Diphenylphosphinoyl-Substituted Ylides. 1. Thermal 1,3-Dipolar Cycloaddition of α-(Diphenylphosphinoyl)glycine Ester Imines. Dipole Formation as the Rate-Determining Step

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The thermal 1,3-dipolar cycloaddition of *N*-benzylidene-α-(diphenylphosphinoyl)glycine esters **4** to *N*-phenylmaleimide is described. With this reactive dipolarophile, dipole formation is the rate-determining step. Addition to less reactive dipolarophiles is covered in the following article. Cycloaddition occurs smoothly below 70 °C to give good yields of two diastereoisomeric endo adducts, which differ in configuration only at the carbon atom, carrying the ester and the phosphine oxide group. The product ratio is dependent on the polarity of the solvent and, only marginally, on the bulk of the ester group. Product isolation is facilitated by the excellent crystallization properties of the phosphine oxides.

Introduction

Recent work in our laboratories has involved the synthesis and application of phosphine oxides that carry one or two heteroatom substituents at the α-carbon atom. Reaction of their anions with carbonyl compounds offers an efficient route to several important classes of compounds, e.g., enol ethers,[1] ketene acetals,[2] enamines, and α-amino ketones.[3]

As part of a program concerning 2-(diphenylphosphinoyl)pyrrolidines,[4] we required a method that would allow the introduction of additional substituents in the five-membered ring. As a general route, the 1,3-dipolar cycloaddition[5] of azomethine ylides,[6] stabilized by a phosphinoyl substituent, was considered. Thus far, little attention appears to have been paid to ylides that carry a phosphorus substituent,[7] although these reagents might well prove to be of value in natural products synthesis.[8]

Scheme I

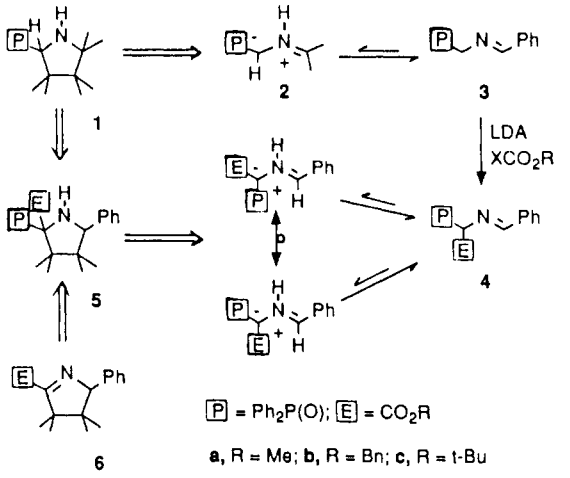


Table I. Synthesis of α-(Diphenylphosphinoyl)glycine Ester Imines 4

entry	R	LDA, equiv	X (equiv)	yield 3	yield 4
1	Bn	1.2	Cl (1.2)	40[b]	50[b]
2	Bn	2.2	Cl (1.2)	29[b]	60[b,c]
3	Bn	2.25[a]	Cl (1.25)		80[d]
4	Me	2.25[a]	Cl (1.25)		76[d]
5	*t*-Bu	2.25[a]	BocO (1.25)		80[d]

[a] Titrative addition of reagents (see Experimental Section). [b] Isolated after flash chromatography. [c] Contaminated by benzyl diisopropylcarbamate. [d] Isolated by filtration after stirring in ether.

First, attention was directed to N-unsubstituted 2-(diphenylphosphinoyl)pyrrolidines **1**. As a method for the generation of the required ylides **2**, formation via a formal [1,2]-hydrogen shift[9] in activated imines of type **3** was envisaged. A tautomeric shift of this kind has been described for the imines of α-amino acid esters[10] and of α-cyano amines.[11] In our hands, the corresponding phos-

(1) (a) Van Schaik, T. A. M.; Van der Gen, A. *Recl. Trav. Chim. Pays-Bas* **1983**, *102*, 465. (b) De Wit, P. P.; Van der Steeg, M.; Van der Gen, A. *Ibid.* **1985**, *104*, 307.

(2) Van Schaik, T. A. M.; Henzen, A. V.; Van der Gen, A. *Tetrahedron Lett.* **1983**, *24*, 1303.

(3) (a) Broekhof, N. L. J. M.; Jonkers, F. L.; Van der Gen, A. *Tetrahedron Lett.* **1979**, *20*, 2433. (b) Broekhof, N. L. J. M.; Jonkers, F. L.; Van der Gen, A. *Ibid.* **1980**, *21*, 2671. (c) Broekhof, N. L. J. M.; Van der Gen, A. *Ibid.* **1981**, *22*, 2799. (d) Van der Gen, A.; Broekhof, N. L. J. M. *ACS Symp. Ser.* **1981**, No. 171, 47. (e) Zorgdrager, J.; Broekhof, N. L. J. M.; Van der Gen, A. *Recl. Trav. Chim. Pays-Bas* **1989**, *108*, 441.

(4) (a) Bakker, B. H.; Tjin A-Lim, D. S.; Van der Gen, A. *Tetrahedron Lett.* **1984**, *25*, 4259. (b) Zorgdrager, J.; Van der Gen, A. *Recl. Trav. Chim. Pays-Bas*. In press.

(5) Padwa, A., Ed. *1,3-Dipolar Cycloaddition Chemistry*; Wiley: New York, 1984; 2 vols.

(6) Some leading references: (a) Imai, N.; Achiwa, K. *Chem. Pharm. Bull.* **1987**, *35*, 593. (b) Ardill, H.; Grigg, R.; Sridharan, V.; Surendrakumar, S. *Tetrahedron* **1988**, *44*, 4953. (c) Joucla, M.; Mortier, J. *Bull. Soc. Chim. Fr.* **1988**, 579. (d) Padwa, A.; Gasdaska, J. R.; Haffmanns, G.; Rebello, H. *J. Org. Chem.* **1987**, *52*, 1027. (e) Chastanet, J.; Roussi, G. *Ibid.* **1988**, *53*, 3808. (f) Tsuge, O.; Kanemasa, S.; Ohe, M.; Takenaka, S. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4079. (g) Tsuge, O.; Kanemasa, S.; Sakamoto, K.; Takenaka, S. *Ibid.* **1988**, *61*, 2513. (h) Vedejs, E.; Grissom, J. W. *J. Org. Chem.* **1988**, *53*, 1876. (i) Yaozhong, J.; Changyou, Z.; Shengde, W. *Synth. Commun.* **1987**, *17*, 33. (j) For a general treatice on azomethine ylides: Tsuge, O.; Kanemasa, S. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R.; Ed.; Academic Press, Inc.: San Diego, 1989; Vol. 45, pp 231–349.

(7) A limited number of papers have delt with azomethine ylides, activated by a phosphonate substituent: (a) Dehnel, A.; Lavielle, G. *Tetrahedron Lett.* **1980**, *21*, 1315. (b) Dehnel, A.; Griller, D.; Kanabus-Kaminska, J. M. *J. Org. Chem.* **1988**, *53*, 1566. (c) Liu, D. *Huaxue Xuebao* **1987**, *45*, 283; *Chem. Abstr.* **1988**, *108*, 5803x. (d) Grigg, R.; Donegan, G.; Gunaratne, H. Q. N.; Kennedy, D. A.; Malone, J. F.; Sridharan, V.; Thianpatanagul, S. *Tetrahedron* **1989**, *45*, 1723. (e) Martin, S. F.; Cheavens, T. H. *Tetrahedron Lett.* **1989**, *30*, 7017. For future application as Horner–Wittig reagents, phosphine oxides appear to be the reagents of choice.[3,4] Cf. Martin, S. F.; Philips, G. W.; Puckette, T. A.; Colapret, J. A. *J. Am. Chem. Soc.* **1980**, *102*, 5866.

(8) Cf. Pearson, W. H. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1988; Vol. 1, pp 323–358.

(9) Grigg, R. *Chem. Soc. Rev.* **1987**, *16*, 89.

(10) (a) Grigg, R.; Kemp, J.; Warnock, W. J. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2275. (b) Amornraksa, K.; Grigg, R.; Gunaratne, H. Q. N.; Kemp, J. *Ibid.* **1987**, 2285. (c) Kaira, A. M.; Hamelin, J. *Tetrahedron Lett.* **1987**, *28*, 1397. (d) Tsuge, O.; Kanemasa, S.; Ohe, M.; Yorozu, K.; Ueno, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4067.

phine oxide **3** gave unsatisfactory results in the thermal cycloaddition. Clearly, the phosphine oxide substituent was not capable of activating the α-proton in **3** to the extent of an ester or a cyano group.

The (temporary) introduction of an additional ester group at the α-position, as in the α-(diphenylphosphinoyl)glycine ester imines **4**, was explored (Scheme I) to overcome this problem. In the corresponding cycloadducts **5** the ester group may presumably be removed[12] to give compounds **1**, in which the α-position is available for a subsequent Horner–Wittig reaction. Alternatively, thermal or acid-catalyzed elimination of the phosphinoyl substituent might lead to functionalized pyrrolines **6**.

In this paper the synthesis of the starting materials **4** and their cycloaddition to *N*-phenylmaleimide are described.[13] With this reactive dipolarophile, dipole formation is the rate-determining step. In the following paper, dipolarophile variation is discussed.[14]

Results

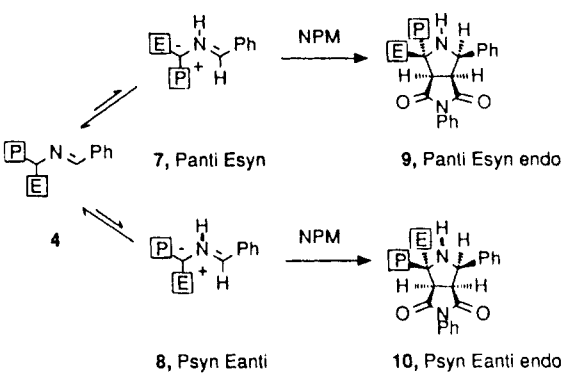
Synthesis of Phosphine Oxides 4. One of the factors affecting the course of cycloaddition might be the steric bulk of the ester group in **4**. For this reason, and also considering their potential removal at a later stage, the following esters were chosen: methyl **4a**, benzyl **4b**, and *tert*-butyl **4c**.

Although phosphine oxides of type **4** have not been described in the literature, the corresponding phosphonates (and free amines) are known.[15] A variety of primary esters has been synthesized by Ratcliffe and Christensen via alkoxycarbonylation of the anion of diethyl *N*-benzylidene(aminomethyl)phosphonate. Mixtures of starting material and product were obtained, from which the desired imines were isolated in approximately 40% yield by column chromatography.[15c]

The starting material **3** for the preparation of phosphine oxides **4** is readily available on a large scale.[16] Reaction of **3** with 1 equiv of LDA and 1 equiv of benzyl chloroformate at low temperature likewise gave a mixture of starting material and product **4b**. These compounds could be separated efficiently by flash chromatography (Table I, entry 1).

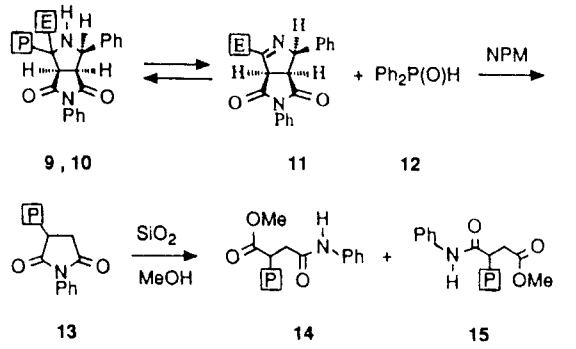
Use of 2 equiv of LDA gave only a marginal increase in conversion of the starting material. This was caused by reaction of part of the LDA with the acylating agent to give benzyl diisopropylcarbamate, which eluted simultaneously with **4b** and prevented efficient crystallization (Table I, entry 2). The starting material **3** was successively treated at low temperature with LDA and acylating agent via a titrative addition of the reagents (see Experimental Section) to suppress this unwanted side reaction. In this way, the α-(diphenylphosphinoyl)glycine ester imines **4** were simply and reproducibly obtained in good yields by merely stirring the crude product in ether overnight (Table I, entries 3–5). No impurities were detectable by NMR or TLC and the products were used as such in the cycloaddition reactions.

Scheme II



P = $Ph_2P(O)$; E = CO_2R, with **a**, R = Me; **b**, R = Bn; **c**, R = t-Bu

Scheme III



P = $Ph_2P(O)$, E = CO_2Bn

Cycloaddition of *N*-Benzylidene-α-(diphenylphosphinoyl)glycinate Esters 4 to *N*-Phenylmaleimide. The analysis of reaction mixtures before purification and separation of the products forms an essential part of cycloaddition chemistry, because of the determination of stereoselectivity.[17] With phosphine oxide substituted azomethine ylides, the use of ^{31}P NMR is especially favorable, because the number and relative amounts of the different phosphorus-containing products become immediately evident. In all cases investigated,[14] a good agreement has been observed with the composition as determined by ^1H NMR, as well as with the yields of products obtained after purification.

First, cycloaddition was carried out, analogous to Grigg[10] and Tsuge,[11] in refluxing toluene using benzyl ester **4b** and *N*-phenylmaleimide (NPM)[18] as the dipolarophile. After 3 h the starting material had been completely consumed according to ^{31}P NMR and two new phosphorus-containing products were formed in a ratio of 4.5:1. The major product was isolated by flash chromatography in 50% yield and was shown to be the Panti Esyn endo adduct **9b**

(11) Tsuge, O.; Ueno, K.; Kanemasa, S.; Yorozu, K. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1809.

(12) Compare: (a) Krapcho, A. P. *Synthesis* **1982**, 805, 893. (b) Pietrusiewicz, K. M.; Zablocka, M.; Monkiewicz, J. *J. Org. Chem.* **1984**, *49*, 1522. (c) Texier, F.; Marchand, E.; Carrie, R. *Tetrahedron* **1974**, *30*, 3185.

(13) Maleic anhydride gave comparable results (^{31}P NMR). However, the two initially formed products proved to be extremely sensitive to all conditions of isolation. Attempts to convert the two adducts to compounds corresponding to dimethyl maleate endo adducts were unsuccessful. Acidic conditions[10a] gave competitive elimination of the phosphinoyl substituent, while under basic conditions product isomerization complicated the picture.[14]

(14) Van Es, J. J. G. S.; Ten Wolde, A.; Van der Gen, A. *J. Org. Chem.*, following paper in this issue.

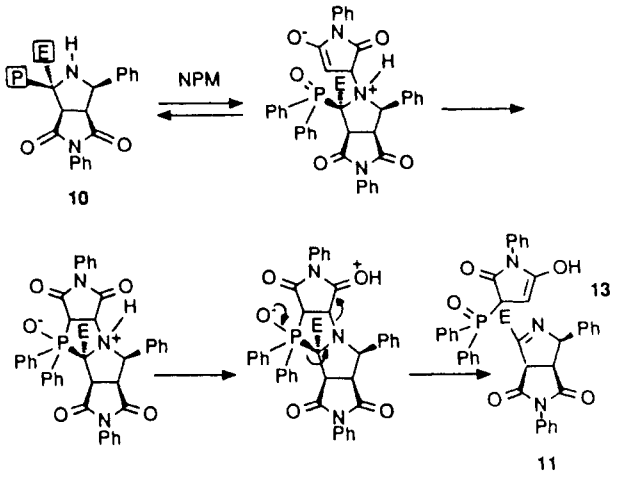
(15) (a) Shiraki, C.; Saito, H.; Takahashi, K.; Urakawa, C.; Hirata, T. *Synthesis* **1988**, 399. (b) Hakimelahi, G. H.; Just, G. *Synth. Commun.* **1980**, *10*, 429. (c) Ratcliffe, R. W.; Christensen, B. G. *Tetrahedron Lett.* **1973**, 4645. (d) Colvin, E. W.; Kirby, G. W.; Wilson, A. C. *Ibid.* **1982**, *23*, 3835. (e) Scope, D. I. C.; Kluge, A. F.; Edwards, J. A. *J. Org. Chem.* **1977**, *42*, 376. (f) Kober, R.; Steglich, W. *Liebigs Ann. Chem.* **1983**, 599.

(16) Redmore, D. In *Phosphorus Chemistry*; Griffith, E. J., Grayson, M., Eds.; Wiley: New York, 1976; Vol. 8, pp 515–585.

(17) Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 1, pp 1–176.

(18) Commercially obtained NPM may contain small amounts of acidic impurities, which may accelerate the cycloaddition.[10b] In our hands, imines **4** did not show a decrease in reactivity, nor a change in selectivity, when purified NPM was used. Therefore the commercial product was used throughout.

Scheme IV



(Scheme II). The endo orientation of the phenyl ring was evident from the cis coupling between H-3 and H-3a (8.0 Hz) and the occurrence of strong NOE effects between these protons.[10b] The anti orientation of the phosphorus substituent clearly followed from its vicinal coupling to H-6a (13.9 Hz), which is typical for a cis $^3J_{HaxPeq}$ in these ring systems.[14,19] The equatorial orientation of the phosphinoyl substituent may be derived from the magnitude of its couplings to C-3 and C-3a.[14,19,20]

The other phosphorus-containing product, 3-(diphenylphosphinoyl)-*N*-phenylsuccinimide (**13**), was unstable to chromatography and underwent methanolysis to give the methyl esters **14** and **15** (Scheme III). These compounds were synthesized and characterized independently (see Experimental Section). Apparently, **13** arises via a Michael-type addition of diphenylphosphine oxide (**12**), formed by thermal elimination from one or more cycloadducts, to NPM. On closer inspection of the reaction mixture, the elimination product **11b** was indeed found and could be isolated in 12% yield.

When the reaction was carried out at 70 °C in toluene, no decomposition was observed and now two cycloadducts were formed in a ratio of 4.2:1. Stirring the mixture in ether overnight afforded these compounds together in 95% yield. Further separation by flash chromatography afforded **9b** as the first eluting product in 76% yield. The second product, isolated in 17% yield, proved to be the Psyn Eanti endo adduct **10b** (Scheme II). Also in this case, the endo orientation was evident from the coupling constant between H-3 and H-3a (10.2 Hz) and from strong NOE effects between these protons.[10b] The Psyn orientation was deduced from the coupling between the phosphorus substituent and H-6a (10.6 Hz), which is a typical value for a trans $^3J_{HaxPax}$ in these systems.[14] The axial orientation of the phosphinoyl substituent was deduced from the fact that coupling of phosphorus to C-3 was zero, while at the same time coupling to C-3a was significantly

Table II. Effect of Solvent Polarity on Product Distribution[a]

			product ratio[b]		
entry	solvent	T (°C)	Panti **9b**	Psyn **10b**	yield,[c] %
1	Tol[d]	70	81	19	93
2	THF	reflux	70	30	94
3	$CHCl_3$	reflux	66	34	94
4	CH_2Cl_2	reflux	60	40	93
5	CH_3CN	70	36	64	95
6	MeOH	reflux	31	69	97

[a] 1.0 g of imine **5b** in 22 mL of solvent. [b] According to ^{31}P NMR. [c] Isolated after precipitation from ether. [d] Suspension.

reduced.[14,19,20] It is worthy of note that the two cycloadducts obtained only differ in relative configuration around C-1, which will be a future center of sp^2-hybridization in several applications foreseen for these cycloadducts (vide supra).

Both adducts were stable in refluxing toluene. Only in the presence of NPM, **10b** decomposed and succinimide **13** was formed as the sole phosphorus-containing product, together with an equimolar amount of pyrroline **11b**. When pyrroline **11b** was refluxed in toluene in the presence of 1 equiv of diphenylphosphine oxide (**12**), no addition to the imine double bond was observed. Thus a bimolecular mechanism, as depicted in Scheme IV, is proposed to account for these observations. It may be concluded that these cycloadditions should not be carried out at temperatures exceeding 70 °C.

The effect of solvent variation in the reaction of benzyl ester **4b** and NPM is presented in Table II. All reactions required approximately 3 h. The Panti/Psyn ratio is largely dependent on the polarity of the solvent. In apolar media an excess of the Panti product **9b** is formed; in more polar[21] solvents the Psyn endo product **10b** predominates. With the exception of toluene (entry 1), the selectivity ratio never rose above approximately 2:1. The combined yields were excellent throughout.

The effect of steric bulk of the ester group on product composition is shown in Table III. In chloroform, similar Panti/Psyn ratios were found for the methyl ester **4a** and the benzyl ester **4b**. Only the *tert*-butyl ester **4c** showed a slight decrease. In the more polar solvent acetonitrile, all esters gave the same product ratio (entries 4–6). In all cases the yields were excellent. Clearly, there is hardly any effect of the bulk of the ester group on the diastereoselectivity of the cycloaddition, when dipole formation is the rate-determining step.

The 1,3-dipolar cycloaddition of imines of α-amino acid esters and of α-cyano amines can be catalyzed by mild acids, when dipole formation is the rate-determining step.[11,23] Using the *tert*-butyl ester of *N*-benzylidene-α-(diphenylphosphinoyl)glycine **4c**, no enhancement in reaction rate was observed when the compound was refluxed in chloroform in the presence of 1 equiv of acetic acid and 1.2 equiv of NPM. The ratio was the same as in the uncatalyzed reaction. The combined yield of isolated adducts was only 70% (after flash chromatography). Also, pyrroline **11c** was isolated in 13%, while diphenylphosphine oxide (**12**) was present in the crude reaction

(19) Compare Rabiller et al. (Rabiller, C.; Dehnel, A.; Lavielle, G. *Can. J. Chem.* **1982**, *60*, 926) for some 2-phosphonopyrrolidines. The coupling constants of phosphine oxides to both hydrogen and carbon will be smaller, due to the smaller electronegativity of phosphine oxides.[20f]

(20) (a) For a general treatice on phosphorus–proton couplings: Bentrude, W. G.; Setzer, W. N. In *Phosphorus-31 NMR Spectroscopy in Stereochemical Analysis*; Verkade, J. G., Quin, L. D., Eds.; VCH: Weinheim, 1987; pp 365–390. (b) For a general treatice on phosphorus–carbon couplings: Quin, L. D., ref 20a, pp 391–424. Some leading references: (c) Quin, L. D.; Gallagher, M. J.; Cunckle, G. T.; Chestnut, D. B. *J. Am. Chem. Soc.* **1980**, *102*, 3136. (d) Thiem, J.; Meyer, B.; Paulsen, H. *Chem. Ber.* **1978**, *111*, 3325. (e) Buchanan, G. W.; Morin, F. G. *Can. J. Chem.* **1980**, *58*, 530 and references cited therein. (f) Neeser, J.; Tronchet, J. M. J.; Charollais, E. J. *Ibid.* **1983**, *61*, 212.

(21) In polar aprotic solvents, e.g., DMSO, only polymerization of NPM was observed. Only in the presence of 10 equiv of water[22] could an 80% conversion be obtained, but the product was of inferior quality. Furthermore, the ratio Psyn/Panti did not exceed the one obtained with methanol as solvent (Table II).

(22) Tsuge, O.; Kanemasa, S.; Hatada, A.; Matsuda, M. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2537.

(23) (a) Grigg, R.; Gunaratne, H. Q. N. *J. Chem. Soc., Chem. Commun.* **1982**, 4457. (b) Grigg, R.; Gunaratne, H. Q. N.; Sridharan, V. *Tetrahedron* **1987**, *43*, 5887.

Table III. Product Distribution in Relation to Ester Structure

entry	solvent[a]	time (h)	imine 4, R	yield, % tot.[b]	yield, % Panti[c]	yield, % Psyn[c]	selectivity[d] Panti 9	selectivity[d] Psyn 10
1	$CHCl_3$	3	a, Me	94	63	28	67	33
2	$CHCl_3$	3	b, Bn	94	61	26	66	34
3	$CHCl_3$	3	c, *t*-Bu	94	50	44	56	44
4	CH_3CN	3	a, Me	99	25	59	36	64
5	CH_3CN	3	b, Bn	95	26	58	36	64
6	CH_3CN	3	c, *t*-Bu	92	28	64	36	64

[a] At reflux (in $CHCl_3$) or at 70 °C (in CH_3CN). [b] Precipitation from ether. [c] After flash chromatography. [d] According to ^{31}P NMR.

product (^{31}P NMR). These products were not observed in the thermal cycloaddition at 60 °C and clearly resulted from acid-catalyzed elimination of the phosphine oxide group from the cycloadduct(s). Therefore, acid catalysis does not appear to be feasible for cycloaddition with α-(diphenylphosphinoyl)glycine ester imines **4**.

Control experiments showed that decomposition only occurred with the Psyn endo compound **10c**: refluxing **10c** in chloroform in the presence of NPM and acetic acid for 3 h gave 15% elimination. Although this elimination is undesirable at this stage, it demonstrates the feasibility of one of the potential applications of these cycloadducts: acid-catalyzed elimination of the phosphine oxide group.

Conclusion

The results obtained here can be explained by assuming that the Panti **7** and Psyn **8** dipoles are formed simultaneously and are trapped rapidly and stereospecifically with *N*-phenylmaleimide to give the endo adducts **9** and **10**, respectively. For imines, activated only by an ester group, no stereomutation was observed in the cycloaddition to maleimides, irrespective of the other substituents on the dipole.[10b] In light of the high reactivity of these dipoles **7** and **8**, as compared to imines only activated by an ester[10] or a cyano[11] group, it seems unlikely that dipole interconversion occurs. In the following paper, cycloaddition to less reactive dipolarophiles is discussed.

Experimental Section

Benzaldehyde was distilled before use. All acylating agents were commercially available. Methyl chloroformate was distilled before use; other acylating agents were used as such. All cycloadditions were carried out in dry and distilled solvents under a nitrogen atmosphere. *N*-Phenylmaleimide (NPM) was commercially obtained.[18]

Flash chromatography was performed on Merck Kieselgel 60 (0.040–0.063 mm) under nitrogen pressure. The eluent is specified for each experiment. All separations were carried out by using distilled solvents. Petroleum ether refers to the fraction boiling at 40–60 °C. TLC analyses were performed on Schleicher and Schuell F1500/LS 254 silica gel plates, using UV detection.

^1H NMR spectra were recorded on a Brucker WM-300 (300 MHz) or on a JEOL NM FX-200 (200 MHz) instrument, using tetramethylsilane (TMS) as the internal standard. ^{13}C NMR spectra were recorded on a JEOL NM FX-200 (50 MHz) spectrometer, using deuteriochloroform as internal standard. Where appropriate, absolute values for coupling constants have been reported. ^{31}P NMR spectra were recorded in deuteriochloroform on a JEOL NM FX-200 (80 MHz) spectrometer, employing 85% aqueous phosphoric acid as external standard. [^{31}P]^1H NMR spectra, carbon–hydrogen correlated NMR spectra, and NOEDIFF spectra were recorded on a Brucker WM-300 spectrometer. Mass spectra were obtained on an AEI MS 9/50 mass spectrometer at an ionization voltage of 70 eV.[24] Infrared spectra were obtained with a Pye Unicam SP3-200 spectrometer. Melting points were determined on a Büchi melting point apparatus and are uncorrected.

(Aminomethyl)diphenylphosphine Oxide. *N*-Benzoyl(aminomethyl)diphenylphosphine oxide was prepared from commercially available chlorodiphenylphosphine and *N*-(hydroxymethyl)benzamide[25] according to the procedure of Kreutzkamp.[26] Hydrolysis of *N*-benzoyl(aminomethyl)diphenylphosphine oxide was performed in an autoclave with ethanol and concentrated hydrochloric acid.[26] Alternatively, the following procedure may be used: 40.0 g (0.119 mol) of *N*-benzoyl(aminomethyl)diphenylphosphine oxide was refluxed in 450 mL of 1-butanol[27] and 150 mL of concentrated hydrochloric acid for 65 h. The solvents were removed in vacuo and the residue was dissolved in dichloromethane and 1 N hydrochloric acid (each 400 mL). The layers were separated and the water layer was washed twice with dichloromethane. Solid sodium hydroxide was added until the solution was basic and the water layer was extracted with dichloromethane (3 × 200 mL). The combined organic layers were washed with water and saturated brine and dried over potassium carbonate. Evaporation of the solvent afforded a white solid that was recrystallized from dichloromethane–hexane: yield 19.90 g (72%); mp 101–102 °C (lit.[26] mp 101–102 °C); IR (KBr) 3350, 3280, 1185 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.4 (br s, 2 H, NH_2), 3.36 (d, 2 H, $J_{H,P}$ = 4.4, CH_2), 7.26–7.41 (m, 6 H), 7.57–7.67 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 41.6 (d, $J_{C,P}$ = 73, CH_2), 128.3 (d, $^3J_{C,P}$ = 12), 129.5 (q-C, d, $^1J_{C,P}$ = 119), 130.6 (d, $^2J_{C,P}$ = 10), 131.6 (d, $^4J_{C,P}$ = 3); ^{31}P NMR ($CDCl_3$) δ 30.73; MS, *m/z* (rel intensity) 231 (8), 230 (4), 202 (base peak), 201 (15), 183 (6), 155 (16), 125 (10), 124 (8), 78 (9), 77 (13), 51 (12); HRMS calcd for $C_{13}H_{14}NOP$ (M) 231.0813, found 231.0813.

***N*-Benzylidene(aminomethyl)diphenylphosphine Oxide (3).** (Aminomethyl)diphenylphosphine oxide (2.31 g, 10 mmol) and benzaldehyde (1.10 g, 1.04 equiv) were stirred in dichloromethane (30 mL) in the presence of magnesium sulfate. After 1 h the product was filtered and the dichloromethane was evaporated. Stirring in ether (25 mL) overnight and filtration afforded **3** as a white powder:[28] yield 3.10 g (97%); mp 120–121 °C; IR (KBr) 1636, 1197 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.61 (dd, 2 H, $^4J_{H,H}$ = 1.1, $^2J_{H,P}$ = 13.2, CH_2), 7.28–7.64 (m, 11 H), 7.85–7.96 (m, 4 H), 8.17 (dt, 1 H, $^4J_{H,H}$ = 1.1, $^4J_{H,P}$ = 4.0, HC=N); ^{13}C NMR ($CDCl_3$) δ 62.0 (d, $^1J_{C,P}$ = 74, CH_2), 128.2, 128.4 (d, $^3J_{C,P}$ = 12), 128.5, 131.0, 131.0 (q-C, d, $^1J_{C,P}$ = 102), 131.5 (d, $^2J_{C,P}$ = 10), 131.9 (d, $^4J_{C,P}$ = 3), 135.7 (q-C, d, $^4J_{C,P}$ = 3), 165.5 (d, $^3J_{C,P}$ = 13, CH=N); ^{31}P NMR ($CDCl_3$) δ 29.75; MS, *m/z* (rel intensity) 319 (M, 0.2), 318 (1), 217 (8), 216 (base peak), 215 (76), 202 (32), 183 (5), 125 (5), 118 (50), 99 (66), 77 (24) and 51 (14); HRMS calcd for $C_{20}H_{18}NOP$ (M) 319.1126, found 319.1130.

***N*-Benzylidene-α-(diphenylphosphinoyl)glycinate Esters 4a–c. General Procedure.**[29] In a dry 1-L three-necked round-bottom flask, equipped with a magnetic stirring bar, ni-

(24) None of the obtained cycloadducts showed a molecular ion peak in the EI spectrum (source temp, 150 °C), due to loss off of diphenylphosphine oxide (Ph_2POH, loss of 202). Thus, HRMS was measured for the (M − 202) peak. In some cases a CI spectrum (ionizing gas ammonia) was measured. In these cases a (M + 1) peak was observed.

(25) Einhorn, A.; Bischkopff, E.; Szelinski, B. *Ann. Chem.* **1905**, *343*, 223.

(26) Kreutzkamp, N.; Herberg, K.; Lämmerhirt, K.; Schmidt-Samoa, E. *Arch. Pharm.* **1971**, *308*, 896.

(27) When the reaction was carried out at normal pressure in ethanol, benzoic acid sublimed and a pellet was formed in the reflux condenser, leading to a potentially dangerous pressure build-up in the reaction vessel. This hazard can be avoided by using 1-butanol as the solvent.

(28) Compare: Zamboni, R.; Just, G. *Can. J. Chem.* **1979**, *57*, 1115.

(29) Likewise, other aliphatic esters may be prepared. Aromatic esters are unstable under the reaction conditions, even at low temperature. Probably phenoxide is eliminated from the anion of **4**.[14]

trogen inlet, septum, and dropping funnel, 9.60 g (30.1 mmol) of imine **3** was dissolved in 390 mL of freshly distilled THF under a nitrogen atmosphere. Benzyl chloroformate (6.4 g, 1.25 equiv) was dissolved in THF, to give a total volume of 25 mL. The flask was cooled to −78 °C. In a separate flask an approximately 0.5 M solution of LDA was prepared by dissolving 7.65 g of diisopropylamine (dried on sodium hydroxide) in 75 mL of THF and adding 47.3 mL of a 1.4 M solution of nBuLi in hexane at −50 °C.

The starting material was treated with 60 mL of the LDA solution (transferred by syringe), 10 mL of the benzyl chloroformate solution, 30 mL of the LDA, 5 mL of the acylating agent, 15 mL of LDA, 5 mL of acylating agent, and finally once more with 15 mL of the LDA solution and 5 mL of the acylating agent. A period of approximately 0.5 h elapsed between each addition, and the temperature of the cooling bath was kept below −60 °C. After these additions, TLC analysis (10:60:30 Et_3N–hexanes–CH_2Cl_2) indicated complete conversion of the starting material. The reaction was quenched with a saturated ammonium chloride solution (250 mL) and was allowed to warm to room temperature. The layers were separated and the water layer was extracted three times with 150 mL of ether. The organic layers were combined and dried over magnesium sulfate and filtered. The solvents were evaporated to give a reddish oil. Traces of THF were removed by coevaporation with petroleum ether and the product was stirred in ether (225 mL) overnight. Filtration of the precipitate afforded part of the product as a pale yellow powder. Stirring the filtrate in 50 mL of ether overnight afforded a second portion. The combined yield amounted to 10.90 g (80%) of **4b**, pure according to ^1H NMR and ^{31}P NMR and used as such in the cycloaddition reactions.

Likewise, the following were prepared: with methyl chloroformate (3.56 g, 1.25 equiv), the methyl ester **4a** (8.65 g, 76%), and with di-*tert*-butyl pyrocarbonate (8.20 g, 1.25 equiv), the *tert*-butyl ester **4c** (10.10 g, 80%).

Methyl *N*-benzylidene-α-(diphenylphosphinoyl)glycinate (4a): powder (ether); mp 108–110 °C; IR (KBr) 1723, 1625, 1189 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.63 (s, 3 H, OMe), 5.16 (d, 1 H, $^2J_{H,P}$ = 15.9, α-H), 7.26–7.64 (m, 11 H), 7.77–7.87 (m, 2 H), 8.03 (d, 1 H, $^4J_{H,P}$ = 3.6, HC=N), 8.02–8.12 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 52.3 (OMe), 75.8 (d, $^1J_{C,P}$ = 66, α-C), 127.9, 128.0, 128.1, 128.2, 128.3, 131.3, 131.7, 131.9, 132.0, 132.1, 132.1 (each C–H), 128.9, 130.3 (each q-C, Ph_2PO), 135.1 (q-C, Ph), 166.0 (d, $^3J_{C,P}$ = 10, HC=N), 167.4 (q-C, CO_2Me); ^{31}P NMR ($CDCl_3$) δ 30.93; MS, *m/z* (rel intensity) 377 (M, 4), 318 (6), 275 (14), 274 (M − PhCN, base peak), 273 (21), 233 (12), 219 (7), 216 (9), 215 (7), 202 (18), 201 (88), 183 (7), 176 (47), 117 (30), 116 (40), 91 (9), 90 (13), 89 (8), 77 (38), 51 (13); HRMS calcd for $C_{22}H_{20}NO_3P$ (M) 377.1181, found 377.1179.

Benzyl *N*-benzylidene-α-(diphenylphosphinoyl)glycinate (4b): powder (ether); mp 125–127 °C; IR (KBr) 1718, 1624, 1187 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.06 (AA′, 2 H, ^2J = 12.0, OBn), 5.19 (d, $^2J_{H,P}$ = 15.6, α-H), 7.15–7.65 (m, 16 H), 7.76–7.87 (m, 2 H), 7.96–8.07 (m, 2 H), 8.07 (d, 1 H, $^4J_{H,P}$ = 3.4, HC=N); ^{13}C NMR ($CDCl_3$) δ 67.1 (OBn), 75.6 (d, $^1J_{C,P}$ = 66, α-C), 127.9, 128.0, 128.0, 128.1, 128.3, 131.2, 131.7, 131.9, 132.0, 132.1 (each C–H), 130.2, 133.5 (each q-C, Ph_2PO), 134.7 (q-C, Bn), 135.1 (q-C, Ph), 166.2 (d, $^3J_{C,P}$ = 10, HC=N), 166.9 (q-C, CO_2Bn); ^{31}P NMR ($CDCl_3$) δ 30.63; MS, *m/z* (rel intensity) 453 (M, 0.1), 436 (11), 435 (33), 419 (11), 418 (38), 417 (41), 277 (21), 260 (14), 220 (12), 219 (base peak), 216 (17), 209 (13), 202 (22), 201 (98), 199 (31), 183 (11), 152 (11), 118 (10), 108 (39), 107 (30), 105 (15), 91 (73), 90 (8), 89 (7), 79 (37), 78 (18), 77 (79); HRMS calcd for $C_{28}H_{24}NO_3P$ (M) 453.1493, found 453.1507.[30]

***tert*-Butyl *N*-benzylidene-α-(diphenylphosphinoyl)-glycinate (4c)**: powder (ether); mp 152–153 °C; IR (KBr) 1734, 1626, 1183 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (s, 9 H, *t*-Bu), 5.07 (d, 1 H, $^2J_{H,P}$ = 15.1, α-H), 7.29–7.65 (m, 11 H), 7.79–7.89 (m, 2 H), 8.03–8.14 (m, 2 H), 8.10 (d, 1 H, $^4J_{H,P}$ = 3.7, HC=N); ^{13}C NMR ($CDCl_3$) δ 27.5 (*t*-Bu), 75.8 (d, $^1J_{C,P}$ = 69, α-C), 82.7 (q-C, *t*-Bu), 127.9, 128.0, 128.2, 128.3, 131.1, 131.8, 131.9, 132.1 (each C–H), 129.2, 129.6 (each q-C, Ph_2PO) 135.4 (q-C, Ph), 165.8 (q-C, d, $^2J_{C,P}$ = 3, CO_2-*t*-Bu) and 166.2 (d, $^3J_{C,P}$ = 10, HC=N); ^{31}P NMR ($CDCl_3$) δ 29.92; MS, *m/z* (rel intensity) 435 (4), 419 (M, 0.02), 418 (4), 417 (4), 363 (2), 346 (2), 345 (2), 319 (4), 318 (13), 317 (8), 316 (36), 261 (19), 260 (M− PhCN − C_4H_8, base peak), 259 (17), 258 (12), 257 (8), 220 (4), 219 (46), 203 (11), 202 (52), 201 (40), 199 (11), 183 (10), 162 (32), 125 (8), 118 (9), 117 (22), 116 (13), 91 (10), 90 (12), 89 (8), 77 (21), 59 (21), 57 (42), 51 (10); HRMS calcd for $C_{24}H_{20}NO_3P$ (M) 419.1651, found 419.1651, for $C_{24}H_{20}O_3P_2$ (diphenylphosphinic acid anhydride) 418.0887, found 418.0902.[30]

Thermal 1,3-Dipolar Cycloaddition: General Procedure (Exemplified for **4b**, R = Bn). Imine **4b** (1.0 g, 2.21 mmol) and 0.45 g (1.18 equiv) of NPM were heated in 22 mL of the appropriate solvent (concentration 0.1 M) for 3 h at the temperature specified in Tables II and III. The solvent was evaporated and the products were stirred in ether (25 mL) overnight to remove the small excess of NPM. A mixture of C-1 epimeric products was obtained after filtration in almost quantitative yield.

The products could be separated by flash chromatography. Eluent for the methyl esters **9a** and **10a** and the benzyl esters **9b** and **10b** was 1.5% methanol–ether, for the *tert*-butyl esters **9c** and **10c**, 1% methanol–ether. In all cases the Panti endo product **9** eluted first. The yields are specified in Table III.

Panti Esyn Endo Methyl Ester. (1α,3α,3aβ,6aβ)-Methyl octahydro-1-(diphenylphosphinoyl)-4,6-dioxo-3,5-diphenylpyrrolo[3,4-*c*]pyrrole-1-carboxylate (9a): white powder; mp 194–195 °C; IR (KBr) 3230, 1718, 1192 cm^{-1}; ^1H NMR ($CDCl_3/CD_3OD \approx 5/1$) δ 3.27 (dd, 1 H, $J_{2,3}$ = 5.8, $J_{H,P}$ = 2.9, H-2), 3.34 (dd, 1 H, $J_{3,3a}$ = 8.3, $J_{3a,6a}$ = 9.8, H-3a), 3.58 (s, 3 H, Me), 4.25 (dd, 1 H, $J_{3a,6a}$ = 9.8, $J_{H,P}$ = 13.9, H-6a), 4.71 (dd, 1 H, $J_{2,3}$ = 5.8, $J_{3,3a}$ = 8.3, H-3), 7.25–7.58 (m, 16 H), 8.00–8.17 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 50.8 (C-6a), 52.7 (OMe), 54.0 (d, $J_{C,P}$ = 4, C-3a), 64.5 (d, $J_{C,P}$ = 9, C-3), 72.9 (q-C, d, $J_{C,P}$ = 81, C-1), 125.7, 126.2, 126.3, 126.8, 126.9, 127.1, 128.0, 128.1, 128.3, 128.4, 128.5, 128.6, 128.6, 128.7, 128.9, 132.2, 132.3, 132.3, 132.5 (each C–H), 130.4, 131.6 (each q-C, Ph_2PO and 5-Ph), 139.5 (q-C, 3-Ph), 170.1 (q-C, d, $J_{C,P}$ = 10, CO_2Me), 173.2 (q-C, d, $J_{C,P}$ = 4, C-6), 174.2 (q-C, C-4); ^{31}P NMR ($CDCl_3$) δ 34.18; MS, *m/z* (rel intensity) 349 (13), 348 (M − Ph_2POH, 42), 316 (14), 290 (10), 289 (52), 203 (8), 202 (66), 201 (86), 183 (15), 175 (12), 170 (22), 155 (12), 142 (48), 125 (16), 124 (29), 115 (41), 113 (22), 105 (32), 78 (28), 77 (44), 51 (base peak); HRMS calcd for $C_{20}H_{16}N_2O_4$ (M − Ph_2POH) 348.1110, found 348.1110.

Psyn Eanti Endo Methyl Ester. (1α,3β,3aα,6aα)-Methyl octahydro-1-(diphenylphosphinoyl)-4,6-dioxo-3,5-diphenylpyrrolo[3,4-*c*]pyrrole-1-carboxylate (10a): white powder; mp 126–127 °C; IR (KBr) 3320, 1720, 1185 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.51 (dd, 1 H, $J_{2,3}$ = 5.8, $J_{H,P}$ = 16.2, H-2), 3.56 (dd, 1 H, $J_{3,3a}$ = 10.2, $J_{3a,6a}$ = 8.2, H-3a), 3.58 (s, 3 H, OMe), 4.27 (dd, 1 H, $J_{2,3}$ = 5.8, $J_{3,3a}$ = 10.2, H-3), 4.58 (dd, 1 H, $J_{3,6a}$ = 8.2, $J_{H,P}$ = 10.3, H-6a), 6.75–6.80 (m, 2 H), 7.18–7.32 (m, 8 H), 7.44–7.64 (m, 6 H), 8.02–8.18 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 51.3 (d, $J_{C,P}$ = 4, C-3a), 52.3 (C-6a), 52.7 (OMe), 64.7 (C-3), 75.2 (q-C, d, $J_{C,P}$ = 81, C-1), 125.4, 125.6, 125.7, 126.9, 127.1, 127.8, 128.2, 128.3, 128.4, 128.6, 128.7, 131.1, 131.3, 132.1, 132.4, 132.6 (each C–H), 129.1, 130.6, 131.0 (each q-C, Ph_2PO and 5-Ph), 138.0 (q-C, 3-Ph), 169.8 (q-C, d, $J_{C,P}$ = 6, CO_2Me), 172.8 (q-C, C-4), 174.3 (q-C, d, $J_{C,P}$ = 13, C-6); ^{31}P NMR ($CDCl_3$) δ 28.53; MS, *m/z* (rel intensity 349 (13), 348 (M − Ph_2POH, 60), 317 (3), 316 (14), 290 (10), 289 (41), 203 (8), 202 (66), 201 (base peak), 183 (13), 142 (13), 125 (10), 124 (32), 115 (10), 78 (29), 77 (45), 51 (43); HRMS calcd for $C_{20}H_{16}N_2O_4$ (M − Ph_2POH) 348.1110, found 348.1121.

Panti Esyn Endo Benzyl Ester. (1α,3α,3aβ,6aβ)-Phenylmethyl octahydro-1-(diphenylphosphinoyl)-4,6-dioxo-3,5-diphenylpyrrolo[3,4-*c*]pyrrole-1-carboxylate (9b): white powder (ether); mp 200–202 °C; IR (KBr) 3280, 1712, 1195 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.23 (dd, 1 H, $J_{2,3}$ = 5.7, $J_{H,P}$ = 2.8, H-2), 3.37 (dd, 1 H, $J_{3,3a}$ = 8.0, $J_{3a,6a}$ = 10.0, H-3a), 4.31 (dd, 1 H, $J_{3a,6a}$ = 10.0, $J_{H,P}$ = 13.9, H-6a), 4.72 (dd, 1 H, $J_{2,3}$ = 5.7, $J_{3,3a}$ = 8.0, H-3), 5.00 (AA′, 2 H, ^2J = 11.9, OBn), 7.01–7.08 (m, 2 H), 7.18–7.58 (m, 19 H), 7.95–8.06 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 51.1 (C-6a), 54.3 (d, $J_{C,P}$ = 4, C-3a), 64.8 (d, $J_{C,P}$ = 9, C-3), 68.4 (OBn), 72.8 (q-C, d, $J_{C,P}$ = 81, C-1), 126.4, 127.0, 128.2, 128.4, 128.5, 128.7, 129.0, 132.2, 132.4, 132.4, 132.5, 132.7, 132.9 (each C–H), 130.5, 131.7

(30) Under the sampling conditions for the EI spectrum, dimerization of the imines **4b** and **4c** occurred, and various fragments were derived from these dimers, most notably diphenylphosphinic acid anhydride (*m/z* 418) and $Ph_2PO_2H_2$ (*m/z* 219). The CI spectrum (ionizing gas ammonia) clearly showed an (M + 1) peak for both imines.

(each q-C, Ph_2PO and 5-Ph), 133.9 (q-C, Bn), 139.6 (q-C, 3-Ph), 169.7 (q-C, d, $J_{C,P}$ = 9, CO_2Bn), 173.4 (q-C, d, $J_{C,P}$ = 4, C-6), 174.3 (q-C, C-4); ^{31}P NMR ($CDCl_3$) δ 33.96; MS, m/z (rel intensity) 425 (2), 424 (M - Ph_2POH, 9), 318 (7), 290 (19), 289 (14), 202 (72), 201 (base peak), 183 (5), 170 (12), 142 (17), 124 (33), 115 (10), 105 (12), 91 (51), 78 (29), 77 (42), 51 (24); HRMS calcd for $C_{26}H_{20}N_2O_4$ (M - Ph_2POH) 424.1423, found 424.1419.

Psyn Eanti Endo Benzyl Ester. (1α,3β,3aα,6aα)-Phenylmethyl octahydro-1-(diphenylphosphinoyl)-4,6-dioxo-3,5-diphenylpyrrolo[3,4-*c*]pyrrole-1-carboxylate (10b): white powder (ether); mp 196 °C; IR (KBr) 3330, 1708, 1190 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.41 (dd, 1 H, $J_{2,3}$ = 5.8, $J_{H,P}$ = 15.8, H-2), 3.51 (dd, 1 H, $J_{3,3a}$ = 10.2, $J_{3a,6a}$ = 8.2, H-3a), 4.32 (dd, 1 H, $J_{2,3}$ = 5.8, $J_{3,3a}$ = 10.2, H-3), 4.47 (dd, 1 H, $J_{3a,6a}$ = 8.2, $J_{H,P}$ = 10.6, H-6a), 5.01 (AA', 2 H, ^2J = 11.9, OBn), 6.68–6.73 (m, 2 H), 7.01–7.53 (m, 19 H), 7.87–8.00 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 51.5 (d, $J_{C,P}$ = 4, C-3a), 52.2 (C-6a), 64.9 (C-3), 68.3 (OBn), 75.0 (q-C, d, $J_{C,P}$ = 81, C-1), 125.7, 125.8, 125.9, 126.4, 127.1, 128.0, 128.1, 128.2, 128.3, 128.4, 128.6, 128.7, 128.9, 131.5, 131.7, 132.3, 132.5, 132.7 (each C-H), 130.9, 131.1, (each q-C, Ph_2PO and 5-Ph), 134.3 (q-C, Bn), 138.2 (q-C, 3-Ph), 169.3 (q-C, d, $J_{C,P}$ = 6, CO_2Bn), 173.3 (q-C, d, $J_{C,P}$ = 3, C-4), 174.2 (q-C, d, $J_{C,P}$ = 13, C-6); ^{31}P NMR ($CDCl_3$) δ 28.83; MS, m/z (rel intensity) 425 (2), 424 (M - Ph_2POH, 12), 318 (7), 290 (34), 289 (27), 216 (16), 215 (15), 202 (72), 201 (96), 183 (17), 170 (21), 142 (30), 125 (11), 124 (32), 115 (12), 113 (12), 91 (base peak), 78 (33), 77 (42), 65 (10), 51 (49); HRMS calcd for $C_{26}H_{20}N_2O_4$ (M - Ph_2POH) 424.1423, found 424.1420.

Panti Esyn Endo *tert*-Butyl Ester. (1α,3α,3aβ,6aβ)-1,1-Dimethylethyl octahydro-1-(diphenylphosphinoyl)-4,6-dioxo-3,5-diphenylpyrrolo[3,4-*c*]pyrrole-1-carboxylate (9c): white powder (ether); mp 185–186 °C; IR (KBr) 3320, 1718, 1187 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (s, 9 H, *t*-Bu), 3.24 (dd, 1 H, $J_{3,3a}$ = 8.0, $J_{3a,6a}$ = 9.9, H-3a), 3.30 (br d, 1 H, $J_{2,3}$ = 5.5, $J_{H,P} \approx 0$, H-2), 4.16 (dd, 1 H, $J_{3a,6a}$ = 9.9, $J_{H,P}$ = 14.1, H-6a), 4.75 (dd, 1 H, $J_{2,3}$ = 5.5, $J_{3,3a}$ = 8.0, H-3), 7.26–7.51 (m, 16 H), 8.03–8.23 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 27.2 (*t*-Bu), 50.6 (C-6a), 54.1 (d, $J_{C,P}$ = 6, C-3a), 63.9 (d, $J_{C,P}$ = 9, C-3), 73.3 (q-C, d, $J_{C,P}$ = 81, C-1), 84.4 (q-C, *t*-Bu), 126.3, 126.8, 127.9, 128.0, 128.1, 128.3, 128.4, 128.8, 132.0, 132.2, 132.5, 132.6 (each C-H), 130.8, 131.0, 131.7 (each q-C, Ph_2PO and 5-Ph), 139.7 (q-C, 3-Ph), 169.0 (q-C, d, $J_{C,P}$ = 9, CO_2-*t*-Bu), 173.3 (q-C, d, $J_{C,P}$ = 4, C-6), 174.4 (q-C, C-4); ^{31}P NMR ($CDCl_3$) δ 33.73; MS, m/z (rel intensity) 391 (M - Ph_2PO, 0.8), 349 (12), 348 (38), 334 (4), 291 (26), 290 (74), 289 (28), 203 (40), 202 (54), 201 (base peak), 183 (12), 170 (34), 143 (59), 142 (36), 131 (13), 125 (37), 117 (66), 116 (14), 115 (52), 113 (10), 105 (19), 91 (14), 90 (33), 89 (24), 78 (28), 77 (58), 57 (20), 56 (19), 51 (53); HRMS calcd for $C_{23}H_{23}N_2O_4$ (M - Ph_2PO) 391.1658, found 391.1707.[24]

Psyn Eanti Endo *tert*-Butyl Ester. (1α,3β,3aα,6aα)-1,1-Dimethylethyl octahydro-1-(diphenylphosphinoyl)-4,6-dioxo-3,5-diphenylpyrrolo[3,4-*c*]pyrrole-1-carboxylate (10c): white powder (ether); mp 172–173 °C; IR (KBr) 3330, 1712, 1188 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18 (s, 9 H, *t*-Bu), 3.34 (dd, 1 H, $J_{3,3a}$ = 10.2, $J_{3a,6a}$ = 8.3, H-3a), 3.66 (dd, 1 H, $J_{2,3}$ = 6.6, $J_{H,P}$ = 19.8, H-2), 3.88 (dd, 1 H, $J_{2,3}$ = 6.6, $J_{3,3a}$ = 10.2, H-3), 4.67 (dd, 1 H, $J_{3a,6a}$ = 8.3, $J_{H,P}$ = 11.0, H-6a), 6.76–6.81 (m, 2 H), 7.16–7.30 (m, 8 H), 7.48–7.68 (m, 6 H), 8.05–8.15 (m, 2 H), 8.20–8.30 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 27.1 (*t*-Bu), 51.4 (d, $J_{C,P}$ = 4, C-3a), 53.1 (C-6a), 65.5 (C-3), 75.7 (q-C, d, $J_{C,P}$ = 88, C-1), 85.0 (q-C, *t*-Bu), 125.8, 128.2, 128.5, 128.6, 128.7, 131.3, 131.4, 132.1, 132.2, 132.8, 133.0, 133.1 (each C-H), 129.9, 131.8 (each q-C, Ph_2PO and 5-Ph), 138.0 (q-C, 3-Ph), 167.8 (q-C, br s, CO_2-*t*-Bu), 173.0 (q-C, C-4), 173.7 (q-C, d, $J_{C,P}$ = 13, C-6); ^{31}P NMR ($CDCl_3$) δ 25.34; MS, m/z (rel intensity) 391 (1), 390 (M - Ph_2POH, 1.5), 334 (14), 291 (12), 290 (36), 203 (48), 202 (66), 201 (base peak), 183 (12), 143 (32), 142 (12), 125 (10), 124 (32), 117 (45), 115 (23), 78 (38), 77 (57), 57 (58), 56 (19), 51 (55); HRMS calcd for $C_{23}H_{22}N_2O_4$ (M - Ph_2POH) 390.1580, found 390.1588.

Cycloaddition in Toluene at Reflux. Benzyl ester **4b** (2.25 g, 5.0 mmol) and 1.00 g (1.16 equiv) of NPM were refluxed in 50 mL of toluene for 3 h. The solvent was evaporated and the residue was subjected to flash chromatography (7:3 ether–petroleum ether). The imine **11b** was isolated as the first fraction (0.25 g, 12%). Increasing the polarity of the eluent (1% methanol–ether) afforded the Panti Esyn endo adduct **9b** (1.56 g, 50%). Elution with 2% methanol–ether afforded the methanolysis products **14** (0.208 g, 10%) and **15** (0.122 g, 6%).

(3α,3aβ,6aβ)-Phenylmethyl hexahydro-4,6-dioxo-3,5-diphenylpyrrolo[3,4-*c*]pyrrole-1-carboxylate (11b): white powder (ether); mp 108–109 °C; IR (KBr) 1708 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.11 (dd, 1 H, $J_{3,3a}$ = 10.0, $J_{3a,6a}$ = 9.1, H-3a), 4.84 (dd, 1 H, $^4J_{3,6a}$ = 1.1, $J_{3a,6a}$ = 9.1, H-6a), 5.21 (AA', 2 H, ^2J not determinable, OBn), 5.47 (br d, 1 H, $J_{3,3a}$ = 10.0, H-3), 7.19 (dd, 2 H, J = 1.5 and 7.0), 7.25–7.52 (m, 11 H), 8.22 (dd, 2 H, J = 1.4 and 7.6); ^{13}C NMR ($CDCl_3$) δ 46.7 (C-3a), 56.8 (C-6a), 67.7 (OBn), 76.0 (C-3), 126.5, 128.3, 128.4, 128.7, 128.9, 129.7, 131.8 (each C-H), 131.3, 131.4 (each q-C, 5-Ph and Bn), 134.8 (q-C, 3-Ph), 169.4, 169.6, 171.2 and 174.2 (each q-C, C-1, C-4, C-6 and CO_2Bn); MS, m/z (rel intensity) 290 (21), 289 (22), 170 (12), 143 (8), 142 (18), 119 (8), 117 (8), 115 (9), 113 (26), 101 (12), 95 (10), 91 (58), 51 (base peak); HRMS calcd for $C_{26}H_{20}N_2O_4$ (M) 424.1423, found 424.1427.

Attempted Catalysis of the Cycloaddition. *tert*-Butyl ester **4c** (1.0 g, 2.4 mmol) and NPM (0.49 g, 1.2 equiv) were refluxed in 24 mL of chloroform in the presence of acetic acid (0.150 g, 1.05 equiv). TLC analysis showed the reaction to be complete within 3 h. It also showed the presence of an extra product, which was subsequently identified as the imine **11c**. The solvents were evaporated and the residue was subjected to flash chromatography (7:3 ether–petroleum ether, and, after the imine **11c** had been collected, 1% methanol–ether). The first fraction contained the imine **11c** (0.122 g, 13%). The second fraction provided the pure Panti Esyn endo compound **9c** (0.560 g, 40%). The third fraction was the Psyn Eanti endo product **10c** (0.430 g, 30%).

(3α,3aβ,6aβ)-1,1-Dimethylethyl hexahydro-4,6-dioxo-3,5-diphenylpyrrolo[3,4-*c*]pyrrole-1-carboxylate (11c): white solid (ether); mp 204 °C; IR (KBr) 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.55 (s, 9 H, *t*-Bu), 3.90 (dd, 1 H, $J_{3,3a}$ = 10.5, $J_{3a,6a}$ = 9.0, H-3a), 4.63 (dd, 1 H, $^4J_{3,6a}$ = 0.7, $J_{3a,6a}$ = 9.0, H-6a), 5.93 (br d, 1 H, $J_{3,3a}$ = 10.5, H-3), 6.63–6.69 (m, 2 H), 7.00–7.04 (m, 2 H), 7.18–7.30 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 27.8 (*t*-Bu), 48.3 (C-3a), 57.2 (C-6a), 78.8 (C-3), 84.3 (q-C, *t*-Bu), 125.8, 127.3, 128.5, 128.8 (each C-H), 131.0 (q-C, 5-Ph), 135.4 (q-C, 3-Ph), 160.0, 163.6, 170.9, 172.6 (each q-C, C-1, C-4, C-6 and CO_2-*t*-Bu); MS, m/z (rel intensity) 390 (M, 14), 375 (12), 335 (22), 334 (base peak), 317 (13), 316 (46), 306 (11), 290 (12), 187 (12), 174 (31), 169 (17), 143 (11), 142 (26), 131 (18), 117 (62), 115 (21), 90 (14), 57 (88); HRMS calcd for $C_{23}H_{22}N_2O_4$ (M) 390.1580, found 390.1575.

3-(Diphenylphosphinoyl)-1-phenylsuccinimide (13). Diphenylphosphine oxide (**12**) (5.0 g, 0.025 mol) (prepared from chlorodiphenylphosphine and water) and 4.35 g (0.025 mol) of NPM were refluxed in 100 mL of toluene under a nitrogen atmosphere. After 8 h the solvent was evaporated and the product was stirred in ether overnight. Filtration gave 6.80 g (73%) of **13** as a white powder: mp 134–136 °C; IR (KBr) 1697 and 1187 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.11 (ddd, 1 H, ^2J = 19.0, $^3J_{3,4c}$ = 9.8, $^3J_{4,Pt}$ = 10.0, H-4), 3.37 (ddd, 1 H, ^2J = 19.0, $^3J_{3,4t}$ = 3.9, $^3J_{4,Pc}$ = 15.6, H-4), 4.12 (ddd, 1 H, $^3J_{3,4}$ = 3.9, 9.8, $^2J_{3,P}$ = 13.8, H-3), 6.94 (m, 2 H), 7.27–7.65 (m, 9 H), 7.72–7.84 (m, 2 H), 7.95–8.07 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 29.9 (C-4), 42.7 (d, $^1J_{C,P}$ = 62, C-3), 126.3, 126.4, 128.6, 128.7, 128.8, 129.0, 131.3, 131.6, 131.6, 131.8, 132.7 (each C-H), 128.0, 130.1 (each q-C, Ph_2PO and Ph), 170.1 (q-C, d, $J_{C,P}$ = 3), 173.7 (q-C, d, $J_{C,P}$ = 4) (each C=O); ^{31}P NMR ($CDCl_3$) δ 31.18; MS, m/z (rel intensity) 375 (M, 48), 203 (8), 202 (95), 201 (base peak), 183 (4), 157 (32), 152 (15), 133 (13), 113 (37), 95 (13), 77 (27), 51 (94); HRMS calcd for $C_{22}H_{18}NO_3P$ (M) 375.1024, found 375.1043.

Methanolysis of 3-(Diphenylphosphinoyl)-1-phenylsuccinimide (13). After treatment of **13** with silica in methanol for 4 days, the products were separated by flash chromatography (2% methanol–ether). This gave **14** as the first-eluting product and **15** as the second.

Methyl α-(diphenylphosphinoyl)-*N*-phenylsuccinamate (14): white powder (ether); mp 220–223 °C; IR (KBr) 3255, 1738, 1685, 1185 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.95 (ddd, 1 H, ^2J = 16.5, ^3J = 2.7, $^3J_{H,P}$ = 9.3, H-3), 3.33 (s, 3 H, OMe), 3.67 (ddd, 1 H, ^2J = 16.5, ^3J = 11.0, $^3J_{H,P}$ = 5.5, 3-H), 4.34 (ddd, 1 H, ^3J = 2.7 and 11.0, $^2J_{H,P}$ = 11.0, H-2), 6.98 (t, 1 H, J = 7.7, *p*-H), 7.19 (t, 2 H, J = 7.7, *m*-H), 7.44–7.63 (m, 8 H), 7.79–7.92 (m, 4 H), 10.4 (br s, 1 H, *N*-H); ^{13}C NMR ($CDCl_3$) δ 32.9 (C-3), 43.9 (d, $^1J_{C,P}$ = 60, C-2), 52.2 (OMe), 119.6, 123.3, 128.3, 128.5, 128.9, 129.1, 130.9, 131.1, 131.3, 132.3, 132.4 (each C-H), 138.9 (q-C, *N*-Ph), 168.5 (q-C, d, $J_{C,P}$ = 15), 168.8 (q-C, d, $J_{C,P}$ = 4) (each C=O) (q-C's of Ph_2PO

not visible); ^{31}P NMR ($CDCl_3$) δ 32.72; MS, m/z (rel intensity) 407 (17), 375 (26), 315 (5), 288 (8), 229 (39), 202 (57), 201 (62), 183 (8), 157 (10), 133 (10), 113 (27), 101 (11), 93 (11), 77 (13), 51 (base peak); HRMS calcd for $C_{23}H_{22}NO_4P$ (M) 407.1286, found 407.1292.

Methyl β-(diphenylphosphinoyl)-*N*-phenylsuccinamate (15): white powder (ether); mp 193–195 °C; IR (KBr) 3255, 1738, 1680, 1175 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.57 (ddd, 1 H, ^2J = 16.8, ^3J = 3.4, $^3J_{H,P}$ = 11.2, H-2), 3.15 (ddd, 1 H, ^2J = 16.8, ^3J = 10.2, $^3J_{H,P}$ = 6.6, H-2), 3.59 (s, 3 H, OMe), 4.20 (ddd, 1 H, ^3J = 3.4 and 10.2, $^2J_{H,P}$ = 17.3, H-3), 6.99–7.08 (m, 1-H), 7.18–7.62 (m, 10 H), 7.73–7.90 (m, 4 H), 9.4 (br s, 1 H, *N*-H); ^{13}C NMR ($CDCl_3$) δ 31.12 (C-2), 45.2 (d, $^1J_{C,P}$ = 60, C-3), 52.2 (OMe), 120.1, 124.3, 128.6, 128.7, 128.9, 129.0, 131.4, 132.5, 132.6, 132.7 (each C–H), 128.9, 129.9, 130.9 (each q-C, Ph_2PO), 137.7 (q-C, *N*-Ph), 165.2 (q-C), 171.4 (q-C, d, $J_{C,P}$ = 15) (each C=O); ^{31}P NMR ($CDCl_3$) δ 34.89; MS, m/z (rel intensity) 407 (M, 9), 376 (6), 375 (12), 315 (32), 287 (12), 274 (18), 232 (12), 231 (21), 229 (11), 202 (58), 201 (68), 167 (22), 113 (27), 101 (14), 77 (28), 51 (base peak); HRMS calcd for $C_{23}H_{22}NO_4P$ (M) 407.1286, found 407.1295.

Diphenylphosphinoyl-Substituted Ylides. 2. 1,3-Dipolar Cycloaddition of α-(Diphenylphosphinoyl)glycine Ester Imines. Dipolar Cycloaddition as the Rate-Determining Step[1]

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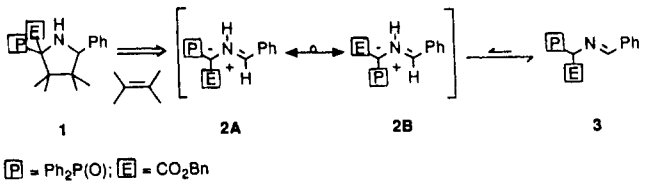
The thermal 1,3-dipolar cycloaddition of benzyl *N*-benzylidene-α-(diphenylphosphinoyl)glycinate (**3**) has been investigated as a general route to polyfunctionalized 2-(diphenylphosphinoyl)pyrrolidines. The Psyn and Panti dipoles **2A** and **2B**, generated via a formal [1,2]-H shift in chloroform or acetonitrile at reflux, were allowed to react with a variety of dipolarophiles to give the desired pyrrolidines, generally in good yields. When dipolar cycloaddition was the rate-determining step, a strong preference for reaction of the Psyn dipole **2A** was observed. With monoactivated dipolarophiles, the activating substituent is exclusively found at C-4 of the pyrrolidine ring, with a strong preference for Psyn 4-endo product formation. Only with cinnamonitrile was a nonregiospecific addition observed. With diactivated dipolarophiles, product distribution was markedly influenced by the substituent present at the β-carbon atom of the dipolarophile. This substituent could either enhance the selectivity for Psyn endo product formation, lead to preferential formation of the 4-exo adduct, or induce preferential addition to the Panti dipole **2B**. Structure eludication of the adducts with the aid of ^1H and ^{13}C NMR is discussed.

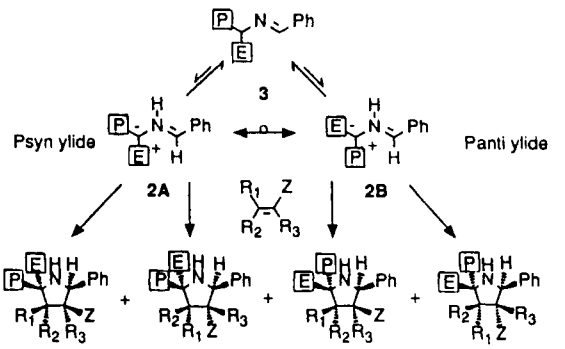
Introduction

The 1,3-dipolar cycloaddition of azomethine ylides,[2,3] stabilized by both a diphenylphosphinoyl and an ester group, has been investigated as a general route to polyfunctionalized 2-(diphenylphosphinoyl)pyrrolidines.[4] For the synthesis of N-unsubstituted pyrrolidines of type **1** (Scheme I), generation of the required ylides **2** via a formal [1,2]-H shift[2b,5] in α-(diphenylphosphinoyl)glycine ester imines such as **3** may be used.

Scheme I



Scheme II



In the preceding article,[1] the synthesis of the required starting materials was described. Also, the results of a study of the addition to the very reactive dipolarophile *N*-phenylmaleimide (i.e., with *dipole formation* as the rate-determining step) were reported. The Psyn Eanti **2A**

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