg (0.6 mmol) of **6** and 282 mg (1.2 mmol) of nitrone **1** in 1.5 ml of toluene was refluxed for two hours. ^{31}P NMR monitoring showed the presence of two compounds in 1.7:1 ratio besides residual phospholene oxide. Purification by flash column chromatography (eluent ethyl acetate-petroleum ether 3:1) gave a fraction containing the pure major isomer **14** (70 mg, 28%), an intermediate fraction containing both the isomers (96 mg, 39%), and a third fraction containing the pure minor isomer **15** (30 mg, 12%). By elution with ethyl acetate some residual phospholene oxide **6** (6.6 mg, 6%) have been recovered (Rf = 0.05), which resulted to be optically active.

(+)-(S)-2,3-Dihydro-1-phenyl-1H-phosphole 1-oxide (**6**): $[\alpha]_D^{25}$ = +91.2 (c 0.33, $CHCl_3$). ^{31}P NMR of an equimolar solution with Yb(hfc)$_3$ gave two signals at 123.01 and 122.40 ppm for *S* and *R* enantiomers respectively, in 95:5 ratio.

(3S,3aS,4R,6aS,4'S)-2-benzyl-3(2,2-dimethyl-1,3-dioxolan-4-yl)-4-phenyl-hexahydro-4H-phospholo-[2,3-d]isoxazole 4-oxide (**14**): mp = 186-187 °C (petroleum ether). $[\alpha]_D^{25}$ = +85.9 (c 0.18, $CHCl_3$). Anal. calcd for $C_{23}H_{28}NO_4P$: C, 66.65; H, 6.81; N, 3.38%; found C, 66.61; H, 6.85; N, 3.48%. R_f = 0.20 (ethyl acetate-petroleum ether 3:1). ^{31}P NMR: δ 57.22; ^1H NMR: δ 7.75-7.62 (m, 2H), 7.55-7.22 (m, 8H), 4.71 (dddd, J = 23.1, 6.1, 4.1, 0.9 Hz, 1H, H5), 4.39 (d, J = 13.9 Hz, 1H), 4.13 (q, J = 6.8 Hz, 1H, H4'), 4.08 (d, J = 13.9 Hz, 1H), 3.91 and 3.89 (XY part of an AXY system, J_{XY} = 8.4 Hz, 2H), 3.87 (dt, J = 16.6, 6.4 Hz, 1H, H3), 2.61 (dt, J = 3.9, 6.3 Hz, 1H, H4), 2.52-2.12 (m, 3H), 1.92-1.60 (m, 1H), 1.28 (s, 6H); ^{13}C NMR: δ 137.58 (s), 133.20 d, J_{PC} = 92.1 Hz) (s), 132.18 (d, J_{PC} = 2.7 Hz) (d), 129.62 (d, J_{PC} = 9.6 Hz) (d, 2C), 128.99 (d, J_{PC} = 11.3 Hz) (d, 2C), 128.88 (d, 2C), 128.26 (d, 2C), 127.30 (d), 109.95 (s), 81.20 (d, J_{PC} = 10.0 Hz) (d), 76.43 (d, J_{PC} = 2.7 Hz) (d), 68.64 (d), 66.53 (t), 61.73 (t), 47.56 (d, J_{PC} = 68.1 Hz) (d), 26.24 (q), 25.12 (q), 25.11 (d, J_{PC} = 8.5 Hz) (t), 24.80 (d, J_{PC} = 66.6 Hz) (t); IR(CCl_4): 3065, 3034, 2987, 1541, 1437, 1381, 1371, 1200, 1157, 1113, 1068 cm^{-1}.

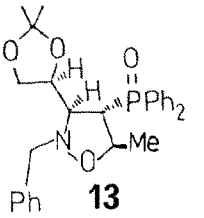
(3R,3aR,4S,6aR,4'S)-2-benzyl-3(2,2-dimethyl-1,3-dioxolan-4-yl)-4-phenyl-hexahydro-4H-phospholo-[2,3- d]isoxazole 4-oxide (**15**): mp = 115-116 °C (diisopropylether). $[\alpha]_D^{25}$ = -83.5 (c 0.28, $CHCl_3$). Anal. calcd for $C_{23}H_{28}NO_4P$: C, 66.65; H, 6.81; N, 3.38%; found C, 66.94; H, 6.97; N, 3.08%. R_f = 0.15 (ethyl acetate-petroleum ether 3:1). ^{31}P NMR: δ 57.70; ^1H NMR: δ 7.75-7.62 (m, 2H), 7.57-7.22 (m, 8H), 4.66 (dddd, J = 23.6, 6.2, 4.0, 1.2 Hz, 1H, H5), 4.21 and 4.14 (AB system, J = 13.5 Hz, 2H), 4.09 (dt, J = 4.1, 6.4 Hz, 1H, H4'), 3.95 (dd, J = 8.5, 6.6 Hz, 1H), 3.77 (ddd, J = 16.0, 5.0, 3.9 Hz, 1H, H3), 3.63 (dd, J = 8.5, 6.3 Hz, 1H), 3.06 (ddd, J = 6.1, 5.1, 3.1 Hz, 1H, H4), 2.53-2.18 (m, 3H), 1.92-1.70 (m, 1H), 1.32 (s, 3H), 1.25 (s, 3H); ^{13}C NMR: δ 136.95 (s), 133.11 (d, J_{PC} = 92.5 Hz) (s), 132.16 (d, J_{PC} = 2.6 Hz) (d), 129.66 (d, J_{PC} = 9.3 Hz) (d), 129.28 (d, 2C), 129.05 (d, J_{PC} = 11.7 Hz) (d, 2C), 128.34 (d, 2C), 127.51 (d), 109.56 (s), 81.08 (d, J_{PC} = 10.0 Hz) (d), 74.88 (d, J_{PC} = 5.7 Hz) (t), 68.50 (d), 66.81 (t), 61.80 (t), 46.08 (d, J_{PC} = 68.8 Hz) (d) , 26.31 (q), 25.16 (d, J_{PC} = 8.9 Hz) (t), 24.89 (q), 24.69 (d, J_{PC} = 66.4 Hz) (t); IR ($CDCl_3$): 3066, 3033, 2938, 1495, 1438, 1372, 1260, 1182, 1155, 1112, 1062 cm^{-1}.

ACKNOWLEDGMENTS

Financial support of this study by Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST) and Consiglio Nazionale delle Ricerche (CNR)-Italy, and Polish Academy of Sciences (CPBP-01.13)-Poland is gratefully acknowledged. Authors thank Mrs. B. Innocenti for technical support.

REFERENCES AND NOTES

1. Brandi, A.; Cicchi, S.; Goti, A.; Pietrusiewicz, K. M.; Wisniewski, W. *Tetrahedron* **1990**, *46*, 7093-7104.
2. Brandi, A.; Cicchi, S.; Goti, A.; Pietrusiewicz, K. M. *Gazz. Chim. Ital.* **1991**, *121*, 285-295.
3. a) Pietrusiewicz, K. M.; Zablocka, M.; Monkiewicz, J. *J. Org. Chem.* **1984**, *49*, 1522-1526. b) Johnson, C. R.; Imamoto, T. *J. Org. Chem.* **1987**, *52*, 2170-2174.
4. a) Brandi, A.; Cicchi, S.; Goti, A.; Pietrusiewicz, K. M.; Zablocka, M.; Wisniewski, W. *J. Org. Chem.* **1991**, *56*, 4383-4388. b) Brandi, A.; Cannavò, P.; Pietrusiewicz, K. M.; Zablocka, M.; Wieczorek, W. *J. Org. Chem.* **1989**, *54*, 3073-3077.
5. Annunziata, R ; Cinquini, M.; Cozzi, F.; Giaroni, P.; Raimondi, L. *Tetrahedron Lett.* **1991**, *32*, 1659-1662.
6. a) Houk, K. N.; Moses, S. R.; Wu, Y.-D., Rondan, N. G.; Jäger, V.; Schohe, R.; Fronczek, F. R. *J. Am. Chem. Soc.* **1984**, *106*, 3880-3882. b) Houk, K. N.; Duh, H.-Y.; Wu, Y.-D.; Moses, S. R. *J. Am. Chem. Soc.* **1986**, *108*, 2754-2755.
7. Brandi, A., Cicchi, S.; Goti, A.; Pietrusiewicz, K. M. *Tetrahedron: Asymmetry*, in press.
8. To our knowledge, the only reported examples of cycloadditions to **6** regard Diels-Alder reactions. a) Chan, T. H.; Wong, L. T. L. *Can. J. Chem.* **1971**, *49*, 530-531. b) Morris, D. L.; Berlin, K. D. *Phosphorus* **1974**, *4*, 69-71.
9. Pietrusiewicz, K. M.; Zablocka, M.; Wieczorek, W.; Bujacz, G.; Brandi, A. *Phosphorus, Sulfur, and Silicon* **1990**, *48*, 11-16.
10. a) DeShong, P.; Lander, S. W ; Leginus, J M.; Dicken, C. M. Dipolar Cycloadditions of Nitrones with Vinyl Ethers and Silane Derivatives. In *Advances in Cycloaddition*; Curran, D. P., Ed.; vol 1, p. 87-128. b) DeShong, P.; Dicken, C. M.; Leginus, J. M.; Whittle, R. R. *J. Am. Chem. Soc.* **1984**, *106*, 5598-5602. c) Fray, J. M.; Jones, R. H.; Thomas, E. J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2753-2761.
11. A very poor selectivity was also observed by us in a preliminary cycloaddition of (*S*) **1** to *E*-1-diphenylphosphinylpropene, which furnished, besides some decomposition product, all the four possible 4-phosphinylisoxazolidines.[12] *Z*-1-diphenylphosphinylpropene also afforded all the possible 4-phosphinyl regioisomers with only a slightly better selectivity, still accompanied by decomposition products. Moreover, the reported cycloadditions of **1** and **2** to diphenylvinylphosphine oxide,[7] which also produced small amounts of 4-phosphinylisoxazolidines, gave a moderate selectivity in that regioisomeric approach.
12. One of these diastereoisomers (^{31}P NMR· δ 27.89 ppm) has been isolated and it was assigned the structure **13** with *trans* C3-C4 and *threo* C3-C4' relative stereochemistry on the basis of the following ^{1}H NMR data: δ 8.00-7.20 (m, 15H), 4.65 (dquintet, J = 19.2, 7.1 Hz, 1H, H5), 4.50 (d, J = 12.4 Hz, 1H), 4.33 (d, J = 12.4 Hz, 1H), 3.88 (q, J = 6.9 Hz, 1H, H4'), 3.79 (dd, J = 8.4, 6.5 Hz, 1H), 3.52 (ddd, J = 7.3, 6.1, 2.6 Hz, 1H, H4), 3.50 (ddd, J = 16.2, 7.5, 2.7 Hz, 1H, H3), 2.99 (dd, J = 8.4, 6.7 Hz, 1H), 1.32 (d, J = 6.7 Hz, 3H), 1.16 (s, 3H), 0.83 (s, 3H).



13

13. Quin, L. D.; Gratz, J. P.; Barket, P. T. *J. Org. Chem.* **1968**, *33*, 1034.
14. Nitrone **1** partially decomposed by prolonged heating in these conditions. In refluxing benzene **1** and **6** were practically unreactive.
15. Other possible isomers lie below the 1% detection threshold of ^{31}P NMR spectroscopy, which was shown to be a very powerful and accurate technique to reveal the presence of phosphorus containing products present in even very little amount.[7]
16. The X-ray analysis was performed in collaboration with W. Wieczorek, Technical University of Lodz - Poland. Full details will be published elsewhere.
17. Quin, L. D. *The Heterocyclic Chemistry of Phosphorus: Systems Based on the Phosphorus-Carbon Bond*; Wiley-Interscience: New York 1981.
18. Part 14 in a series on Optically Active Phosphine Oxides. For Part 13, see ref. 7.
19. The data of a better resolved ^{1}H NMR spectrum are reported herein.