Stereoselective Nitrone Additions to Vinylphosphine Derivatives: Effect of Phosphorus Substituents on Reaction Diastereoselectivity

Alberto Brandi,* Stefano Cicchi, and Andrea Goti

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,* Maria Zablocka, and Witold Wisniewski

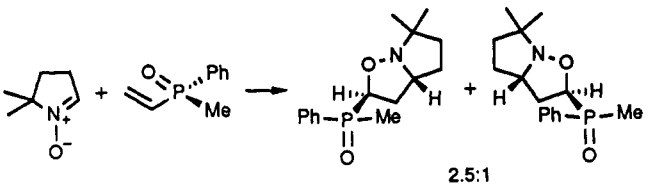
Polish Academy of Sciences, Centre of Molecular and Macromolecular Studies, Sienkiewicza 112, 90-363 Lodz, Poland

Received February 7, 1991

Meaningful diastereofacial selectivity in cycloaddition of 2,2-dimethyl-3,4-pyrroline *N*-oxide (DMPO) to 12 structurally diversified vinylphosphine derivatives 1–12 has been achieved by proper choice of the polar substituent on phosphorus combined with effective steric differentiation of the remaining substituents. The unique sense of induction in all these reactions is consistent with the assumption that vinylphosphorus dipolarophiles prefer an s-cisoid array of C=C—P=X fragments in their reactive conformations. Use of divinylphosphine derivatives in such reactions exemplifies the possibility of synthesizing chiral phosphine oxides and sulfides from prochiral precursors in a highly selective and stereochemically predictable manner. An observation that in ^{31}P NMR spectra the adducts of type I are uniformly found at lower field than adducts of type II facilitates the stereochemical assignments.

Diastereofacial selectivity of additions to allylic double bonds in acyclic systems is currently of great synthetic and theoretical importance.[1,2] Especially noteworthy are the additions to olefins containing an allylic oxygen-bearing stereocenter that often afford adducts with a stereochemically predictable outcome.[3] The observed stereochemistries, however, do not appear to lend themselves to a single transition state (TS) rationale common for all the additions. In a related study on cycloadditions of nitrile oxides and nitrones to a model P-chiral vinylphosphine oxide we have noted that the facial selectivity in these reactions can also be effectively controlled by the oxygenated phosphorus stereocenter (Scheme I).[4]

Scheme I



In this paper we report on a series of cycloaddition experiments that give some insight into the possible origin of the observed selectivity, which, in turn, is now shown to reach over 90% in the most favorable cases. Cycloadditions of nitrones to vinylphosphine derivatives provide attractively functionalized isoxazolidines and have already been shown to be very broad in scope.[5]

Results and Discussion

2,2-Dimethyl-3,4-pyrroline *N*-oxide (DMPO) chosen to serve as the model nitrone was reacted with 12 structurally diversified chiral and prochiral vinylphosphine derivatives, including seven oxides, **1–5**, **10**, and **11**, three sulfides, **6**, **8**, and **12**, a selenide **9**, and a phosphinimine **7**. The yields and selectivity data are collected in Table I.

Proof of stereochemistry for entry 1 was obtained from the detailed spectral analysis supported by an X-ray measurement as described previously.[4] For the other entries stereochemical assignments were made by analogy based on the highly diagnostic patterns of the isoxazolidine ring proton resonances in the major and the minor isomers.[4] Further confirmation of the assignment of the stereochemistry of the adducts derived from *tert*-butylphosphine derivatives comes also from an X-ray analysis of the major product of entry 12 for which the relative configuration corresponding to I was accordingly found.[6] Stereochemistry of the novel phosphinimine adducts of entry 7 followed in turn from their conversions into the corresponding phosphine oxides of known configuration (see Experimental Section). It is of interest to note that all the products assigned ultimately the favored stereo-

(1) For general references, see: (a) Control of Acyclic Stereochemistry. Mukaiyama, T., Ed. *Tetrahedron: Symposia-in-print* **1984**, *40*, 2197–2343. (b) *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York; 1983; Vol. 2; 1984; Vol. 3.

(2) (a) Paddon-Row, M. N.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 7162. (b) Houk, K. N.; Paddon-Row, M. N.; Rondan, N. G.; Wu, Y.-D.; Brown, F. K.; Spellmeyer, D. C.; Metz, J. T.; Li, Y.; Loncharich, R. J. *Science* **1986**, *231*, 1108. (c) Kahn, S. D.; Pau, C. F.; Overman, L. E.; Hehre, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 7381. (d) Kahn, S. D.; Pau, C. F.; Hehre, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 7396. (e) Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 7399. (f) Kahn, S. D.; Pau, C. F.; Chamberlin, A. R.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 650. (g) Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 663. (h) Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 666. (i) Chamberlin, A. R.; Mulholland, R. L., Jr.; Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 672.

(3) For some recent examples, see the following references. Diels–Alder reaction: (a) Greé, R.; Kessabi, J.; Mosset, P.; Martelli, J.; Carrié, R. *Tetrahedron Lett.* **1984**, *25*, 3697. (b) Franck, R. W.; Argade, S.; Subramanian, C. S.; Frechet, D. M. *Tetrahedron Lett.* **1985**, *26*, 3187. (c) Franck, R. W.; John, T. V.; Olejniczak, K.; Blount, J. F. *J. Am. Chem. Soc.* **1982**, *104*, 1106. (d) Horton, D.; Machinami, T.; Takagi, Y. *Carbohydr. Res.* **1983**, *121*, 135. Simmons-Smith reaction: (e) Ratier, M.; Castaing, M.; Godet, J.-Y.; Pereyre, M. *J. Chem. Res. (S)* **1978**, 179. Oxidation: (f) Rossiter, B. E.; Verhoeven, T. R.; Sharpless, K. B. *Tetrahedron Lett.* **1979**, 4733. Hydroboration: (g) Still, W. C.; Barrish, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 2487. Iodoacetylation: (h) Chamberlin, A. R.; Mulholland, R. L., Jr. *Tetrahedron* **1984**, *40*, 2297. 1,3-Dipolar cycloaddition: (i) 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. (j) Houk, K. N.; Duh, H.-Y.; Wu, Y.-D.; Moses, S. R. *J. Am. Chem. Soc.* **1986**, *108*, 2754. (k) Annunziata, R.; Cinquini, M.; Cozzi, F.; Gennari, C.; Raimondi, L. *J. Org. Chem.* **1987**, *52*, 4674. (l) Curran, D. P.; Gothe, S. A. *Tetrahedron* **1988**, *44*, 3945. (m) De Amici, M.; De Micheli, C.; Ortisi, A.; Gatti, G.; Gandolfi, R.; Toma, L. *J. Org. Chem.* **1989**, *54*, 793. Osmylation: (n) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247 and references cited therein. (o) Vedejs, E.; McClure, C. K. *J. Am. Chem. Soc.* **1986**, *108*, 1094. (p) Vedejs, E.; Dent, W. H. III *J. Am. Chem. Soc.* **1989**, *111*, 6861. (q) Evans, D. A.; Kaldor, S. W. *J. Org. Chem.* **1990**, *55*, 1698. (r) Stork, G.; Kahn, M. *Tetrahedron Lett.* **1983**, *24*, 2951.

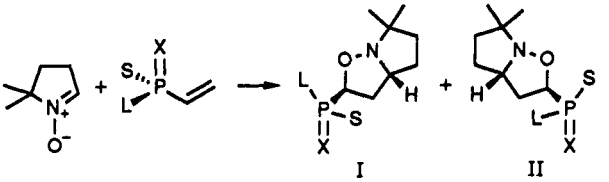
(4) Brandi, A.; Cannavò, P.; Pietrusiewicz, K. M.; Zablocka, M.; Wieczorek, M. *J. Org. Chem.* **1989**, *54*, 3073.

(5) Brandi, A.; Cicchi, S.; Goti, A.; Pietrusiewicz, K. M.; Wisniewski, W. *Tetrahedron* **1990**, *46*, 7093.

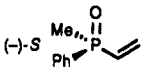
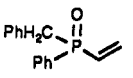
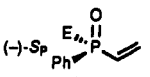
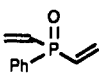
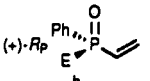
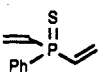
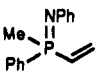
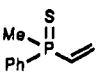
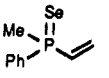
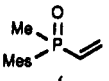
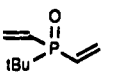
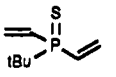
(6) Wieczorek, W. Technical University of Lodz, to be published.

0022-3263/91/1956-4383$02.50/0

Table I. 1,3-Dipolar Cycloadditions of DMPO to Chiral and Prochiral Vinylphosphine Derivatives



I II

entry	dipolarophile	yield,[a] %	δ^{31}P NMR I	δ^{31}P NMR II	diastereomeric ratio I:II
1	 1	87 (95)	37.6	37.5	71:29
2	 2	84 (89)	36.6	35.9	44:56
3	 3[b]	89 (100)	32.4	32.0	50:50
4	 4	47 (73)[c]	27.7	26.8	60:40
5	 5[b]	85 (91)	33.5	33.1	67:33
6	 6	68 (82)[d]	40.8	38.6	73:27
7	 7	–[e] (85)	10.2	9.0	76:24
8	 8	95 (100)	42.1	40.6	80:20
9	 9	89 (95)	31.3	29.2	80:20
10	 10[f]	73 (91)	43.5	42.8	90:10
11	 11	84 (92)	47.2	44.9	92:8
12	 12	80 (100)	62.0	61.6	96:4

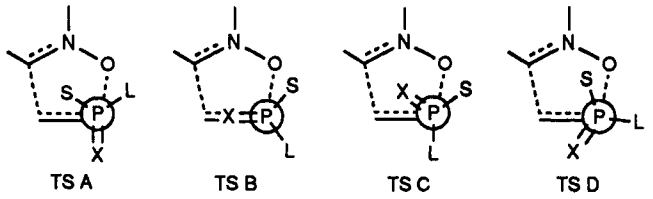
[a] Isolated compounds; in parentheses are the ^{31}P NMR yields. [b] E represents CH_2CO_2-L-menthyl. [c] 84% conversion. [d] 80% conversion. [e] Converted into the oxides without isolation. [f] Mes represents 2,4,6-trimethylphenyl.

chemistry (type I) were uniformly found in ^{31}P NMR spectra at lower field than those of relative stereochemistry of type II. Although the origin and range[7] of this behavior remains to be established, the observation seems to be of some practical value in aiding prompt recognition of the two stereoisomeric products in the studied reactions. For example it has already served in this work to suggest the assignment for products in entry 2 for which distinctions of all isoxazolidine ring protons in their ^{1}H NMR spectra were less straightforward than in all other cases.

Several features of the data set are noteworthy. Comparison of entries 1–4 indicates that diastereoselectivity of the studied cycloadditions is practically lost when the small Me group in 1 is replaced with any sterically more demanding substituent (cf. also entries 6 and 8). Even though the one of the P-epimeric menthoxycarbonylmethyl

(7) It seems that monocyclic isoxazolines derived from nitrile oxide addition to methylphenylvinylphosphine oxide are likely to follow the same trend.[4]

Chart I



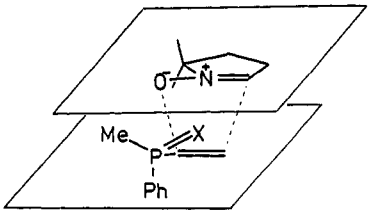


Figure 1.

oxides, i.e., **5**, contained apparently a cooperating pair of the chiral phosphorus and menthyl moieties, the diastereoselectivity in its reaction with DMPO was found still lower than in the reaction of oxide **1**. On the other hand, substitution of the large phenyl group with a larger mesityl group leads to a nearly 4 times improvement of selectivity (cf. entries 1 and 10), underscoring the importance of steric factors in the studied cycloadditions. This effect is even more evident in prochiral divinyl compounds where the substitution of the phenyl group with a still larger *tert*-butyl group leads to a remarkable 8 times improvement of selectivity (cf. entries 4–11 and 6–12). In turn, variation of the heteroatom substituent on phosphorus revealed that the size of the heteroatom and/or the polarity and distance of its bonding to phosphorus are also likely factors to influence the ultimate stereochemical results, with the larger and the less electronegative substituent affording the more diastereoselective reaction (cf. entries 1, 7, 8, and 9, as well as 11 and 12). The found trend is well illustrated by the comparison of the atomic radii, electronegativity, and P=X distances for oxygen, nitrogen, sulfur, and selenium.[8] Unfortunately, a similar comparison with the parent methylphenylvinylphosphine could not be made since, in contrast to diphenylvinylphosphine,[9] it was oxidized by DMPO prior to cycloaddition.

Several plausible TS models could be considered in analysis of the stereochemical course of the studied cycloadditions to give the major isomers (Chart I). Model TS A assumes that the vinylphosphine derivative adopts a conformation in which the most polar substituent is oriented anti with respect to the incoming dipole in analogy to models suggested recently for related intramolecular cycloadditions,[10] and in accord with the product solid-state geometry.[3j,4] A "syn coplanar" model TS B is based upon the ground-state conformational effects[3f,11] and an implied bias for conjugated olefins to react thermally in the s-cis array.[12] Distortion from the coplanarity in either of the two directions creates in turn two further likely constructs, i.e. TS C and TS D, resembling Houk's 1,3-dipolar cycloaddition to allyl ethers[3i,j] and Vedejs' osmylation[3o,p] transition states, respectively. In fact, all of these models are equally consistent with the observed enhancement of diastereoselection on maximizing the size difference between the two less polar substituents at phosphorus (S, smaller; L, larger). Variation of the polar substituent X, however, could reasonably be expected to affect only the stereoselectivity of cycloadditions proceeding through TS C. In the other models the X group is either oriented away from the face of attack of the nitrone or it is coplanar with the double bond and therefore unable to exert any discriminating effect on the two olefin diastereofaces.

The implied preference for TS C resembling closely Houk's "inside alkoxy" TS[3i,j] allows us to infer that Houk's argument that the allylic oxygen prefers an inside vs an outside position in order to minimize electronic and steric repulsions[3j] applies to the studied cycloadditions with a possible extension of the effects also on other heteroatom groupings. The observed differences in selectivity connected with the change of the heteroatom substituent on phosphorus might either have resulted from palpable differences in conformational preference of the studied vinylphosphine derivatives or, more probably, from the difference in polar and/or steric effects imposed on the organophosphorus dipolarophile by the incoming nitrone.

To conclude, we have demonstrated that by judicious selection of substituents on phosphorus, a considerable diastereofacial selectivity in additions of nitrones to chiral vinylphosphine derivatives can be achieved. It also appears that the transition state shown in Figure 1 may serve as a useful construct for predicting the sense of induction for these reactions. Of particular interest in this respect are the results of entries 11 and 12 in Table I, which provide unique examples of synthesis of chiral phosphine oxides and sulfides from prochiral precursors in a highly stereoselective and predictable manner. Further studies along this line are in progress in our laboratories.[13]

Experimental Section

All reactions were carried out under nitrogen. R_f values refer to TLC, carried out on 0.25-mm silica gel plates (Merck F254). Melting points are uncorrected. NMR spectra were taken in $CDCl_3$. 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. In case of divinyl derivatives the ratio changed with time, as double addition took partially place; in Table I is reported the initial ratio. (−)-(*S*)-methylphenylvinylphosphine oxide (**1**) and enantiomeric vinylphosphine oxides **3** and **5** were synthesized according to ref 14. Racemic vinylphosphine oxides **2** and **10** were available from another study.[15] Racemic methylphenyl-

(8) Compare the following properties of oxygen, nitrogen, sulfur, and selenium, respectively. Atomic radii: 0.6, 0.92, 1.27, and 1.4 Å. Electronegativity: 3.5, 3.0, 2.5, and 2.4. P=X distance: 1.48 Å (see ref 4), 1.58 Å (Imhoff, P.; van Asselt, R.; Elsevier, C. J.; Vrieze, K.; Goubitz, K.; van Malsen, K. S.; Stamm, C. H. *Phosphorus Sulfur Silicon* **1990**, *47*, 401), 1.95 Å (Samuel, D.; Zhang, S. Y.; Kagan, H. B. *Phosphorus Sulfur* **1984**, *21*, 145) and 2.1 Å (Wieczorek, W. Technical University of Lodz, private information).

(9) Brandi, A.; Goti, A.; Pietrusiewicz, K. M. *J. Chem. Soc., Chem. Commun.* **1989**, 388.

(10) (a) Kozikowski, A. P.; Ghosh, A. K. *J. Org. Chem.* **1984**, *49*, 2762. (b) Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L. *Tetrahedron* **1987**, *43*, 2369.

(11) Vinylphosphine oxides **3** and **4** have been found to favor the s-cis conformation in the crystal state: Pietrusiewicz, K. M.; Kuznikowski, M.; Wieczorek, W.; Maniukiewicz, W.; Rospenk, M. *Heteroatom Chem.*, in press. Similar assessments for vinyl sulfoxides have already been published.[12e] See also: Kahn, S. D.; Hehre, W. J. *Tetrahedron Lett.* **1986**, *27*, 6041. For ground-state conformations of related α,β-unsaturated carbonyl compounds, see: Loncharich, R. J.; Schwartz, T. R.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 14. Chamberlin, A. R.; Reich, S. H. *J. Am. Chem. Soc.* **1985**, *107*, 1440.

(12) (a) Curran, D. P.; Kim, B. H.; Piyasena, H. P.; Loncharich, R. J.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 2137. (b) Pyne, S. G.; Griffith, R.; Edwards, M. *Tetrahedron Lett.* **1988**, *29*, 2089. (c) Koizumi, T.; Arai, Y.; Takayama, H.; Kuriyama, K.; Shiro, M. *Tetrahedron Lett.* **1987**, *28*, 3689 and references cited therein. See also ref 2e.

(13) This paper constitutes Part 11 in a series on Optically Active Phosphine Oxides. For Part 10, see ref 11.

(14) (a) Bodalski, R.; Rutkowska-Olma, E.; Pietrusiewicz, K. M. *Tetrahedron* **1980**, *36*, 2353. (b) Pietrusiewicz, K. M.; Zablocka, M.; Monkiewicz, J. *J. Org. Chem.* **1984**, *49*, 1552.

vinylphosphine sulfide (8), and selenide (9) were synthesized from methylphenylvinylphosphine[16] by treatment with sulfur and selenium, respectively. Divinylphenylphosphine oxide (4) and sulfide (6) were synthesized according to ref 15. DMPO is available from Aldrich.

Synthesis of *tert*-Butyldivinylphosphine Oxide (11) and *tert*-Butyldivinylphosphine Sulfide (12). To the solution of vinylmagnesium bromide prepared from 3 g (0.125 mol) of Mg and 13.4 g (0.125 mol) of vinyl bromide in 50 mL of THF was added slowly at room temperature 6.25 g (0.04 mol) of *tert*-butyldichlorophosphine in 20 mL of THF. After 2 h all the THF was distilled off at normal pressure, and the residue was added to 250 mL of petroleum ether and 35 mL of pyridine. The resulting precipitate was filtered off, and the solvent was removed from the filtrate by distillation at normal pressure. The residue was then Kugelrohr distilled at 50 °C under reduced pressure (water aspirator, dry ice cooling of the receiver). The distillate containing pyridine and the expected *tert*-butyldivinylphosphine as judged by ^{31}P NMR monitoring was divided into two equal parts, which were directly used for synthesis of *tert*-butyldivinylphosphine oxide (11) and *tert*-butyldivinylphosphine sulfide (12) by treatment with aqueous H_2O_2 in benzene and excess of S_8 in benzene, respectively. After the oxidations were completed (^{31}P NMR monitoring) the benzene solutions were washed three times with 5% HCl and water and finally dried over $MgSO_4$.

Concentration of the phosphine oxide solution in vacuo furnished crude oxide 11, which has been purified by sublimation at 50 °C (10^{-2} mmHg). 11: 0.45 g (15%). Anal. Calcd for $C_8H_{15}OP$ (sealed vessel): C, 60.75; H, 9.56. Found: C, 60.84; H, 9.67. ^{31}P NMR: δ 37.86. ^1H NMR: δ 6.34–6.10 (m, 6 H), 1.08 (d, J = 15.1 Hz, 9 H). ^{13}C NMR: δ 134.8 (t), 128.2 (d, J_{PC} = 89 Hz) (d), 31.51 (d, J_{PC} = 75 Hz) (s), 23.94 (q). MS: m/e (rel intensity) 159 ($M + 1^+$, 8), 158 (M^+, 1), 102 (100), 57 (30), 55 (63).

Concentration of the phosphine sulfide solution provided crude sulfide 12, which was purified by chromatography using CCl_4 as eluant. 12: 0.56 g (16%), mp 70.5–71.5 °C. Anal. Calcd for $C_8H_{15}PS$: C, 55.15; H, 8.68. Found: C, 54.88; H, 8.60. ^{31}P NMR: δ 54.2. ^1H NMR: δ 6.54–6.11 (m, 6 H), 1.17 (d, J = 16.5 Hz, 9 H). ^{13}C NMR: δ 133.06 (t), 128.24 (d, J_{PC} = 72 Hz) (d), 33.58 (d, J_{PC} = 57 Hz) (s), 24.70 (q). MS: m/e (rel intensity) 174 (M^+, 49), 118 (100), 57 (62), 55 (33).

Cycloaddition of DMPO to (*S*)-(−)-Methylphenylvinylphosphine Oxide (1). A solution of 133 mg (0.88 mmol) of oxide 1 and 108 mg (0.96 mmol) of DMPO in 1.5 mL of $CHCl_3$ was left at 25 °C for 20 days. Purification by chromatography (CH_2Cl_2–MeOH, 20:1, R_f = 0.35) yielded 154 mg (87%) of the two isomeric products as a colorless oil. Repeated chromatographic separations provided small amounts of spectroscopically pure diastereoisomers for which specific rotation values, $[\alpha]^{25}_D$ = +18.0° (c = 3.4, $CHCl_3$) and $[\alpha]^{25}_D$ = −22.5° (c = 1.7, $CHCl_3$), were recorded for the major and minor isomers, respectively. Other physical and spectral properties of the two isomers were found to be identical with those found previously for their racemic counterparts (see ref 4).

Cycloaddition of DMPO to Benzylphenylvinylphosphine Oxide (2). A solution of 363 mg (1.5 mmol) of oxide 2 and 192 mg (1.7 mmol) of DMPO in 1.5 mL of CH_2Cl_2 was left at 25 °C for 7 days. Purification by chromatography (CH_2Cl_2–MeOH, 10:1, R_f = 0.45), yielded 448 mg (84%) of the two isomeric products as a colorless waxy solid. Anal. (mixture of isomers) Calcd for $C_{21}H_{26}NO_2P$: C, 70.97; H, 7.37; N, 3.94. Found: C, 70.82; H, 7.23; N, 3.82. MS: m/e (rel intensity) 355 (M^+, 1), 216 (20), 140 (99), 125 (42), 91 (100). IR ($CDCl_3$): 3065 (w), 3032 (w), 2904 (w), 1602 (m), 1437 (m), 1199 (vs), 1183 (vs) cm^{-1}.

Major. ^{31}P NMR: δ 35.95. ^1H NMR: δ 7.95–7.05 (m, 10 H), 4.22 (ddd, J = 9.8. 7.0, 2.4 Hz, 1 H), 3.71 (m, 1 H), 3.57 (dd, J = 14.6, 11.1 Hz, 1 H), 3.38 (dd, J = 16.3, 14.6 Hz, 1 H), 1.42 (s, 3 H), 1.06 (s, 3 H). ^{13}C NMR: δ ipso carbons not detected, 131.60 (d, J_{PC} = 2.6 Hz) (d), 130.97 (d, J_{PC} = 8.7 Hz) (d), 130.04 (d, J_{PC} = 5.3 Hz) (d), 128.09 (d), 127.97 (d, J_{PC} = 7.1 Hz) (d), 126.35 (d, J_{PC} = 3.0 Hz) (d), 74.67 (d, J_{PC} = 83.0 Hz) (d), 69.54 (s), 64.01 (d, J_{PC} = 5.3 Hz) (d), 38.16 (t), 36.46 (t), 33.10 (d, J_{PC} = 61.4 Hz) (t), 31.29 (t), 27.30 (q), 24.32 (q).

Minor. ^{31}P NMR: δ 36.56. ^1H NMR: δ 7.95–7.05 (m, 10 H), 4.43 (dt, J = 8.1, 6.1 Hz, 1 H), 4.07–3.95 (m, 1 H), 3.55 (d, J = 14.2 Hz, 2 H), 1.44 (s, 3 H), 1.14 (s, 3 H). ^{13}C NMR: δ ipso carbons not detected, 132.01 (d, J_{PC} = 2.7 Hz) (d), 132.00 (d, J_{PC} = 8.3 Hz) (d), 130.05 (d, J_{PC} = 5.2 Hz) (d), 128.45 (d), 128.30 (d, J_{PC} = 8.5 Hz) (d), 126.78 (d, J_{PC} = 3.2 Hz) (d), 72.92 (d, J_{PC} = 86.6 Hz) (d), 69.59 (s), 64.29 (d, J_{PC} = 7.2 Hz) (d), 38.36 (t), 36.93 (d, J_{PC} = 61.7 Hz) (t), 36.81 (t), 30.91 (t), 27.30 (q), 24.32 (q).

Cycloaddition of DMPO to (−)-(S_P)-((Menthoxycarbonyl)methyl)phenylvinylphosphine Oxide (3). A solution of 522 mg (1.5 mmol) of oxide 3 and 192 mg (1.7 mmol) of DMPO in 1 mL of CH_2Cl_2 was left at 25 °C for 7 days. Purification by chromatography (ethyl acetate) yielded 620 mg (89%) of the two isomeric products as a colorless oil. Anal. (mixture of isomers) Calcd for $C_{26}H_{40}NO_4P$: C, 67.65; H, 8.73; N, 3.03. Found: C, 67.25, H, 8.92; N, 3.06. IR ($CHCl_3$): 2962 (vs), 2873 (s), 1724 (vs), 1601 (w), 1465 (m), 1267 (vs), 1112 (m) cm^{-1}.

Type I. R_f = 0.2 (ethyl acetate). $[\alpha]^{25}_D$ = −45.2° (c = 10, $CHCl_3$). ^{31}P NMR: δ 32.42. ^1H NMR: δ 7.95–7.86 (m, 2 H), 7.57–7.43 (m, 3 H), 4.49 (dt, J = 4.3, 12.8 Hz, 1 H), 4.35 (q, J = 8.1 Hz, 1 H), 3.98–3.92 (m, 1 H), 3.08–2.92 (m, 1 H), 1.32 (s, 3 H), 1.05 (s, 3 H), 0.78 (d, J = 6.8 Hz, 3 H), 0.75 (d, J = 6.8 Hz, 3 H), 0.52 (d, J = 7.0 Hz, 3 H). ^{13}C NMR: δ 165.72 (d, J_{PC} = 4.9 Hz) (s), 131.95 (d, J_{PC} = 2.9 Hz) (d), 131.06 (d, J_{PC} = 9.2 Hz) (d), 128.13 (d, J_{PC} = 11.7 Hz) (d), 74.73 (d, J_{PC} = 86.5 Hz) (d), 69.33 (s), 63.96 (d, J_{PC} = 4.6 Hz) (d), 46.36 (d), 40.17 (t), 37.54 (t), 34.24 (d, J_{PC} = 56.5 Hz) (t), 33.89 (t), 31.24 (t), 31.06 (t), 27.20, 25.49, 24.12, 22.88, 21.69, 20.56, 15.77.

Type II. R_f = 0.1 (ethyl acetate). $[\alpha]^{25}_D$ = +11.5° (c = 4.8, $CHCl_3$). ^{31}P NMR: δ 32.00. ^1H NMR: δ 7.95–7.86 (m, 2 H), 7.57–7.42 (m, 3 H), 4.67–4.57 (m, 2 H), 3.72–3.69 (m, 1 H), 3.35 (t, J = 13.5 Hz, 1 H), 3.20 (t, J = 13.5 Hz, 1 H), 1.33 (s, 3 H), 0.99 (s, 3 H), 0.83 (d, J = 6.6 Hz, 3 H), 0.81 (d, J = 7.1 Hz, 3 H), 0.64 (d, J = 6.9 Hz, 3 H). ^{13}C NMR: δ 165.63 (d, J_{PC} = 6.1 Hz) (s), ortho carbons not discerned, 132.00 (d, J_{PC} = 8.7 Hz) (d), 128.25 (d, J_{PC} = 11.8 Hz) (d), 128.00 (d, J_{PC} = 97.2 Hz) (d), 73.90 (d, J_{PC} = 77.9 Hz) (d), 69.48 (s), 64.45 (d, J_{PC} = 7.2 Hz) (d), 46.59 (d), 40.44 (t), 38.21 (t), 37.08 (d, J_{PC} = 51.3 Hz) (t), 34.00 (d), 31.22 (t), 31.15, 27.31, 25.75, 24.01, 23.02, 21.78, 20.65, 15.89.

Cycloaddition of DMPO to Phenyldivinylphosphine Oxide (4). A solution of 89 mg (0.5 mmol) of oxide 4 and 56 mg (0.5 mmol) of DMPO in 1 mL of $CHCl_3$ was left at 25 °C for 17 days. Purification by chromatography (CH_2Cl_2–MeOH, 10:1, R_f = 0.35) yielded 68 mg (47%) of the two isomeric products as a colorless hygroscopic oil. Anal. (mixture of isomers) Calcd for $C_{16}H_{22}NO_2P$: C, 65.96; H, 7.61; N, 4.81. Found: C, 65.55; H, 7.76; N, 5.24. MS: m/e (rel intensity) 291 (M^+, 1) 179 (4), 152 (10), 151 (15), 140 (100), 96 (10). IR (CCl_4): 3060 (w), 2971 (s), 1591 (w), 1437 (s), 1382 (m), 1366 (m), 1190 (s) cm^{-1}.

Major. ^{31}P NMR: δ 27.70. ^1H NMR: δ 7.95–7.82 (m, 2 H), 7.56–7.45 (m, 3 H), 6.66 (ddd, J = 28.2, 18.9, 12.6 Hz, 1 H), 6.50–6.13 (m, 2 H), 4.35 (ddd, J = 10.0, 7.0, 4.1 Hz, 1 H), 3.92 (m, 1 H), 2.83–2.65 (m, 1 H), 2.45 (dt, J = 12.5, 7.0 Hz, 1 H), 2.24–2.02 (m, 1 H), 1.75–1.20 (m, 3 H), 1.28 (s, 3 H), 1.04 (s, 3 H). ^{13}C NMR: δ ipso carbon not discerned, 135.35 (t), 131.70 (d, J_{PC} = 2.8 Hz) (d), 130.80 (d, J_{PC} = 9.1 Hz) (d), 128.25 (d, J_{PC} = 11.6 Hz) (d), 127.88 (d, J_{PC} = 91.6 Hz) (d), 74.46 (d, J_{PC} = 89.3 Hz) (d), 69.49 (s), 64.07 (d, J_{PC} = 5.8 Hz) (d), 38.39 (t), 36.39 (t), 31.32 (t), 27.18 (q), 24.10 (q).

Minor. ^{31}P NMR: δ 26.83. ^1H NMR: δ 7.78–7.65 (m, 2 H), 7.56–7.45 (m, 3 H), 4.40–4.30 (m, 1 H), 3.72 (m, 1 H), 2.50–2.23 (m, 2 H), 2.18–1.95 (m, 1 H), 1.75–1.40 (m, 3 H), 1.29 (s, 3 H), 0.99 (s, 3 H). ^{13}C NMR: δ only vinylic signal detected, aromatic signals not detected, 134.3 (t), 75.73 (d, J_{PC} = 89.5 Hz) (d), 69.64 (s), 64.17 (d, J_{PC} = 6.8 Hz) (d), 38.68 (t), 36.95 (t), 31.19 (t), 27.43 (q), 24.11 (q).

Cycloaddition of DMPO to (+)-(R_P)-((Menthoxycarbonyl)methyl)phenylvinylphosphine Oxide (5). A solution of 125 mg (0.36 mmol) of oxide 5 and 49 mg (0.4 mmol) of DMPO in 1 mL of CH_2Cl_2 was left at 25 °C for 7 days. Purification by chromatography (ethyl acetate, R_f = 0.2) yielded 140 mg (85%) of the two isomeric products as a colorless oil. Anal. (mixture of isomers) Calcd for $C_{26}H_{40}NO_4P$: C, 67.65; H, 8.73; N, 3.03. Found: C, 67.67; H, 8.80; N, 2.66. MS: m/e (rel intensity) 461 (M^+, 2), 211 (20), 185 (50), 167 (18), 140 (100), 125 (20). IR

(15) Pietrusiewicz, K. M.; Wisniewski, W., to be published elsewhere.
(16) Kabachnik, M. I.; Chang, C.-Y.; Tsvetkov, E. N. *Dokl. Akad. Nauk SSSR* **1960**, *135*, 603; *Chem. Abstr.* **1961**, *55*, 12272a.

($CHCl_3$): 2959 (vs), 2871 (s), 1726 (vs), 1591 (w), 1455 (m), 1264 (vs), 1199 (s), 1110 (m) cm^{-1}.

Major. ^{31}P NMR: δ 33.52. ^1H NMR: δ 7.90–7.75 (m, 2 H), 7.52–7.33 (m, 3 H), 4.49 (dt, J = 4.5, 11.0 Hz, 1 H), 4.31 (q, J = 8.1 Hz, 1 H), 3.97–3.86 (m, 1 H), 2.95 (dddd, J = 15.4, 12.8, 8.5, 7.1 Hz, 1 H), 1.18 (s, 3 H), 1.01 (s, 3 H). ^{13}C NMR: δ ipso carbon not discerned, 165.81 (d, J_{PC} = 5.7 Hz) (s), 131.90 (d, J_{PC} = 8.9 Hz) (d), 131.06 (d, J_{PC} = 9.2 Hz) (d), 128.22 (d, J_{PC} = 11.5 Hz) (d), 75.20 (d), 74.78 (d, J_{PC} = 86.8 Hz) (d), 69.39 (s), 63.98 (d, J_{PC} = 4.6 Hz) (d), 46.35 (d), 40.16 (t), 36.89 (d, J_{PC} = 73.5 Hz) (t), 33.90 (t), 33.83 (t), 33.60 (t), 31.29 (t), 31.05, 27.22, 25.37, 25.10, 24.14, 22.75, 21.70, 20.63, 15.69.

Minor. ^{31}P NMR: δ 33.14. ^1H NMR: δ 7.90–7.75 (m, 2 H), 7.52–7.33 (m, 3 H), 4.62 (dt, J = 4.5, 11.0 Hz, 1 H), 4.53 (ddd, J = 9.5, 7.1, 2.4 Hz, 1 H), 3.63 (ddd, J = 6.3, 4.3, 2.0 Hz, 1 H), 1.29 (s, 3 H), 0.95 (s, 3 H). ^{13}C NMR: δ the only carbon discerned, 165.53 (d, J_{PC} = 6.2 Hz) (s), 128.21 (d, J_{PC} = 11.8 Hz) (d), 75.43 (d), 74.55 (d, J_{PC} = 85.2 Hz) (d), 69.43 (s), 64.29 (d, J_{PC} = 7.2 Hz) (d), 46.50 (d), 40.42 (t), 37.40 (d, J_{PC} = 76.4 Hz) (t), 34.72 (t), 33.60 (t), 27.15, 25.51, 23.94, 22.82, 15.74.

Cycloaddition of DMPO to Phenyldivinylphosphine Sulfide (6). A solution of 92 mg (0.5 mmol) of sulfide 6 and 56 mg (0.5 mmol) of DMPO in 1 mL of $CHCl_3$ was left at 25 °C for 17 days. Purification by chromatography (ethyl acetate–hexane, 1:1, R_f = 0.50) yielded 100 mg (68%) of the two isomeric products as a colorless oil. Anal. (mixture of isomers) Calcd for $C_{16}H_{22}NOPS$: C, 62.52; H, 7.21; N, 4.56. Found: C, 62.57; H, 7.48; N, 4.19. IR (CCl_4): 3063 (w), 2972 (s), 2874 (w), 1546 (w), 1437 (w), 1382 (w), 1157 (s), 1100 (s) cm^{-1}.

Major. ^{31}P NMR: δ 40.84. ^1H NMR: δ 8.12–8.01 (m, 2 H), 7.55–7.43 (m, 3 H), 6.94 (ddd, J = 24.5, 17.8, 11.5 Hz, 1 H), 6.57 (ddd, J = 24.7, 17.8, 1.8 Hz, 1 H), 6.34 (ddd, J = 46.2, 11.7, 1.8 Hz, 1 H), 4.44 (dt, J = 7.2, 8.7 Hz, 1 H), 3.87 (m, 1 H), 2.81–2.65 (m, 1 H), 2.54–2.42 (m, 1 H), 2.22–2.04 (m, 1 H), 1.80–1.20 (m, 3 H), 1.30 (s, 3 H), 1.05 (s, 3 H). ^{13}C NMR: δ ipso carbon not detected, 135.93 (d, J_{PC} = 2.2 Hz) (t), 131.61 (d, J_{PC} = 9.2 Hz) (d), 131.55 (d, J_{PC} = 2.8 Hz) (d), 128.75 (d, J_{PC} = 11.8 Hz) (d), 127.22 (d, J_{PC} = 73.2 Hz) (d), 78.58 (d, J_{PC} = 67.4 Hz) (d), 69.44 (s), 64.06 (d, J_{PC} = 5.3 Hz) (d), 39.14 (t), 36.12 (t), 31.32 (t), 27.06 (q), 24.08 (q).

Minor. ^{31}P NMR: δ 38.57. ^1H NMR: δ 8.12–8.01 (m, 2 H), 7.55–7.43 (m, 3 H), 4.47 (q, J = 9.6 Hz, 1 H), 3.64 (m, 1 H), 1.31 (s, 3 H), 0.97 (s, 3 H) (the only assigned signals in the mixture of isomers). ^{13}C NMR: δ phenyl and vinyl carbons not discerned, 80.02 (d, J_{PC} = 69.8 Hz) (d), 69.44 (s), 63.85 (d, J_{PC} = 6.6 Hz) (d), 39.29 (t), 36.63 (t), 30.82 (t), 27.06 (q), 24.08 (q).

Cycloaddition of DMPO to *N*,*P*-Diphenylmethylvinylphosphinimine (7). To a solution, rigorously protected from air and moisture, of 0.97 g (6.5 mmol) of methylphenylvinylphosphine[14] (freshly distilled from NaH) in 10 mL of toluene precooled to 0 °C was added 0.77 g (6.5 mmol) of dried ($MgSO_4$) phenyl azide slowly at such a rate as to maintain the reaction temperature in the range of 0–5 °C. After the evolution of N_2 ceased, the reaction mixture was allowed to warm up to the ambient temperature. A ^{31}P NMR analysis of the resulting toluene solution revealed the presence of the expected *N*,*P*-diphenylmethylvinylphosphinimine (7) (δ = −2.85 ppm, 97.5%) contaminated only with one other species resonating at δ = −6.08 ppm (2.5%, not assigned). To this solution was added at room temperature 1.1 g of DMPO, and the progress of the cycloaddition was monitored by ^{31}P NMR. After 2 days the ^{31}P NMR spectrum revealed the presence of the two phosphinimine cycloadducts (ν_P = 10.2 and 9.0 ppm in a ratio of 3.15:1). The identity of these adducts was subsequently verified by their in situ conversion into the corresponding oxides by treatment of half of the crude phosphinimine solution with water in THF (1 h, room temperature), as well as by reacting the other half with an equimolar amount of *p*-chlorobenzaldehyde (toluene, 1 h, room temperature). The final ratios (^{31}P NMR) of the oxides in the hydrolysis and the aza-Wittig reaction were found 1:1.4 and 2.9:1, respectively, in full agreement with the expected stereochemistry of the conversions, i.e., predominant inversion in the hydrolysis and retention in the Wittig reaction. The two oxides from the Wittig reactions were also isolated and shown to be identical with those obtained directly in the addition of DMPO to methylphenylvinylphosphine oxide (ref 4).

Cycloaddition of DMPO to Methylphenylvinylphosphine Sulfide (8). A solution of 100 mg (0.55 mmol) of sulfide 8 and 124 mg (1.1 mmol) of DMPO in 1.5 mL of $CHCl_3$ was left at 25 °C for 4 days. Purification by chromatography (CH_2Cl_2–MeOH, 20:1, R_f = 0.6) yielded 155 mg (96%) of the two isomeric products as a colorless oil. Anal. (mixture of isomers) Calcd for $C_{15}H_{22}NOPS$: C, 60.99; H, 7.51; N, 4.74. Found: C. 60.82; H, 7.73; N, 4.72. IR ($CDCl_3$): 2974 (s), 2875 (s), 1463 (s), 1438 (s), 1290 (s), 1103 (s), 1068 (m) cm^{-1}.

Major. ^{31}P NMR: δ 42.10. ^1H NMR: δ 8.12–7.95 (m, 2 H), 7.54–7.42 (m, 3 H), 4.30 (dt, J = 7.4, 9.2 Hz, 1 H), 3.97 (dt, J = 9.1, 6.0 Hz, 1 H), 2.99–2.83 (m, 1 H), 2.54 (ddt, J = 12.9, 0.9, 7.7 Hz, 1 H), 1.99 (d, J = 13.2 Hz, 3 H), 1.30 (s, 3 H), 1.06 (s, 3 H). ^{13}C NMR: δ 131.62 (d, J_{PC} = 76.0 Hz) (s), 131.45 (d, J_{PC} = 3.0 Hz) (d), 131.39 (d, J_{PC} = 9.8 Hz) (d), 128.05 (d, J_{PC} = 12.0 Hz) (d), 78.09 (d, J_{PC} = 67.0 Hz) (d), 69.52 (s), 64.11 (d, J_{PC} = 5.1 Hz) (d), 39.17 (d, J_{PC} = 2.5 Hz) (d), 36.26 (t), 31.23 (t), 27.15 (q), 24.08 (q), 15.53 (d, J_{PC} = 54.3 Hz) (q).

Minor. ^{31}P NMR: δ 40.56. ^1H NMR: δ 8.12–7.95 (m, 2 H), 7.54–7.42 (m, 3 H), 4.46 (dt, J = 6.6, 9.6 Hz, 1 H), 3.62–3.55 (m, 1 H), 2.41–2.31 (m, 1 H), 2.03 (d, J = 13.3 Hz, 3 H), 1.31 (s, 3 H), 0.95 (s, 3 H). ^{13}C NMR: δ the only carbon discerned, 79.10 (d, J_{PC} = 67.1 Hz) (d), 72.58 (s), 63.10 (d, J_{PC} not discerned) (d), 37.96 (d, J_{PC} = 1.6 Hz) (t), 35.85 (t), 30.21 (t).

Cycloaddition of DMPO to Methylphenylvinylphosphine Selenide (9). A solution of 135 mg (0.59 mmol) of selenide 9 and 80 mg (0.71 mmol) of DMPO in 1 mL of $CHCl_3$ was left at 25 °C for 12 days. Purification by chromatography (ethyl acetate–petroleum ether, 1:1) yielded 180 mg (89%) of the two isomeric products as a colorless oil. Anal. (mixture of isomers) Calcd for $C_{15}H_{22}NOPSe$: C, 52.50; H, 6.46, N, 4.08. Found: C, 52.47; H, 6.60; N, 3.80. IR ($CDCl_3$): 3062 (w), 2973 (vs), 1437 (vs), 1100 (vs) cm^{-1}.

Major. R_f = 0.45. ^{31}P NMR: δ 31.31. ^1H NMR: δ 8.15–8.02 (m, 2 H), 7.53–7.45 (m, 3 H), 4.37 (dt, J = 11.0, 8.5 Hz, 1 H), 4.11–3.93 (m, 1 H), 3.00–2.84 (m, 1 H), 2.58 (dt, J = 13.0, 8.0 Hz, 1 H), 2.17 (d, J = 13.2 Hz, 3 H), 1.92–1.45 (m, 4 H), 1.30 (s, 3 H), 1.05 (s, 3 H). ^{13}C NMR: δ 131.73 (d, J_{PC} = 9.9 Hz) (d), 131.35 (d, J_{PC} = 76.8 Hz) (s), 131.26 (d, J_{PC} = 2.7 Hz) (d), 127.75 (d, J_{PC} = 11.7 Hz) (d), 77.57 (d, J_{PC} = 56.7 Hz) (d), 69.22 (s), 63.77 (d, J_{PC} = 4.8 Hz) (d), 39.31 (d, J_{PC} = 3.3 Hz) (t), 36.89 (t), 35.85 (t), 26.80 (q), 23.82 (d, $^5J_{PC}$ = 2.7 Hz) (q), 15.34 (d, J_{PC} = 17.5 Hz) (q).

Minor. R_f = 0.38. ^{31}P NMR: δ 29.17. ^1H NMR: δ 8.15–8.02 (m, 2 H), 7.53–7.45 (m, 3 H), 4.57 (ddd, J = 11.8, 9.5, 6.9 Hz, 1 H), 3.58 (m, 1 H), 2.41 (m, 1 H), 2.24 (d, J = 13.3 Hz, 3 H), 2.21–2.03 (m, 2 H), 1.72–1.66 (m, 1 H), 1.62–1.48 (m, 2 H), 1.32 (s, 3 H), 0.96 (s, 3 H). ^{13}C NMR: δ ortho carbon not discerned, 130.63 (d, J_{PC} = 80.2 Hz) (s), 130.33 (d, J_{PC} = 10.7 Hz) (d), 128.29 (d, J_{PC} = 10.1 Hz) (d), 79.6 (d, J_{PC} = 55.7 Hz) (d), 69.02 (s), 63.77 (d, J_{PC} = 4.8 Hz) (d), 38.58 (d, J_{PC} = 2.0 Hz) (t), 36.17 (t), 30.51 (t), 22.31 (q), 19.63 (q).

Cycloaddition of DMPO to Methyl(2,4,6-trimethylphenyl)vinylphosphine Oxide (10). A solution of 80 mg (0.38 mmol) of oxide 10 and 52 mg (0.46 mmol) of DMPO in 1 mL of $CHCl_3$ was left at 25 °C for 10 days. Purification by chromatography (ethyl acetate–MeOH, 10:1, R_f = 0.28) yielded 90 mg (73%) of the major isomer.

Major. Mp: 78–79 °C. Anal. Calcd for $C_{18}H_{28}NO_2P$: C, 67.27; H, 8.78; N, 4.36. Found: C, 67.02; H, 8.85; N, 4.25. IR (CCl_4): 2970 (s), 2875 (m), 1605 (w), 1452 (w), 1382 (w), 1173 (vs), 1102 (s) cm^{-1}. ^{31}P NMR: δ 43.48. ^1H NMR: δ 6.86 (s, 1 H), 6.84 (s, 1 H), 4.36 (q, J = 7.7 Hz, 1 H), 3.95 (m, 1 H), 2.93 (dddd, J = 15.9, 12.6, 8.9, 6.9 Hz, 1 H), 2.57 (s, 6 H), 2.47–2.28 (m, 1 H), 2.24 (s, 3 H), 2.18–2.03 (m, 1 H), 1.92 (d, J = 13.2 Hz, 3 H), 1.80–1.43 (m, 3 H), 1.23 (s, 3 H), 1.02 (s, 3 H). ^{13}C NMR: δ ipso carbon not discerned, 142.62 (d, J_{PC} = 10.2 Hz) (s), 131.00 (d, J_{PC} = 4.3 Hz) (d), 75.91 (d, J_{PC} = 82.4 Hz) (d), 69.47 (s), 64.60 (d, J_{PC} = 4.6 Hz) (d), 38.18 (t), 36.41 (t), 31.43 (t), 27.31 (q), 25.26 (q), 23.58 (d, J_{PC} = 2.8 Hz) (q), 20.90 (q), 16.28 (d, J_{PC} = 68.1 Hz) (q).

Minor. ^{31}P NMR: δ 42.79. ^1H NMR: δ the only hydrogens discerned 4.33 (m, 1 H), 3.88–3.74 (m, 1 H), 1.95 (d, J = 12.9 Hz, 3 H).

Cycloaddition of DMPO to *tert*-Butyldivinylphosphine Oxide (11). A solution of 76 mg (0.48 mmol) of oxide 11 and 67 mg (0.6 mmol) of DMPO in 1 mL of $CHCl_3$ was left at 25 °C for

15 days. Purification by chromatography (CH_2Cl_2-MeOH, 10:1) yielded 110 mg (84%) of the major isomer as a colorless oil.

Major. R_f = 0.35. Anal. Calcd for $C_{14}H_{26}NO_2P$: C, 61.97; H, 9.66; N, 5.16. Found: C, 61.51; H, 9.56; N, 4.85. MS: *m/e* (rel intensity) 271 (M^+, 4), 184 (20), 140 (100), 124 (12), 96 (25), 57 (80). IR (CCl_4): 3080 (w), 2973 (vs), 1626 (w), 1462 (vs), 1164 (s) cm^{-1}. ^{31}P NMR: δ 47.24. ^1H NMR: δ 6.47-6.15 (m, 3 H), 4.37 (ddd, J = 10.8, 6.3, 4.9 Hz, 1 H), 3.88 (m, 1 H), 2.75-2.58 (m, 1 H), 2.46-2.30 (m, 1 H), 2.22-2.06 (m, 1 H), 1.74-1.42 (m, 4 H), 1.28 (s, 3 H), 1.18 (d, J = 15.9 Hz, 9 H), 1.03 (s, 3 H). ^{13}C NMR: δ 137.39 (t), 124.42 (d, J_{PC} = 82.3 Hz) (d), 71.44 (d, J_{PC} = 80.7 Hz) (d), 69.59 (s), 63.46 (d, J_{PC} = 6.3 Hz) (d), 39.30 (t), 36.64 (t), 31.89 (d, J_{PC} = 67.8 Hz) (s), 31.14 (t), 26.78 (q), 23.56 (q).

Minor. ^{31}P NMR: δ 44.90.

Cycloaddition of DMPO to *tert*-Butyldivinylphosphine Sulfide (12). A solution of 26 mg (0.15 mmol) of sulfide **12** and 25 mg (0.22 mmol) of DMPO in 1 mL of $CHCl_3$ was left at 25 °C for 15 days. Purification by chromatography (ethyl acetate-hexane, 1:1, R_f = 0.32) yielded 35 mg (80%) of the major isomer as white crystals.

Major. Mp: 85 °C. Anal. Calcd for $C_{14}H_{26}NOPS$: C, 58.51; H, 9.12; N, 4.87. Found: C, 58.44; H, 9.28; N, 4.82. IR ($CDCl_3$): 2970 (s), 2871 (m), 1460 (s), 1381 (s), 1365 (s), 1157 (m), 1112 (m) cm^{-1}. ^{31}P NMR: δ 62.03. ^1H NMR: δ 6.82-6.26 (m, 3 H), 4.49 (dt, J = 9.5, 6.8 Hz, 1 H), 3.87-3.74 (m, 1 H), 2.66-2.34 (m, 2 H), 2.22-2.01 (m, 1 H), 1.78-1.42 (m, 3 H), 1.28 (d, J = 2.2 Hz, 9 H), 1.20 (s, 3 H), 1.01 (s, 3 H). ^{13}C NMR: δ 138.80 (t), 129.94 (d, J_{PC} = 64.2 Hz) (d), 75.66 (d, J_{PC} = 62.4 Hz) (d), 69.80 (s), 63.65 (d, J_{PC} = 6.3 Hz) (d), 40.82 (t), 36.72 (t), 34.19 (d, J_{PC} = 49.9 Hz) (s), 31.44 (t), 27.02 (q), 25.82 (q), 24.45 (q).

Minor. ^{31}P NMR: δ 61.58.

Acknowledgment. Financial support of this study by the MURST-40% and MURST-60%, Italy, and the Polish Academy of Sciences (CPBP-01.13)-Poland is gratefully acknowledged.

Syntheses of 6-Oxodecahydroisoquinoline-3-carboxylates. Useful Intermediates for the Preparation of Conformationally Defined Excitatory Amino Acid Antagonists

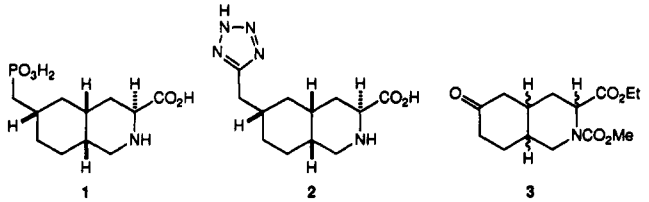
Paul L. Ornstein,* M. Brian Arnold, Nancy K. Augenstein, and Jonathan W. Paschal

Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, Indiana 46285

Received January 25, 1991

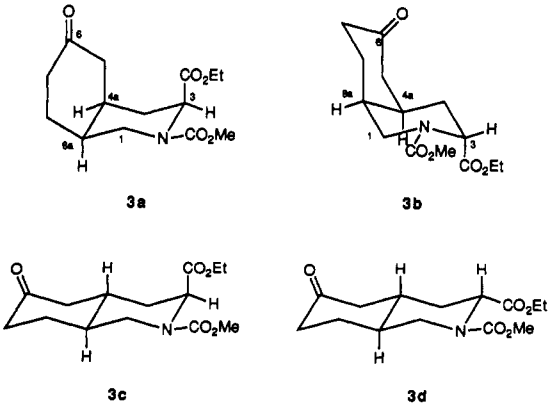
We have prepared three of the four possible diastereomers of ethyl 6-oxo-2-(methoxycarbonyl)decahydroisoquinoline-3-carboxylic acid (two cis- ring and one trans ring juncture ketones, **3a-c**) by a convergent route from (±)-*m*-tyrosine. These ketones are useful intermediates for the preparation of conformationally constrained acidic amino acids as *N*-methyl-D-aspartic acid (NMDA) receptor antagonists, e.g., LY274614 and LY233536 (**1** and **2**, respectively). The cis ring juncture ketones were prepared selectively by hydrogenation of a key tetrahydroisoquinoline intermediate **7**, while the corresponding trans ring juncture ketone was prepared selectively by consecutive dissolving metal reductions of the tetrahydroisoquinoline **8**. One of the ketones, **3b**, that possesses the optimal stereochemical array for NMDA antagonist activity, was resolved via the α-methylbenzylamine salts of the corresponding acid to allow for determination of the active optical isomer of these amino acids. The synthesis and resolution of the keto esters can easily be performed on a multigram scale.

As a part of a program aimed at the synthesis of novel 6-substituted decahydroisoquinoline-3-carboxylic acids, e.g., **1** and **2** (LY274614 and LY233536, respectively),[1] we required large quantities of the four possible diastereomers of 6-keto-3-carboxyisoquinoline **3**. We believed that these



1 **2** **3**

hitherto unknown ketones could be readily elaborated to a variety of substituted amino acids that could serve as novel *N*-methyl-D-aspartic acid (NMDA) receptor antagonists.[2,3] Because of the rigid nature of these bicyclic ketones, the amino acids thus derived would be of limited conformational mobility and therefore provide some useful insight into structural requirements for activity at NMDA receptors. We report here the convergent synthesis of multigram quantities of three of the four possible diastereomers of the title compound **3** and the subsequent resolution of the ketone **3b**.



3a **3b** **3c** **3d**

We envisioned that the cis or trans ring juncture in **3** could be introduced selectively by the appropriate choice of reduction conditions for a suitably protected tetrahydroisoquinoline intermediate such as **4**, which can be obtained from the readily available (±)-*m*-tyrosine. The cis isomers should be available by hydrogenation of **4**,[4] and

(1) Ornstein, P. L.; Schoepp, D. D.; Leander, J. D.; Lodge, D. In *Excitatory Amino Acids 1990* Meldrum, B., Moroni, F., Simon, R., Woods, J., Eds.; Fidia Research Foundation Symposium Series Raven Press: New York, 1991; in press.
(2) Ornstein, P. L.; Schoepp, D. D. *Curr. CNS Patents* **1990**, *1*, 413.
(3) Collingridge, G. L.; Lester, R. A. J. *Pharmacol. Rev.* **1989**, *40*, 143.
(4) Rapala, R. T.; Lavagnino, E. R.; Shepard, E. R.; Farkas, E. *J. Am. Chem. Soc.* **1957**, *79*, 3770.

0022-3263/91/1956-4388$02.50/0