oxygen, which was kept isotropic. The function minimized in the refinement was $\sum w(F_o^2 - F_c^2)^2$, where weights w were $1/\sigma^2(F_o^2)$. Atomic form factors were from Doyle and Turner,[13] and, for hydrogen, from Stewart, Davidson, and Simpson.[14] In the final refinement cycle, all shifts were $<0.2\sigma$. The final difference Fourier peaks were <0.30 e Å^{-3}, except those very close to known atoms.

One water hydrogen is located on a center of symmetry. The water molecule is half-populated; however, if both centrically related waters happened to be present in the same cell, they would share this hydrogen, and be separated by a fairly short hydrogen-bond distance, 2.645 (5) Å. The other water hydrogen was not found in difference Fouriers, but must be located between the water oxygen and the chlorine ion because these atoms are hydrogen-bonded (d = 3.16 Å). The nitrogen of the N-dimethyl group is protonated, and hydrogen-bonds to the chlorine ion with a distance of 3.043 (3) Å. There is also a close intermolecular contact between the ortho chlorine on the aromatic ring and the carbonyl oxygen of the amide group in the molecule related by: $-x, y + {}^1/_2, 1{}^1/_2 - z$. The final agreement index R = 0.079 for all 4566 reflections, and the standard deviation of fit = 2.14. The CRYM system of computer programs was used.[12] The atomic coordinates and thermal parameters are deposited at the Cambridge Crystallographic Data Centre. In addition, tables of bond lengths and angles, torsion angles, and close intermolecular contacts are available as supplementary material.

Acknowledgment. We thank the Upjohn Company for supporting this research. Also we are indebted to a referee for Figure 1 and for clarification of the stereochemical argument associated with it.

Supplementary Material Available: Additional X-ray data and ^{1}H NMR for compounds **4**, **5**, **7b**, **8a**, and **12** (12 pages). Ordering information is given on any current masthead page.

(13) Doyle, P. A.; Turner, P. S. *Acta Crystallogr.* **1968**, *A24*, 390.
(14) Stewart, R. F.; Davidson, E. R.; Simpson, W. T. *J. Chem. Phys.* **1965**, *42*, 3175.

Preparation, Alkylation Reactions, and Conformational Analysis of Esters of Phospholanic Acid. Preparation and Reactivity of (2*S**,5*S**)-1,2,5-Tribenzyl-1-oxophospholane

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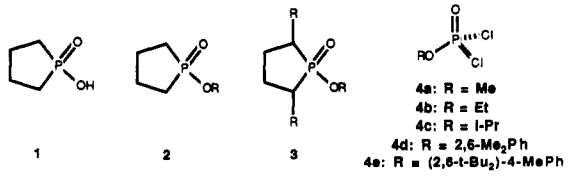
Optimum conditions for the reaction of 1,4-butanediyldimagnesium dibromide and alkyl phosphorodichloridates are described. The general geometric requirements of the cyclization reaction transition state are discussed. Alkylation reactions of phospholanate esters **2b** and **2c** are reported. Conformational analysis of various phospholanate esters is discussed in terms of $^3J_{PC}$ and $^3J_{PH}$ data, NOE experiments, and crystal structures of related phospholane derivatives. *trans*-2,5-Dibenzyl phosphinate esters **15b** and **15c** were converted to (2*S**,5*S**)-1,2,5-tribenzyl-1-oxophospholane **18** by reductive alkylation. Phosphine oxide **18** was shown to participate in an olefination reaction with 4-*tert*-butylcyclohexanone.

Phospholanic acid (**1**, 1-hydroxy-1-oxophospholane; tetramethylenephosphinic acid) represents the parent compound of a class of saturated five-membered ring phosphinic acid derivatives.[1] Since phosphinate esters can be converted by straightforward methods into substances of potential utility to organic and organometallic chemistry, we initiated an investigation of the development of practical methods for the preparation of phospholanate esters **2** and ring alkylated derivatives **3**. This paper describes the chemistry and conformational analysis of racemic phosphinate esters **2** and **3**. Future publications will address the preparation of these materials in chiral form.



1 2 3

Classical methods of preparation of phosphorus(IV) derivatives of phospholane have involved reaction of 1,4-butanediyldimagnesium dibromide with amidous phosphorodichloridates,[2] intramolecular Arbuzov reaction of 4-chlorobutyl diethyl phosponite,[3] and McCormack cycloaddition of 1,3-butadiene with phosphorus trichloride.[4] Each of these methods suffered from low overall yield.

In an attempt to establish a practical alternative for the preparation of phospholanic esters, we investigated reactions of alkyl phosphorodichloridates[5] **4** with 1,4-butanediyldimagnesium dibromide.[6] During the course of these studies two independent reports describing the preparation

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† In part.

(1) Reviews of methods of phosphorus heterocycle ring construction: Quin, L. D. *The Heterocyclic Chemistry of Phosphorus*; Wiley: New York, 1981; Chapter 2. Hellwege, D. M.; Berlin, K. D. *Top. Phosphorus Chem.* **1969**, *6*, 1. Mann, F. G. In *The Chemistry of Heterocyclic Compounds: Heterocyclic Derivatives of Phosphorus, Arsenic, Antimony, and Bismuth*; Weissberger, A., Taylor, E. C., Eds.; Wiley: New York, 1070; pp 12–61.
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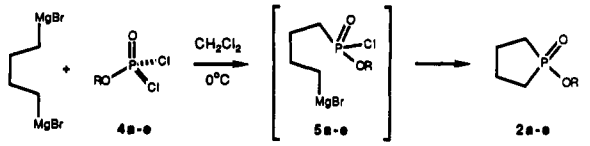
(5) Petrov, K. A.; Bliznyuk, N. K.; Korotkova, V. P. *Zh. Obshch. Khim.* **1960**, *30*, 2995.
(6) Several recipes are available for the preparation of 1,4-butanediyldimagnesium dibromide. Nenitzescu, C. D.; Nesciou, I. *J. Am. Chem. Soc.* **1950**, *72*, 3483. Yvernault, T.; Casteignau, G.; Estrade, M. *C. R. Acad. Sci. Paris* **1969**, *269*, 169. We employed an equivalent of dibromoethane to enhance di-Grignard formation relative to Wurtz coupling and to provide an additional equivalent of $MgBr_2$ to drive the Schlenk equilibrium $2[(BrMg)CH_2CH_2CH_2CH_2(MgBr)] \rightleftharpoons ([CH_2)_4]Mg)_2 + 2MgBr_2$ in favor of the monomeric di-Grignard reagent: Holtkamp, H. C.; Schat, G.; Blomberg, C.; Bickelhaupt, F. *J. Organomet. Chem.* **1982**, *240*, 1.

0022-3263/91/1956-3137$02.50/0

Table I. Cyclization Reactions



entry	[di-Grignard]	[phosphoro-dichloridate]	R	additn time (h)	yield (%)
1	0.5 M	**4a**, 0.5 M	Me	0.5	21
2	0.5 M	**4b**, 0.5 M	Et	0.5	34
3	0.5 M	**4c**, 0.5 M	*i*-Pr	0.5	34
4	0.5 M	**4d**, 0.5 M	2,6-Me_2Ph	0.5	23
5	0.5 M	**4e**, 0.5 M	2,6-*t*-Bu_2-4-MePh	0.5	16
6	0.2 M	**4b**, 0.2 M	Et	0.5	37
7	0.2 M	**4b**, 0.2 M	Et	9	50
8	0.2 M	**4c**, 0.2 M	*i*-Pr	8.5	48

of trans-2,5-disubstituted phospholanes were published.[7]

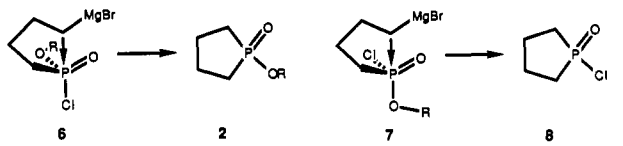
Results and Discussion

Methyl-, ethyl-, and isopropyl phosphorodichloridates **4a–c** were prepared by the method of Saunders,[8] while 2,6-dimethylphenyl phosphorodichloridate[9] (**4d**) and 4-methyl-2,6-di-*tert*-butylphenyl phosphorodichloridate (**4e**) were prepared by reaction of the lithium phenolate with phosphorus oxytrichloride in ether at 0 °C. The cyclization reaction was effected by slowly cannulating an ice-cold solution of di-Grignard reagent and a separate ice-cold solution of phosphorodichloridate into a reaction vessel precooled to 0 °C. Dichloromethane was selected as solvent because exploratory experiments conducted in either ether or tetrahydrofuran produced a complex mixture of products and much lower yields of phospholanate ester. The results of various such experiments are presented in Table I.

In comparing entries 1–5 it is evident that yields of the phosphinate esters were uniformly low. The reactions of 1,4-butanediyldimagnesium dibromide with aryl phosphorodichloridates **4d–e** resulted in formation of a significant amount of the free phenol, suggesting that for these substrates, displacement of phenoxide was competitive with displacement of chloride from the bifunctional intermediate **5**. In the hopes of improving the yield of the cyclization reaction, several experiments were conducted at higher dilution. As documented by entries 2 and 6 of Table I, it was observed that reducing substrate concentration from 0.5 M to 0.2 M resulted in a 3% increase in yield of the phospholanate ester. However, it was observed that by slowly mixing the reactants together, much higher yields (48–50%) of phospholanate ester were obtained (entries 7 and 8). The response of the cyclization reaction of 1,4-butanediyldimagnesium dibromide with phosphorodichloridates **4b** and **4c** to concentration and mixing time suggests that a competing side reaction is polymerization. It is instructive to consider the physical reasons for this behavior.

Nucleophilic displacements at P(IV) centers are generally recognized[10] to proceed by one of three pathways: (1) $S_N1(P)$, (2) $S_N2(P)$, and (3) addition–elimination. The reaction of 1,4-butanediyldimagnesium dibromide with alkyl or aryl phosphorodichloridates and subsequent cyclization of intermediate **5** most likely occur by either $S_N2(P)$ or addition–elimination pathways. Since the yield of the cyclization reaction depends on the fate of intermediate **5**, we focus disucssion on the chemistry of **5**. In thinking about possible mechanisms involved in the ring closure step, the addition–elimination path involves a trigonal bipyramid (tbp) as a discrete intermediate, while the $S_N2(P)$ mechanism involves a trigonal-bipyramidal transition state.

The $S_N2(P)$ mechanism involves inversion of configuration at phosphorus. Hence, formation of phospholanate ester by an $S_N2(P)$ pathway involves a geometry similar to **6**. An alternative mode of the $S_N2(P)$ mechanism involving displacement of alkoxide or phenoxide via trajectory **7** is also conceivable. This latter reaction would be expected to be more favorable for phosphorodichloridates **4d** and **4e**, since phenoxides are much better leaving groups than alkoxides and nucleophilic displacement at phosphoryl centers shows a significant dependence on the strength of the covalent bond between phosphorus and the leaving group.[10] Nucleophilic attack according to the geometry depicted in **7** also represents the least sterically hindered trajectory of attack. Such steric hindrance is most likely significant in the cases of **6d** (R = 2,6-Me_2Ph) and **6e** (R = 2,6-*t*-Bu_2-4-MePh) since in these cases the R groups are very bulky. The phosphinic acid chloride **8** produced by displacement of phenoxide would be expected to form dimer or higher oligomer by further reaction with a Grignard reagent present in the reaction medium.[11]



The phospholanate esters **2** are themselves susceptible to nucleophilic attack by Grignard reagents.[12] Berlin, Mislow, and Cram have demonstrated that phosphinate esters react with Grignard reagents to form phosphine oxides.[12] In order to ascertain the compatibility of the phospholanate esters **2** and the di-Grignard reagent, we conducted two series of control experiments. In separate experiments, ethyl phospholanate (**2b**) and 2,6-dimethylphenyl phospholanate (**2d**) (1 mmol) were each reacted with 1,4-butanediyldimagnesium dibromide (1 mmol) in dichloromethane (0.1 M in each reactant) at 0 °C for periods of time ranging from 1 to 8 h. Surprisingly, neither **2b** nor **2d** underwent any detectable reaction with the di-Grignard reagent. This result suggests that the phospholanate esters are stable to 1,4-butanediyldimagnesium dibromide under the conditions in which the phosphinate esters are formed. The lack of reactivity of **2d** suggests that for aryl phosphorodichloridate reagents **4d** and **4e**, the major side reaction competing with displacement of chloride is displacement of phenoxide in either substrates **4d–e** or intermediates **5d–e**.

Returning to the question of cyclization of intermediate **5**, the first step of the addition–elimination mechanism is similar in geometry to the direct S_N2 pathway. Thus, nucleophilic attack at phosphorus can occur by trajectories **6** and **7**, producing **9** and **10**. The least sterically hindered attack trajectory corresponds to **7**. An added complexity associated with this reaction path is the possibility of

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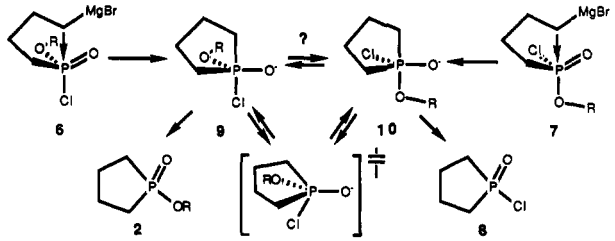
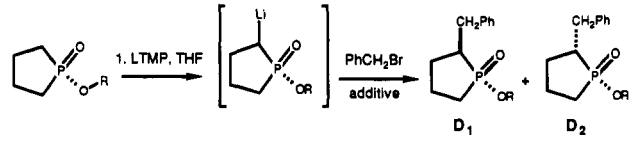
(8) Saunders, B. C.; Stacey, G. C.; Wild, F.; Wilding, I. G. E. *J. Chem. Soc.* **1948**, 699.
(9) Kosolapoff, G. A.; Arpke, C. K.; Lamb, R. W.; Reich, H. *J. Chem. Soc. C* **1968**, 815.
(10) Emsley, J.; Hall, D. *The Chemistry of Phosphorus*; Harper and Row: New York, 1976; Chapter 8.
(11) Ikai, K.; Iida, A.; Yamashita, M. *Synthesis* **1989**, 595.
(12) Berlin, K. D.; Pagilagan, R. U. *J. Org. Chem.* **1967**, *32*, 129. Korpiun, O.; Mislow, K. *J. Am. Chem. Soc.* **1967**, *89*, 4784. Nudelman, A.; Cram, D. J. *J. Am. Chem. Soc.* **1968**, *90*, 3869.



pseudorotation[13a] on the tbp intermediates **9** and/or **10** prior to expulsion of the leaving group. In trigonal-bipyramidal intermediates with a sterically demanding phenoxy moiety, the tbp **9** is expected to be more stable than tbp **10** since bulky substituents prefer equatorial positions in molecules of trigonal-pyramidal geometry.[14a] Thus, in cyclizations of **5d** and **5e** steric approach control favors production of a tbp intermediate of geometry **10**, while tbp stability most likely favors **9**. The decomposition of tbp species is believed to occur by departure of the leaving group from an apical position.[13b] This decomposition process would presumably be rapid for intermediates **9d,e** and **10d,e**, which possess very bulky OR groups, since these tbp intermediates most likely possess significant B-strain. The strain is released upon departure of the leaving group. In general, the presence of a five-membered ring in trigonal-bipyramidal phosphorus intermediates leads to enhanced rates of pseudorotation relative to acyclic structures. The pseudorotation of one trigonal bipyramid to an isomeric trigonal bipyramid occurs by way of a square pyramidal transition state.[14a] In pentavalent phosphorus intermediates of square-pyramidal geometry:[14a] (1) five-membered rings preferentially span basal positions, (2) electronegative ligands prefer to occupy basal sites, (3) π-donor ligands prefer to occupy the axial site, and (4) steric effects are minimized by positioning bulky groups in the apical position. The pseudorotation of **10** to **9** (and vice versa) with the oxy anion acting as pivot produces a square-pyramidal transition state in which criteria 1–3 are satisfied. However, the bulky phenoxide moiety is forced into a basal position. Since the bond angles between adjacent basal positions in an idealized square pyramid are 86°, the conversion of either **9** or **10** to the square-pyramidal transition state forces adjacent ligands into a closer proximity to the phenoxide moiety than in either **9** or **10** (90° and 120° bond angles to nearest neighbors). Hence, an increase in intramolecular nonbonded interactions occurs on passage of either **9** or **10** to the square pyramid. This increase in steric strain most likely produces an energy barrier for pseudorotation. Thus it is possible that the **10** → **9** interconversion might be slow relative to expulsion of the axial phenoxy leaving group and formation of acid chloride **8**. Hence, the formation of significant amounts of the free phenol in reactions of phosphorodichloridates **4d** and **4e** can be rationalized by preferential formation of tbp **10** by steric approach control, followed by loss of phenoxide in direct competition with pseudorotation to tbp **9**. A mechanistic analogy for this situation can be drawn to the hydrolysis of sterically hindered acyclic phosphonium salts.[14b]

Table II. Alkylation Reactions

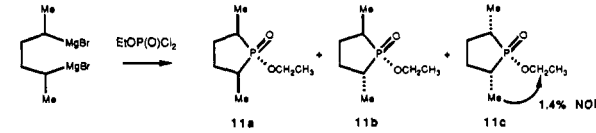


entry	additive	R	D_1:D_2	yield (%)
1	none	Et	60:40 (**12b**:**13b**)	91
2	2-HMPA	Et	25:75 (**12b**:**13b**)	83
3	2 HMPA[a]	Et	33:66 (**12b**:**13b**)	75
4	none	*i*-Pr	70:30 (**12c**:**13c**)	72
5	2 HMPA	*i*-Pr	23:77 (**12c**:**13c**)	78

[a] Deprotonation carried out in the presence of HMPA.

The alkoxy analogues **5a–c** undergo cyclization competitively via trajectories **6** and **7**. It seems reasonable to postulate that pentacoordinated intermediates are formed and undergo pseudorotation in these cases since **10** is predicted to be the kinetic tbp intermediate formed on both steric and electronic grounds. Since the phospholanate esters **2b,c** are produced in these reactions, pseudorotation to **9** followed by departure of chloride must occur. The dependence of yield of **2b** and **2c** to mixing time (Table I, entries 2, 3, 7, and 8) indicates that in all cases the ring closure reaction experiences a significant activation barrier. It is only when the reactants are mixed together slowly that ring closure can compete with the bimolecular polymerization reaction.

The reaction of 2,5-hexanediyldimagnesium dibromide[15] with ethyl phosphorodichloridate produced a 1:2:1 mixture of three diastereomers (**11a**:**11b**:**11c**), which were separable by medium pressure liquid chromatography. The structural assignments were based on ^{1}H NMR analyses.[16] Thus, the methyl groups attached to the 2 and 5 positions of the phospholane ring in compounds **11a** and **11c** appeared in each case as a chemically equivalent doublet of doublets (**11a**: δ 1.20, J_{HH} = 7.3 Hz, J_{PH} = 16.0 Hz) and (**11c**: δ 1.14, J_{HH} = 7.0 Hz, J_{PH} = 14.8 Hz). Since the methyl groups bonded to positions 2 and 5 of the phospholane ring of trans derivative **11b** are chemically nonequivalent, each of these groups appeared as a distinct doublet of doublets: (δ 1.18, J_{HH} = 7.1 Hz, J_{PH} = 15.9 Hz and δ 1.22, J_{HH} = 7.1 Hz, J_{PH} = 15.9 Hz). Evidence for the orientation of the ethoxy moiety relative to the 2,5-methyl groups in **11a** and **11c** was provided by NOE experiments. Isomer **11c**, upon irradiation of the methyl



signals at δ 1.14 showed a 1.4% enhancement of the OCH_2 signal. Isomer **11a** did not display any NOE effect. The observed 1.4% NOE effect in **11c** is consistent with a cis orientation of methyl and ethoxy moieties. The observation that a statistical ratio of the three cyclization products **11a–c** was formed in the reaction suggested that we pursue

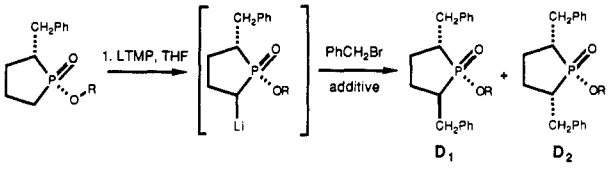
(13) (a) Berry, R. S. *J. Chem. Phys.* **1960**, *32*, 933. (b) Westheimer, F. H. *Acc. Chem. Res.* **1968**, *1*, 70. Hudson, R. F.; Brown, C. *Acc. Chem. Res.* **1972**, *5*, 204. Trippett, S. *Pure Appl. Chem.* **1974**, *74*, 545.

(14) (a) Holmes, R. R. *Pentacoordinated Phosphorus*, ACS Monograph 176, Vol. 2; American Chemical Society: Washington, DC, 1980. (b) Corfield, J. R.; De'Ath, N. J.; Trippett, S. *J. Chem. Soc. C* **1971**, 1930. In these reactions, kinetic attack of hydroxide on the phosphonium salt by steric approach control produced a tbp with a bulky substituent occupying an axial position. The bulky substituent experienced competitive expulsion from the tbp intermediate despite the fact that a better leaving group was directly attached to phosphorus. These observations were rationalized by suggesting that pseudorotation of the initially formed tbp intermediate was disfavored since for steric reasons the pseudorotation process possessed a high activation barrier. Consequently, the better leaving group experienced difficulty in gaining access to an apical position, hence its departure was inhibited.

(15) McDermott, J. X.; White, J. F.; Whitesides, G. M. *J. Am. Chem. Soc.* **1976**, *98*, 6521.

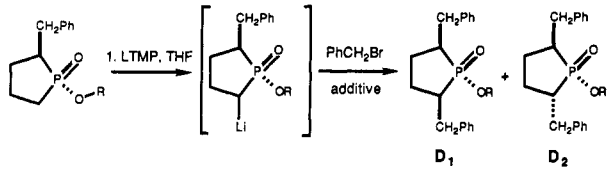
(16) Related ^{1}H NMR analyses for *cis*-2,5-dimethyl derivatives of the phosphol-3-ene ring system have been reported: Quin, L. D.; Barket, T. P. *J. Am. Chem. Soc.* **1970**, *92*, 4303. Bond, A.; Green, M.; Pearson, S. C. *J. Chem. Soc. B* **1968**, 929.

Table III. Alkylation Reactions



entry	additive	R	D_1:D_2	yield (%)
1	none	Et	78:22 (**14b**:**15b**)	78
2	2-HMPA	Et	39:61 (**14b**:**15b**)	88
3	none	*i*-Pr	86:14 (**14c**:**15c**)	75
4	2 HMPA	*i*-Pr	57:43 (**14c**:**15c**)	71

Table IV. Alkylation Reactions



entry	additive	R	D_1:D_2	yield (%)
1	none	Et	60:40 (**15b**:**16b**)	88
2	none	*i*-Pr	55:45 (**15c**:**16c**)	59

other, conceivably more stereoselective routes to 2,5-disubstituted derivatives of phospholanic acid. Consequently, we directed our attention to alkylation reactions of phospholanate esters **2b** and **2c**.

To the best of our knowledge, our work constitutes the first study of the stereochemistry of alkylation reactions of esters of phospholanic acid.[17] The phospholanate esters **2b** and **2c** were deprotonated with lithium 2,2,6,6-tetramethylpiperidide (LTMP)[18] at −78 °C and then reacted with benzyl bromide in either the presence or absence of HMPA. Inspection of Tables II–IV reveals that the lithium phosphinate anion in THF tends to prefer to alkylate syn to the phosphinyl oxygen moiety. However, in the presence of HMPA the trans diastereomer D_2 is formed preferentially. The configurational assignments of various phospholanate esters **12–16** were established by ^{1}H NOE experiments. The NOE experiments were interpreted by consideration of preferred conformations of each ester. The preferred conformations were determined by analysis of the ^{1}H and ^{13}C NMR spectra of the phospholanate esters.

The conformational analysis of organophosphorus compounds benefits greatly from the NMR active phosphorus nucleus and the dependence of ^2J, ^3J, and ^4J on the spatial relationship between phosphorus and other nuclei.[19-21] Several independent investigations[22,23] probing the relationship of the magnitude of the $^3J_{POCH}$ coupling constant to the POCH dihedral angle have established that trans POCH rotamers (θ = 180°) possess large coupling constants (22–28 Hz) while gauche POCH rotamers (θ = 60°) possess much smaller values (2–3 Hz). Inspection of entries 2–8 of Table V reveals a fairly constant value of approximately 8 Hz for $^3J_{POCH}$ in derivatives of ethyl phospholanate, suggesting that these substances possess a fairly uniform average POCH conformation. The magnitude of the value of $^3J_{POCH}$ is consistent with a three-site model favoring a significant population of an anti P–O–C–C conformation. Further evidence for this preferred conformation is provided by $^3J_{POCC}$. Large $^3J_{POCC}$ values (≥8 Hz) indicate a 180° dihedral angle between phosphorus(IV) and carbon while smaller values (≤2 Hz) are characteristic for a gauche relationship.[24] Derivatives **2b** and **12b–15b** possess $^3J_{POCC}$ values of approximately 6 Hz, consistent with a three-site model bearing a preference for the trans POCC rotamer.

Table V. Coupling Constants[a]

entry	compd	$^3J_{POCH}$	$^3J_{POCC}$	$^2J_{POC}$	$^3J_{PCCPh}$
1	**2a**	10.7		6.8	
2	**2b**	7.8	6.0	6.6	
3	**2c**	8.3	4.0	6.8	
4	**12b**	7.6	6.0	6.6	11.2
5	**13b**	7.7	5.6	6.5	12.9
6	**14b**	7.5	5.9	6.9	11.4
7	**15b**	7.6	5.7	7.1	9.8, 12.3
8	**16b**	7.8	5.0	6.5	12.2
9	**12c**	8.5	3.8, 4.5	6.7	11.2
10	**13c**	7.8	3.9[b]	6.7	13.1
11	**14c**	8.3	3.8	6.7	11.5
12	**15c**	7.9	3.5, 4.1	7.0	9.5, 12.7
13	**16c**	7.3	3.9	6.9	13.1
14	**17**				13.1

[a] Spectra were recorded in $CDCL_3$ and the absolute values of the coupling constants are reported in hertz. [b] Broad doublet, probably an unresolved, overlapped doublet of doublets.

A related issue concerns the preferred O=P—O—C conformation. In a seminal investigation, Siddall and Prohaska[25] recorded and analyzed the ^{1}H NMR spectra of 61 organophosphorus esters. The two important observations were that rotation about the P–O–C linkage is rapid and that the esters possess a large population of a single preferred general conformation. We propose a more refined version of the general conformational model of Siddall in which the phospholanate esters described in this paper prefer an s-cis conformation about the O=P—O—C linkage. The s-cis conformation benefits from resonance interaction[26] of an oxygen lone pair with the pπ–dπ P=O bond (primary stereoelectronic effect)[27] and interaction of a second oxygen lone pair with the P–O σ^* orbital (secondary stereoelectronic effect).[27] We assume that the ester oxygen moiety is sp^2 hybridized and that the oxygen-centered orbitals involved in the primary and secondary stereoelectronic effects are orthogonal.

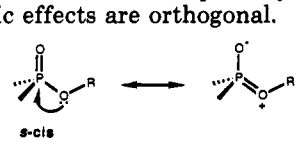


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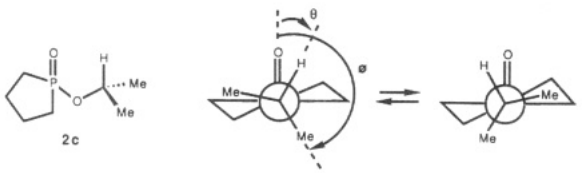
Figure 1.

Inspection of Table V reveals that $^3J_{POCH}$ of isopropyl phospholanate esters is larger than $^3J_{POCH}$ of ethyl phospholanate esters. This behavior is inconsistent with a three-site model, which would predict that $^3J_{POCH}$ would be smaller for **2c** than **2b**, since a larger population of gauche POCH rotamers would be expected for **2c** relative to **2b**. By analogy to results obtained in the spectral analyses of oligonucleotides,[21b] the isopropyl phospholanate esters may be described by a two-site model, where the P=O bond makes equal angles $\pm\theta$ with the C–H bond of the isopropyl moiety. On the basis of the equation[20c,21b] $^3J_{POCH} = 18.1 \cos^2\theta - 4.8 \cos\theta$, the two-site model with $\theta \sim 35°$ is consistent with the observed J values. The $^3J_{POCC}$ coupling constants are also consistent with this analysis. The concept is most readily understood with a symmetrical compound like isopropyl phospholanate (**2c**). If the entire population consists of two rotamers in rapid equilibrium, then a constant value of $J_{sum} = {}^3J_{POCC(a)} + {}^3J_{POCC(b)}$ should be observed, where C(a) and C(b) are the methyl groups of an isopropyl moiety of one rotamer of the pair. Calculating[21b] the $^3J_{POCC}$ values using the



equation $^3J_{POCC} = 9.5 \cos^2\phi - 0.6 \cos\phi$ and dihedral angles ϕ of 85° and 155° produces values of $^3J_{POCC(a)} = 0.1$ and $^3J_{POCC(b)} = 8.3$ or $J_{sum} = 8.4$ Hz. Since the conformational equilibrium involves two mirror image rotamers, time averaging makes the methyl groups in **2c** magnetically equivalent and $^3J_{POCC(a)} = {}^3J_{POCC(b)} = {}^1/_2J_{sum} = \sim 4.2$ hz, which compares well with the experimental value of 4.0 Hz. For compounds that are unsymmetrical, with C(a) and C(b) chemically nonequivalent (**12c**, **15c**), the J_{sum} values are 8.3 and 7.6 Hz, respectively.

Finally, the dihedral angle dependence of $^3J_{PCCC}$ in phosphine oxides,[28] phosphonates,[29] and other P(IV) derivatives[30] has been determined. Typical values are $^3J_{PCCC} = 14$ Hz for $\theta = 180°$, 6 Hz for $\theta = 60°$, and 18–20 Hz for $\theta = 0°$. The values of $^3J_{PCCPh}$ of the coupling reported in Table V between phosphorus and the ipso carbon of the aromatic ring of the benzyl side chain is usually in the range of 11–13 Hz, suggesting a significant population of the trans P–C–C–Ph rotamer in solution.

To the best of our knowledge, there have not been any systematic studies of the conformational analysis of the saturated phospholane ring system[31] in which phosphorus is present as P(IV).[32] Relevant to this issue, however, is an X-ray structure determination[33a] of phospholanic acid. The key finding of this study was that the heterocyclic ring was nonplanar. The gross features of the ring conformation in the crystal structures of methyl phenyl phospholanium iodide[33b] and other phospholane derivatives[33c–e] are similar to those of phospholanic acid. As a basis for discussion, a selected view of the crystal structure of phospholanic acid was generated from the original published coordinates[33a] with the computer program Molecular Editor[34] and is reproduced in Figure 1. Viewing phospholanic acid from the corner of the ring at which phosphorus resides (Figure 1) provides a structure that resembles a half-chair form.

Table VI. ^{13}C NMR Chemical Shifts and J_{PC} Coupling Constants[a]

entry	compd	C_2	C_3	C_4	C_5
1	**2a**	22.9 (89.9)	22.2 (12.0)	22.2 (12.0)	22.9 (89.9)
2	**2b**	24.6 (90.0)	23.2 (12.0)	23.2 (12.0)	24.6 (90.0)
3	**2c**	25.1 (90.3)	22.9 (12.1)	22.9 (12.1)	25.1 (90.3)
4	**2d**	25.8 (88.9)	22.9 (12.6)	22.9 (12.6)	25.8 (88.9)
5	**2e**	28.5 (90.1)	22.7 (13.3)	22.7 (13.3)	28.5 (90.1)
6	**12b**	38.3 (89.2)	30.3 (16.1)	20.7 (9.7)	25.4 (88.8)
7	**13b**	39.8 (90.4)	29.5 (15.3)	20.7 (9.9)	25.0 (86.6)
8	**14b**	38.2 (86.9)	26.8 (14.8)	26.8 (14.8)	38.2 (86.9)
9	**15b**	40.6 (89.3)[b]	28.9 (13.4)[c]	28.0 (12.3)[c]	39.8 (86.0)[b]
10	**16b**	39.0 (86.0)	26.3 (14.1)	26.3 (14.1)	39.0 (86.0)
11	**12c**	38.6 (89.6)	30.0 (16.1)	20.5 (9.8)	25.9 (88.8)
12	**13c**	39.2 (91.4)	28.9 (15.1)	20.3 (9.8)	25.2 (86.0)
13	**14c**	38.4 (87.2)	26.4 (14.7)	26.4 (14.7)	38.4 (87.2)
14	**15c**	40.2 (90.0)[d]	28.7 (13.3)[e]	27.6 (12.3)[e]	40.0 (85.8)[d]
15	**16c**	38.8 (85.9)	25.8 (13.8)	25.8 (13.8)	38.8 (85.9)
16	**11a**	29.7 (88.0)	29.6 (15.0)	29.6 (15.0)	29.7 (88.0)
17	**11c**	31.6 (87.8)	29.3 (14.3)	29.3 (14.3)	31.6 (87.8)
18	**17**	39.3 (89.7)	27.9 (13.2)	27.9 (13.2)	39.3 (89.7)

[a] Spectra were recorded in $CDCl_3$ and the chemical shifts are reported relative to tetramethylsilane; coupling constants are in parentheses and reported in hertz. [b] These values may be interchanged. [c] These values may be interchanged. [d] These values may be interchanged. [e] These values may be interchanged.

The most useful piece of spectroscopic data relating to ring conformation for the various phosphinate esters described in this report are ^{13}C chemical shifts and J_{PC} coupling constants. Such data are presented in Table VI. Inspection of entries 1–5 of Table VI reveals that for unsubstituted phospholanate esters **2a–e** C_2 and C_5 are equivalent and C_3 and C_4 are equivalent both in terms of chemical shift and J_{PC}. This suggests the presence of a single symmetrical conformation or the presence of several rapidly equilibrating conformations, with the values of δ and J_{PC} in Table VI representing time-averaged values. Given the crystal structure data, we favor the latter hypothesis. We propose as a working model that the conformational energy surface of the phospholanate ring

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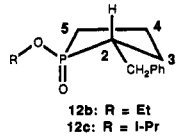
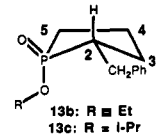
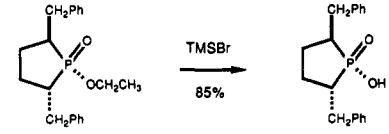
system contains two low-energy half-chair forms that are in rapid equilibrium. The rapid conformational equilibrium assures the time-averaged magnetic and geometric equivalence of $C_2 \leftrightarrow C_5$ and $C_3 \leftrightarrow C_4$ on the NMR time scale. It appears reasonable that substitution at C_3 or C_4 would tend to favor a large population of that conformer which places the C_3 substituent in a pseudoequatorial position. This conclusion is supported by the crystal structures of 3-methylphospholanium salts.[33c,e] The effect of substitution at C_2 of the phospholanate ring on ring conformation is less predictable. The relevant chemical shift and J_{PC} values for various C_2-substituted phospholanate esters appear as entries 6–7 and 11–12 of Table VI. In these cases, ring carbons C_2 and C_5 were distinguished by application of a combination of ^1H–^1H decoupling and two-dimensional NMR heteronuclear correlation spectroscopy (APT[35] and HETCOR[36]). Both the decoupling and HETCOR experiments established the proton–carbon connectivities, and the APT spectrum differentiated C_2 from C_5 on the basis of methine vs methylene type carbon. The downfield shift of C_2 in these derivatives relative to the parent compounds was also consistent with these assignments.[37] The assignments of C_3 and C_4 was made on the basis of treating the CH_2Ph moiety as a group and assuming a β-deshielding effect of this group and a small γ shielding effect.[37] The J_{PC} coupling constants to C_3 and C_4 in **12b**, **13b**, **12c**, and **13c** are significantly different. This suggests that these structures spend a significant amount of time in a conformation in which C_3 and C_4 assume different dihedral angle relationships to P. We interpret these results in the following way. Substitution of the phospholane ring at C_2 forces the heterocycle to assume a conformation that minimizes steric repulsions between the C_2 substituent and the exocyclic substituents attached to phosphorus. In effect, the CH_2Ph moiety should prefer to be gauche to both the P=O and POR groups of the phosphinate ester moiety. The J_{PC} data of Table VI require that the dihedral angle relationship of C_3 and C_4 to P must be nonequivalent in the most highly populated conformer. This effectively limits the possibilities to one structure: an envelope form with C_2 occupying the flap position. Since molecular models indicate that steric repulsions are minimized and that the P–C–C–C_3 and P–C–C–C_4 dihedral angles are significantly different in this structure, we suggest that the envelope form best describes the C_2-substituted derivatives.



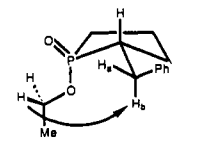


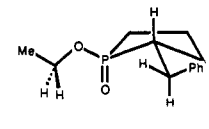
On the other hand, cis-2,5 disubstitution, regardless of configuration at phosphorus (Table VI, entries 8, 10, 13, 15, 16, and 17) restores symmetry and J_{PC} at C_3 becomes identical with J_{PC} at C_4. We suggest that in these cases both the C_2 and C_5 substituents tend to assume a geometry that places both substituents in a staggered relationship with respect to the P=O and POR groups of the phosphinate moiety. This requires phosphorus to reside at the flap of the envelope, with the two benzyl groups assuming pseudoequatorial orientations.

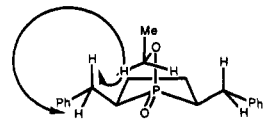
Finally, in the trans-2,5-disubstituted phosphinate esters **15b** and **15c** all the ring carbon atoms are distinct in terms of chemical shift and J_{PC}. Although we can spectroscopically distinguish all ring carbons in these systems, we cannot assign C_2, C_3, C_4, and C_5 with certainty. However, the similarity of both chemical shift and J_{PC} of C_3 and C_4 in these derivatives suggests that they are very symmetric in structure. We suggest that **15b** and **15c** exist in true or slightly distorted half-chair conformations in which the benzyl substituents occupy pseudoequatorial positions. In such structures the steric interactions between the benzyl groups and the exocyclic substituents attached to phosphorus are minimized. Furthermore, the dihedral angles between P and C_3 and P and C_4 are very similar, consistent with the J_{PC} data appearing in Table VI. Support for this conformational model was obtained from the ^{13}C NMR spectrum of *trans*-2,5-dibenzylphospholanic acid (**17**). The acid was obtained by dealkylation of phosphinate ester **15b** with trimethylsilyl bromide.[38] Apparently, inter- or intramolecular exchange of the phosphinic acid proton occurs rapidly on the NMR time scale. The ^{13}C NMR of **17** reveals only seven signals, implying that the acid possesses a C_2 axis of symmetry. The observed spectral behavior is consistent with a half-chair conformation of the heterocycle.



The relative configurations of the stereogenic centers at phosphorus and carbon in **12b,c**–**16b,c** were assigned by ^1H NMR NOE experiments. The observed results are consistent with the conformational models proposed earlier. Consider the ethyl phospholanate series **12b**–**16b**: the preferred O=P—O—C rotamer is s-cis, the preferred P–O–C–C rotamer is anti, and the preferred P–C–C–Ph rotamer is anti. Isomer **12b** in which the benzyl and ethoxy moieties are cis-related displays a 1% NOE between the more upfield of the two diastereotopic benzylic protons and the OCH_2 signal. The deshielding of protons located γ to the P=O moiety of phosphine oxides is known.[39] Based upon rigid model systems, it is believed that deshielding occurs for those γ protons that assume an orientation pseudoparallel to the P=O bond axis.[39] Thus, in phosphinate ester **12b** H_a represents the deshielded proton and







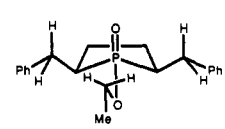


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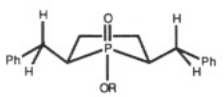
Table VII. ^{31}P NMR Chemical Shifts[a]

2a 82.8	**12b** 77.3	**12c** 75.6	**11a** 79.8
2b 80.5	**13b** 76.2	**13c** 74.2	**11b** 76.0
2c 79.2	**14b** 75.8	**14c** 74.8	**11c** 77.4
2d 80.2	**15b** 72.1	**15c** 71.2	**17** 75.9
2e 79.8	**16b** 75.0	**16c** 73.5	

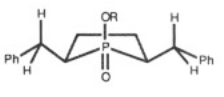
[a] The spectra were recorded in $CDCl_3$ and the chemical shifts are reported in ppm downfield from 85% H_3PO_4.

H_b corresponds to the shielded or upfield proton of the diasterotopic benzylic proton pair. Hence, H_b is responsible for the observed NOE in **12b**. Isomer **13b** did not show any observable NOE effect. In the 2,5-dibenzylated series, isomer **16b** showed magnetization transfer from the OCH_2 moiety to both H_c and H_d (and vice versa). Isomer **14b** in which the benzyl and ethoxy moieties are trans did not display an NOE effect. The relative configurations of the phosphorus and carbon stereogenic centers in the isopropyl ester series were made by analogous NOE experiments.

Before leaving this general discussion, it is instructive to consider the ^{31}P chemical shifts of the various phosphinate esters (Table VII). An internal consistency that appeared for each 2,5-disubstituted phospholanate ester (**11a–c**, **14b–16b**, and **14c–16c**) is that the trans-2,5-disubstituted derivative always resonated at the lowest field of the three isomers of a given set. This observation may prove to be of diagnostic value.

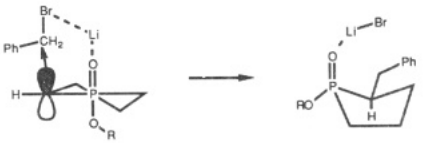


14b: R = Et
14c: R = i-Pr

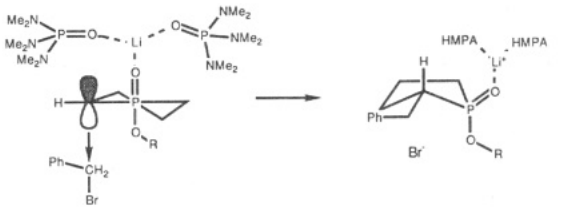


16b: R = Et
16c: R = i-Pr

As documented in Tables II–IV, the coordination environment around lithium appears to play a strong role in determining the stereoselectivity of the alkylation reactions. Although detailed studies of the solution structure of metallo phosphinate anions are lacking, several investigations of anions derived from phosphonates,[40] phosphonamidates,[41] and phosphine oxides[42] have been published. Spectroscopic data (^1H, ^{13}C, ^{31}P) of the lithium dimethyl benzylphosphonate anion suggested that the carbanionic center was sp^2 hybridized (planar), the electron pair of the anion occupied a p orbital, and the lithium cation associated with the anionic center was ligated to the phosphonyl oxygen moiety.[40] Similar observations have been made by Denmark on a phosphonamidate anion.[41] The crystal structure of the phosphonamidate anion was fully consistent with the conclusions drawn from the spectrosopic data: the carbanion center was sp^2 hybridized.[41] By analogy to these results, we presume the carbanionic center of the lithium phosphinate anions reported here is also sp^2 hybridized. Hence, stereoselection in the alkylation reaction is dependent upon which diastereoface of the carbanionic center is approached by the electrophile. If lithium is coordinated to the oxygen atom of the phosphinyl moiety, it seems reasonable to expect that alkylation should proceed syn to this moiety so that the Li^+Br^- ion pair is formed as a tight ion pair rather than a solvent-separated ion pair. Increasing the steric bulk

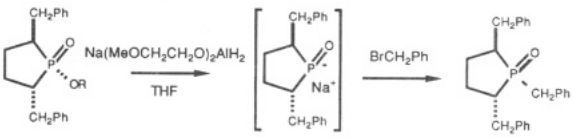


of the alkyl chain of the ester moiety appears to reinforce this stereochemical preference (Table II, entries 1 and 4). HMPA strongly solvates cations.[43] Hence, addition of HMPA to a lithium phosphinate anion should result in solvation of the lithium by HMPA. If enough HMPA molecules ligate to each lithium, then this will result in a net steric shielding of the carbanion on that π face syn to the phosphinyl oxygen moiety. According to this model, in the presence of HMPA alkylation should proceed trans to the phosphinyl oxygen moiety, as is observed experimentally.



As expected, the hindered lithium amide base kinetically selected the least hindered proton adjacent to phosphorus in each monobenzylated ester (Tables III and IV). The lack of stereochemical control in the second alkylation reaction by the resident carbon stereogenic center can be explained by assuming that the resident benzyl group occupies a pseudoequatorial disposition in each carbanion. In a pseudoequatorial position the benzyl group cannot sterically bias the stereochemistry of the alkylation reaction.

Consistent with our earlier observations with **2b** and **2d**, dibenzylphospholanate ester **15b** was totally inert toward reaction with ethylmagnesium bromide, even after extended reflux with excess reagent in tetrahydrofuran. However, both ethyl and isopropyl phospholanate esters **15b** and **15c** underwent reduction with sodium bis(methoxyethoxy)aluminum dihydride to produce an intermediate sodium (dibenzyltetramethylene)phosphine oxide ion pair, which then reacted subsequently with benzyl bromide to form[44] the tribenzylphosphine oxide **18**.



15b: R = Et
15c: R = i-Pr

18 (66% from 15b)
(62% from 15c)

The phosphine oxide **18** underwent regioselective metalation at the exocyclic benzylic center with *n*-BuLi in THF at 0 °C. The resultant yellow anion participated in a Wittig–Horner[45] olefination reaction with 4-*tert*-butylcyclohexanone to afford 1-benzylidene-4-*tert*-butylcyclohexane.[47a] The reaction products were easily separated and isolated by simple acid–base chemistry.

This result demonstrated the feasibility of phosphine oxide **18** and related derivatives as possible chiral reagents for effecting enantioselective Wittig olefination reactions.[46]

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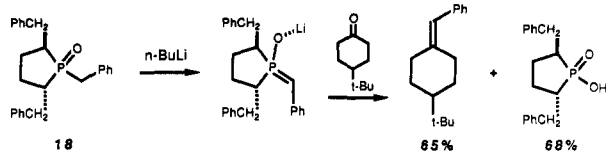

The benzylidenecyclohexane case illustrated here is but one example of a class of simple olefins of established configuration and optical rotation possessing an axial element of chirality.[47] We are currently directing our efforts toward the preparation of 18 and related phosphine oxides and phosphines in homochiral form, and the evaluation of these substances in both stoichiometric and catalytic stereoselective bond-forming reactions.

Experimental Section

General. Melting points are uncorrected. Abbreviations for ^{1}H NMR data are s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, dd = doublet of doublets, and td = triplet of doublets. Coupling constants are in hertz. ^{31}P chemical shifts are relative to external 85% H_3PO_4. Analytical gas–liquid chromatography (GC) was carried out on a 30 m × 0.32 mm fused silica capillary column wall coated with DB-5. Dichloromethane and 2,2,6,6-tetramethylpiperidine were distilled from calcium hydride and tetrahydrofuran and diethyl ether were distilled from sodium/benzophenone prior to use. Flash chromatography was carried out with kieselgel 60 (230–400 mesh) silica gel. All reactions were run under a nitrogen atmosphere.

Preparation of Phospholanic Esters. An oven-dried 100-mL three-necked flash was charged with a stir bar, oven-dried magnesium (1.05 g, 43.4 mmol), iodine (two crystals), and ether (5 mL). The mixture was warmed to 40 °C and stirred vigorously while a solution of 1,2-dibromoethane (1.21 mL, 14 mmol) and 1,4-dibromobutane (1.67 mL, 14 mmol) in ether (25 mL) was added dropwise over a period of 40 min. The mixture was then refluxed for 1 h. The two-phase mixture was allowed to settle for 2–4 h and the top ethereal layer removed by cannulation under a positive pressure of nitrogen. The residue was dissolved in anhydrous dichloromethane (70 mL) and cannulated into a clean 100-mL flask.

An ice-cold solution of alkyl or aryl phosphorodichloridate (14 mmol) in CH_2Cl_2 (70 mL) and the ice-cold di-Grignard solution were simultaneously added to a precooled 250-mL reaction vessel under a positive pressure of nitrogen over a period of 7–8 h. The solution was gradually warmed to room temperature and then stirred overnight. The solution was quenched by addition of 10% NH_4Cl (35 mL) and brine (10 mL) and extracted 4–5× with dichloromethane, and the extracts were dried (Na_2SO_4 + $MgSO_4$), filtered, and concentrated to afford an oil. The oil was flash chromatographed on 3.5 × 7.5 cm of silica gel with the gradient EtOAc → 5:95 → 10:90 → 15:85 MeOH/EtOAc to afford the phospholanate esters. The esters contained a small amount of high molecular weight material, so they were further purified by bulb-to-bulb distillation or recrystallization to afford the title compounds as clear, mobile oils or white crystalline solids.

Methyl phospholanate[48] (2a): bp 70 °C at 0.05 mmHg; IR (NaCl, neat) 1200 cm^{-1} (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.53 (d, 3 H, J_{PH} = 10.7, OCH_3), 1.43–1.83 (m, 8 H, $CH_2CH_2CH_2CH_2$); ^{31}P NMR (121.4 MHz, $CDCl_3$) δ 82.8; ^{13}C NMR (75 MHz, $CDCl_3$) δ 50.3 (J_{PC} = 6.8), 22.9 (J_{PC} = 89.9), 22.2 (J_{PC} = 12.0); MS (CI, NH_3) m/e 135 (MH^+, base peak); HRMS (FAB) calcd for $C_5H_{12}O_2P$ $(MH^\bullet)^+$ 135.0575, found 135.0578.

Ethyl phospholanate[4] (2b): bp 50 °C at 0.01 mmHg; IR (NaCl, neat) 1310 (s), 1270 cm^{-1} (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.08 (dt, 2 H, J_{HH} = 7.0, J_{PH} = 7.8, OCH_2CH_3), 1.65–2.00 (m, 4 H, $(CH_2)_4P$), 1.36 (t, 3 H, J = 7.0, OCH_2CH_3); ^{31}P NMR (121.4 MHz, $CDCl_3$) δ 80.5; ^{13}C NMR (75 MHz, $CDCl_3$) 60.6 (J_{PC} = 6.6), 24.6 (J_{PC} = 90.0), 23.2 (J_{PC} = 12.0), 16.6 (J_{PC} = 6.0); MS (CI, NH_3/CH_4) m/e 149 (MH^+, base peak); HRMS (FAB) calcd for $C_6H_{14}O_2P$ $(MH^\bullet)^+$ 149.0731, found 149.0734.

Isopropyl phospholanate (2c): bp 140 °C at 0.2 mmHg; IR: (NaCl, neat) 1220 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.67 (sp, 1 H, J_{PH} = 8.4, J_{HH} = 6.2, $CHCH_3$), 1.65–1.94 (m, 8 H, $CH_2CH_2CH_2CH_2$), 1.33 (d, 6 H, J = 6.2, $CH(CH_3)_2$); ^{31}P NMR (121.4 MHz, $CDCl_3$) δ 79.2; ^{13}C NMR (75 MHz, $CDCl_3$) δ 69.2 (J_{PC} = 6.8), 25.1 (J_{PC} = 90.3), 24.0 (J_{PC} = 4.0), 22.9 (J_{PC} = 12.1); MS (CI, NH_3) m/e 163 (MH^+, base peak); HRMS (FAB) calcd for $C_7H_{16}O_2P$ $(MH^\bullet)^+$ 163.0888, found 163.0891.

2,6-Dimethylphenyl phospholanate (2d): bp 150 °C at 0.05 mmHg; IR (NaCl, neat) 3050 (m), 1235 cm^{-1} (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 (d, J = 7.4, 2 H, ArH_2), 6.98 (dd, J = 8.6, 6.6, 1 H, ArH), 2.36 (s, 6 H, $Ar(CH_3)_2$), 1.85–2.00 (m, 8 H, $CH_2CH_2CH_2CH_2$); ^{31}P NMR (121.4 MHz, $CDCl_3$) δ 80.2; ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.4 (J_{PC} = 10.6), 129.6 (J_{PC} = 3.0), 128.7 (J_{PC} = 1.6), 124.3 (J_{PC} = 1.7), 25.8 (J_{PC} = 88.9), 22.9 (J_{PC} = 12.6), 17.7; MS (CI, NH_3) m/e 225 (MH^+, base peak); HRMS (FAB) calcd for $C_{12}H_{18}O_2P$ $(MH^\bullet)^+$ 225.1044, found 225.1046.

2,6-Di-*tert*-butyl-4-methylphenyl phospholanate (2e): mp 170–171 °C; IR ($CHCl_3$) 1180 cm^{-1} (s), 915 cm^{-1} (vs); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (s, 2 H, ArH_2), 2.26–2.44 (m, 2 H, $CHHCH_2CH_2CHH$), 2.27 (s, 3 H, $ArCH_3$), 1.89–2.11 (m, 6 H, $CHHCH_2CH_2CHH$), 1.47 (s, 18 H, $Ar(C(CH_3)_3)_2$); ^{31}P NMR (121.4 MHz, $CDCl_3$) δ 79.8; ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.6 (J_{PC} = 11.9), 141.6 (J_{PC} = 2.8), 133.1 (J_{PC} = 1.7), 127.1 (J_{PC} = 1.8), 35.1, 31.3, 28.5 (J_{PC} = 90.1), 22.7 (J_{PC} = 13.3), 21.0; MS (CI, NH_3) m/e 340 (M + NH_4^+, base peak), 323 (MH^+); HRMS (FAB) calcd for $C_{19}H_{32}O_2P$ $(MH^\bullet)^+$ 323.2140, found 323.2133.

***meso*-Ethyl *cis*-2,5-dimethylphospholanate (11a)**: IR (NaCl, neat) 1220 (s), 1040 cm^{-1} (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.04 (dt, 2 H, J_{HH} = 7.1, J_{PH} = 7.3, OCH_2CH_3), 1.89 (m, 4 H, $CH(CH_2)_2CH$), 1.58 (m, 2 H, $PCHCH_3$), 1.32 (t, 3 H, J = 7.0, OCH_2CH_3), 1.20 (dd, 6 H, J_{HH} = 7.3, J_{PH} = 16.0, $2PCHCH_3$); ^{31}P NMR (121.4 MHz, $CDCl_3$) δ 79.8; ^{13}C NMR (75 MHz, $CDCl_3$) δ 60.4 (J_{PC} = 6.9), 29.7 (J_{PC} = 88.0), 29.6 (J_{PC} = 15.0), 16.7 (J_{PC} = 5.9), 13.9 (J_{PC} = 2.5); MS (CI, NH_3/CH_4) m/e 177 (MH^+, base peak); HRMS (FAB) calcd for $C_8H_{18}O_2P$ $(MH^\bullet)^+$ 177.1044, found 177.1046.

Ethyl (2*R,5*R**)-2,5-dimethylphospholanate (11b)**: IR (NaCl, neat) 1210 (s), 1040 cm^{-1} (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.10 (dt, 2 H, J_{HH} = 7.1, J_{PH} = 7.6, OCH_2CH_3), 1.69–2.20 (m, 6 H, $CHCH_2CH_2CH$), 1.33 (t, 3 H, J = 7.0, OCH_2CH_3), 1.22 (dd, 3 H, J_{HH} = 7.1, J_{PH} = 15.9, $CHCH_3$), 1.18 (dd, 3 H, J_{HH} = 7.1, J_{PH} = 15.3, $CHCH_3$); ^{31}P NMR (121.4 MHz, $CDCl_3$) δ 76.0; ^{13}C NMR (75 MHz, $CDCl_3$) δ 60.4 (J_{PC} = 6.7), 32.8 (J_{PC} = 90.5), 30.8 (J_{PC} = 88.1), 30.3 (J_{PC} = 13.3), 16.8 (J_{PC} = 5.5), 13.7 (J_{PC} = 2.3), 12.7 (J_{PC} = 4.4); MS (CI, NH_3/CH_4) m/e 177 (MH^+, base peak); HRMS (FAB) calcd for $C_8H_{18}O_2P$ $(MH^\bullet)^+$ 177.1044, found 177.1045.

***meso*-Ethyl *cis*-2,5-dimethylphospholanate (11c)**: IR (NaCl, neat) 1210 (s), 1040 cm^{-1} (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.17 (dt, 2 H, J_{HH} = 7.1, J_{PH} = 7.6, OCH_2CH_3), 1.88–2.10 (m, 4 H, $CH(CH_2)_2CH$), 1.40–1.58 (m, 2 H, $2CHCH_3$), 1.34 (t, 3 H, J = 7.1, OCH_2CH_3), 1.14 (dd, 6 H, J_{HH} = 7.0, J_{PH} = 14.8, $2CHCH_3$); ^{31}P NMR (121.4 MHz, $CDCl_3$) δ 77.4; ^{13}C NMR (75 MHz, $CDCl_3$) δ 60.7 (J_{PC} = 6.9), 31.6 (J_{PC} = 87.8), 29.3 (J_{PC} = 14.3), 16.8 (J_{PC} = 5.1), 13.4 (J_{PC} = 4.8); MS (CI, NH_3/CH_4) m/e 177 (MH^+, base peak); HRMS (FAB) calcd for $C_8H_{18}O_2P$ $(MH^\bullet)^+$ 177.1044, found 177.1050.

Alkylation Procedure. A 0.20 M solution of lithium tetramethyliperidide in THF was prepared at 0 °C and cooled to −78 °C. A 0.4 M solution of the phosphinate ester in THF was added dropwise, and the resultant solution was stirred at −78 °C for 1 h. A 1.3 M solution of benzyl bromide in THF was then added. The solution was stirred at −78 °C for 2 h and quenched by the addition of 1 N HCl (10 mL). The THF was removed on a rotary evaporator, and the aqueous residue was extracted with EtOAc (5 × 25 mL). The extracts were dried, filtered, concentrated, and purified by flash chromatography on silica gel.

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For reactions run in the presence of HMPA, neat HMPA was added dropwise to the phosphinate anion solution at −78 °C. The HMPA dissolved over a period of 15 min. The benzyl bromide was then added, and the solution stirred at −78 °C for 2 h, quenched, worked up, and purified as described above.

(P_S*,2S*)-Ethyl 2-benzylphospholanate (12b): IR (NaCl, neat) 1210 (s), 1020 cm^{-1} (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18–7.34 (m, 5 H, ArH), 3.85 (dd, 1 H, J_{HH} = 10.1, J_{PH} = 7.6, OC*H*HCH$_3$), 3.77 (dd, 1 H, J_{HH} = 10.1, J_{PH} = 7.6, OCH*H*CH$_3$), 3.15 (m, 1 H, CHCH*H*Ph), 2.68 (m, 1 H, CHC*H*HPh), 1.46–2.10 (m, 7 H, C*H*(CH$_2$)$_3$P), 1.26 (t, 3 H, J = 7.0, OCH$_2$C*H*$_3$); ^{31}P NMR (121.4 MHz, $CDCl_3$) δ 77.3; ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.4 (J_{PC} = 11.4), 128.9, 128.5, 126.3, 60.6 (J_{PC} = 6.6), 38.3 (J_{PC} = 89.2), 34.4, 30.3 (J_{PC} = 16.1), 25.4 (J_{PC} = 88.8), 20.7 (J_{PC} = 9.7), 16.6 (J_{PC} = 6.0); MS (CI, NH_3/CH_4) m/e 239 (MH^+, base peak). Anal. Calcd for $C_{13}H_{19}O_2P$: C, 65.53; H, 8.04. Found: C, 65.39; H, 7.85.

(P_S*,2S*)-Isopropyl 2-benzylphospholanate (12c): IR (NaCl, neat) 1200 cm^{-1} (s), 994 cm^{-1} (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13–7.31 (m, 5 H, ArH), 4.45–4.54 (m, 1 H, J_{PH} = 8.5, J_{HH} = 6.2, OC*H*(CH$_3$)$_2$), 3.07–3.15 (m, 1 H, C*H*HPh), 2.60–2.73 (m, 1 H, CH*H*Ph), 1.48–2.02 (m, 7 H) 1.17 (d, 3 H, J_{HH} = 6.2, OCH(C*H*$_3$)CH$_3$), 1.10 (d, 3 H, J_{HH} = 6.2, OCH(CH$_3$)C*H*$_3$; ^{31}P NMR (121.4 MHz, $CDCl_3$) δ 75.6; ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.2 (J_{PC} = 11.2), 128.8, 128.3, 126.0, 69.1 (J_{PC} = 7.1), 38.6 (J_{PC} = 89.6), 34.1, 30.0 (J_{PC} = 16.1), 25.9 (J_{PC} = 88.8), 24.2 (J_{PC} = 3.8), 24.1 (J_{PC} = 4.5), 20.5 (J_{PC} = 9.8); MS (CI, NH_3) m/e 253 (MH^+). Anal. Calcd for $C_{14}H_{21}O_2P$: C, 66.65; H, 8.39. Found: C, 64.99; H, 8.19.

(P_S*,2R*)-Ethyl 2-benzylphospholanate (13b): IR (NaCl, neat) 1215 (s), 1035 cm^{-1} (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15–7.35 (m, 5 H, ArH), 4.14 (dt, 2 H, J_{HH} = 7.1, J_{PH} = 7.7, OC*H*$_2$CH$_3$), 3.16 (m, 1 H, CHC*H*HPh), 2.54 (m, 1 H, CHCH*H*Ph), 1.60–2.21 (m, 7 H, C*H*(CH$_2$)$_3$P), 1.36 (t, 3 H, J = 7.1, OCH$_2$C*H*$_3$); ^{31}P NMR (121.4 MHz, $CDCl_3$) δ 76.2; ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.1 (J_{PC} = 12.9), 128.6, 128.5, 126.3, 60.8 (J_{PC} = 6.5), 39.8 (J_{PC} = 90.4), 33.8 (J_{PC} = 2.8), 29.5 (J_{PC} = 15.3), 25.0 (J_{PC} = 86.6), 20.7 (J_{PC} = 9.9), 16.8 (J_{PC} = 5.6); MS (CI, NH_3/CH_4) m/e 239 (MH^+, base peak). Anal. Calcd for $C_{13}H_{19}O_2P$; C, 65.53; H, 8.04. Found: C, 65.48; H, 8.23.

(P_S*,2R*)-Isopropyl 2-benzylphospholanate (13c): IR (NaCl, neat) 1215 (s), 985 cm^{-1} (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18–7.32 (m, 5 H, ArH), 4.69–4.83 (m, 1 H, J_{HH} = 6.1, J_{PH} = 7.8, OC*H*(CH$_3$)$_2$), 3.10–3.21 (m, 1 H, C*H*HPh), 2.43–2.59 (m, 1 H CH*H*Ph), 1.61–2.09 (m, 6 H), 1.32–1.50 (m, 1 H), 1.36 (d, 6 H, J_{HH} = 6.1, OCH(C*H*$_3$)$_2$); ^{31}P NMR (121.4 MHz, $CDCl_3$) δ 74.2; ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.6 (J_{PC} = 13.1), 128.1, 127.9, 125.7, 68.8 (J_{PC} = 6.7), 39.2 (J_{PC} = 91.4), 33.4, 28.9 (J_{PC} = 15.1), 25.2 (J_{PC} = 86.0), 23.8 (J_{PC} = 3.9), 20.3 (J_{PC} = 9.8); MS (CI, NH_3) m/e (MH^+). Anal. Calcd for $C_{14}H_{21}O_2P$: C, 66.65; H, 8.39. Found: C, 66.61; H, 8.37.

***meso*-Ethyl *cis*-2,5-dibenzylphospholanate (14b)**: mp 65–66.5 °C; IR (NaCl, neat) 1220 (s), 1030 cm^{-1} (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15–7.45 (m, 10 H, ArH), 3.80 (dt, 2 H, J_{HH} = 7.1, J_{PH} = 7.5, OC*H*$_2$CH$_3$), 3.18 (m, 2 H, 2 CHCH*H*Ph), 2.68 (m, 2 H, 2CHCH*H*Ph), 2.05–2.25 (m, 2 H, 2PC*H*), 1.60–1.90 (m, 4 H, CH(C*H*$_2$)$_2$CH), 1.19 (t, 3 H, J = 7.1, OCH$_2$C*H*$_3$); ^{31}P NMR (121.4 MHz, $CDCl_3$) δ 75.8; ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.3 (J_{PC} = 11.4), 129.0, 128.5, 126.3, 60.4 (J_{PC} = 6.9) 38.2 (J_{PC} = 86.9), 34.4, 26.8 (J_{PC} = 14.8) 16.3 (J_{PC} = 5.9); MS (CI, NH_3/CH_4) m/e 329 (MH^+, base peak). Anal. Calcd for $C_{20}H_{25}O_2P$: C, 73.15; H, 7.67. Found: C, 73.46; H, 7.60.

***meso*-Isopropyl *cis*-2,5-dibenzylphospholanate (14c)**: IR (NaCl, neat) 1225 (s), 980 cm^{-1} (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10–7.29 (m, 10 H, ArH), 4.33–4.46 (m, 1 H, J_{PH} = 8.3, J_{HH} = 6.1, OC*H*(CH$_3$)$_2$), 3.11–3.36 (m, 2 H, 2C*H*Hph), 2.58–2.73 (m, 2 H, CH*H*Ph), 2.04–2.18 (m, 2 H, 2PC*H*), 1.58–1.79 (m, 4 H, –PCHC*H*$_2$C*H*$_2$–), 1.17 (d, 6 H, J_{HH} = 6.1, OCH(C*H*$_3$)$_2$); ^{31}P NMR (121.4 MHz, $CDCl_3$) δ 74.8; ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.9 (J_{PC} = 11.5), 128.6, 128.1, 125.8, 68.9 (J_{PC} = 6.7), 38.4 (J_{PC} = 87.2), 34.0, 26.4 (J_{PC} = 14.7), 23.9 (J_{PC} = 3.8); MS (CI, NH_3) m/e 343 (MH^+). Anal. Calcd for $C_{21}H_{27}O_2P$: C, 73.66; H, 7.95. Found: C, 73.34; H, 7.89.

Ethyl (2S*,5S*)-2,5-dibenzylphospholanate (15b): IR (NaCl, neat) 1215 (s), 1030 cm^{-1} (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20–7.80 (m, 10 H, ArH), 3.86 (dd, 1 H, J_{HH} = 10.4, J_{PH} = 7.6, OC*H*HCH$_3$), 3.75 (dd, 1 H, J_{HH} = 10.4, J_{PH} = 7.6, OCH*H*CH$_3$), 3.08–3.22 (m, 2 H, 2CHC*H*HPh), 2.50–2.80 (m, 2 H, 2CHCH*H*Ph), 1.30–2.60 (m, 6 H, C*H*(CH$_2$)$_2$C*H*), 1.22 (t, 3 H, J_{HH} = 7.1, OCH$_2$C*H*$_3$); ^{31}P NMR (121.4 MHz, $CDCl_3$) δ 72.1; ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.2 (J_{PC} = 9.8), 139.9 (J_{PC} = 12.3), 129.0, 128.6, 128.52, 128.47, 126.32, 126.30, 60.5 (J_{PC} = 7.1), 40.6 (J_{PC} = 89.3), 39.8 (J_{PC} = 86), 35.1 (J_{PC} = 3.2), 34.5 (J_{PC} = 3.0), 28.9 (J_{PC} = 13.4), 28.0 (J_{PC} = 12.3), 16.7 (J_{PC} = 5.7); MS (CI, NH_3/CH_4) m/e 329 (MH^+, base peak). Anal. Calcd for $C_{20}H_{25}O_2P$: C, 73.15; H, 7.67. Found: C, 72.98; H, 7.48.

Isopropyl (2S*,5S*)-2,5-dibenzylphospholanate (15c): IR (NaCl, neat) 1219 (s), 985 cm^{-1} (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11–7.30 (m, 10 H, ArH), 4.40–4.52 (m, 1 H, J_{PH} = 7.9, J_{HH} = 6.1, OC*H*(CH$_3$)CH$_3$), 3.08–3.19 (m, 2 H, 2C*H*HPh), 2.63–2.78 (m, 1 H, CH*H*Ph), 2.48–2.58 (m, 1 H, CH*H*Ph), 1.70–2.22 (m, 4 H, –PCHC*H*$_2$C*H*$_2$–), 1.30–1.46 (m, 1 H, PC*H*), 1.24 (d, 3 H, J_{HH} = 6.1, OCH(C*H*$_3$)CH$_3$), 1.17–1.24 (m, 1 H, PC*H*), 1.11 (d, 3 H, J_{HH} = 6.1, OCH(CH$_3$)C*H*$_3$): ^{31}P NMR (121.4 MHz, $CDCl_3$) δ 71.2; ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.9 (J_{PC} = 9.5), 138.8, (J_{PC} = 12.7), 128.6, 128.2, 128.1, 125.9, 68.8 (J_{PC} = 7.0), 40.2 (J_{PC} = 90.0), 40.0 (J_{PC} = 8.5), 34.8, 34.2, 28.7 (J_{PC} = 13.3), 27.6 (J_{PC} = 12.3), 24.0 (J_{PC} = 4.1), 23.9 (J_{PC} = 3.5); MS (CI, NH_3) m/e 343 (MH^+). Anal. Calcd for $C_{21}H_{27}O_2P$: C, 73.66; H, 7.95. Found: C, 72.69; H, 7.93.

***meso*-Ethyl *cis*-2,5-dibenzylphospholanate (16b)**: IR (NaCl, neat) 1215 (s), 1040 cm^{-1} (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14–7.31 (m, 10 H, ArH), 4.09 (dt, 2 H, J_{HH} = 6.9, J_{PH} = 6.9, OC*H*$_2$CH$_3$), 3.05–3.15 (m, 2 H, 2C*H*HPh), 2.51–2.62 (m, 2 H, 2CH*H*Ph), 2.19–2.37 (m, 2 H, 2PC*H*), 1.62–1.80 (m, 2 H), 1.50–1.62 (m, 2 H), 1.30 (t, 3 H, J_{HH} = 6.9, OCH$_2$C*H*$_3$); ^{31}P NMR (121.4 MHz, $CDCl_3$) δ 75.0; ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.8 (J_{PC} = 12.2), 128.5, 126.3, 61.4 (J_{PC} = 6.5), 39.0 (J_{PC} = 86.0), 34.3, 26.3 (J_{PC} = 14.1), 16.8 (J_{PC} = 4.4); MS (CI, NH_3) m/e 329 (MH^+). Anal. Calcd for $C_{20}H_{25}O_2P$: C, 73.15; H, 7.67. Found: C, 73.12; H, 7.51.

***meso*-Isopropyl *cis*-2,5-dibenzylphospholanate (16c)**: IR (NaCl, neat) 1214 (s), 990 cm^{-1} (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13–7.32 (m, 10 H, ArH), 4.77–4.90 (m, 1 H, J_{PH} = 7.3, J_{HH} = 6.1, OC*H*(CH$_3$)$_2$, 3.05–3.19 (m, 2 H, 2C*H*HPh), 2.46–2.58 (m, 2 H, 2 CH*H*Ph), 2.17–2.35 (m, 2 H, 2PC*H*) 1.48–1.78 (m, 4 H, –PCHC*H*$_2$C*H*$_2$–), 1.36 (d, 6 H, J_{HH} = 6.1, OCH(C*H*$_3$)$_2$); ^{31}P NMR (121.4 MHz, $CDCl_3$) δ 73.5; ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.7 (J_{PC} = 13.1), 128.4, 128.3, 126.1, 69.5 (J_{PC} = 6.9), 38.8 (J_{PC} = 85.9), 34.2, 25.8 (J_{PC} = 13.8), 24.3 (J_{PC} = 3.9); MS (CI, NH_3) m/e 343 (MH^+). Anal. Calcd for $C_{21}H_{27}O_2P$: C, 73.66; H, 7.95. Found: C, 72.71; H, 7.92.

(2S*,5S*)-2,5-Dibenzylphospholanic Acid (17). Neat trimethylsilyl bromide (50 μL, 4 equiv) was added to a solution of phosphinate **16b** (30.5 mg, 0.1 mmol) in anhydrous CH_2Cl_2 (2 mL). The solution was stirred for 20 h at ambient temperature, and the volatiles were removed in vacuo. The residue was dissolved in CH_2Cl_2, water (0.25 mL) added, and the mixture stirred vigorously for 15 min. The mixture was diluted with CH_2Cl_2, dried, filtered, and concentrated in vacuo to afford phosphinic acid **17** as an off-white solid: 23.7 mg, 85%; IR (NaCl, $CHCl_3$) 1210 cm^{-1} (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14–7.35 (m, 10 H, ArH), 3.13–3.28 (m, 2 H, 2C*H*HPh), 2.57–2.72 (m, 2 H, 2CH*H*Ph), 2.10–2.27 (m, 2 H, 2PCH), 1.90–2.00 (m, 1 H) 1.78–1.88 (m, 1 H), 1.23–1.38 (m, 2 H); ^{31}P NMR (121.4 MHz, $CDCl_3$) δ 75.9; ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.8 (J_{PC} = 13.1), 128.6, 128.3, 126.1, 39.3 (J_{PC} = 89.7), 34.3 (J_{PC} = 1.4), 27.9 (J_{PC} = 13.2); MS (CI, NH_3) m/e 301 (MH^+, base peak). Anal. Calcd for $C_{18}H_{21}O_2P$: C, 71.98; H, 7.05. Found: C, 71.79; H, 6.87.

(2S*,5S*)-1,2,5-Tribenzyl-1-oxophospholane (18). Sodium bis(methoxyethoxy)aluminum dihydride (0.2 mL, 3.4 M in toluene) was added dropwise at 0 °C to a solution of phosphinate **15b** or **15c** (0.15 mmol) in THF (2 mL). After bubbling had ceased, the solution was warmed and allowed to stir at room temperature overnight. Neat benzyl bromide (0.08 mL) was added, and the solution was stirred for 10 h. The mixture was quenched by slow addition of 0.1 N Na–K tartrate. The THF was removed on a rotary evaporator, and the residue was extracted 4× with CH_2Cl_2. The combined organic extracts were dried, filtered, and concentrated, and the residue was flash chromatographed on silica gel (20:80 → 60:40 → 80:20 EtOAc/hexane → EtOAc) to afford phosphine oxide **18** as a white crystalline solid, mp 185–187 °C: IR (NaCl, $CHCl_3$) 1168 cm^{-1} (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10–7.45 (m, 13 H, ArH), 6.85 (d, 2 H, J = 6.5, ArH), 3.31–3.49 (m, 2 H), 2.84 (dd, 1 H, J = 14.3, J = 6.3, C*H*HPh), 2.42–2.62 (m, 1 H), 2.38–2.40 (m, 2 H), 1.92–2.06 (m, 1 H), 1.82–1.91 (m, 2 H),

1.76-1.84 (m, 1 H), 1.40-1.56 (m, 1 H), 1.01-1.18 (m, 1 H); ^{31}P NMR (121.4 MHz, $CDCl_3$) δ 63.5; ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.3 (J_{PC} = 13.2), 139.6 (J_{PC} = 12.9), 131.4 (J_{PC} = 8.4), 130.0, 129.9, 128.87, 128.64, 128.5, 128.3, 127.1, 126.5, 126.1, 44.5 (J_{PC} = 59.6), 39.3 (J_{PC} = 65), 35.5 (J_{PC} = 52.1), 34.8, 29.4 (J_{PC} = 7.5), 28.8 (J_{PC} = 10.5); MS (CI, CH_4) m/e 375 (MH^+, base peak). Anal. Calcd for $C_{25}H_{27}OP$: C, 80.19; H, 7.27. Found: C, 79.73; H, 7.07.

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Supplementary Material Available: ^1H NMR spectra of compounds **2a**, **2b**, **2c**, **2d**, **2e**, **11a**, **11b**, and **11c** and ^{13}C spectra of compounds **2d** and **2e** (10 pages). Ordering information is given on any current masthead page.

Cysteine Alkylation in Unprotected Peptides: Synthesis of a Carbavasopressin Analogue by Intramolecular Cysteine Alkylation

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An expedient method that allows modification of a cysteine residue side chain through alkylation of unprotected peptides is described. In order to test the generality of the method, an unprotected cysteine-containing tetrapeptide possessing several potentially competing nucleophilic functionalities such as amino, hydroxy, and carboxyl groups was chosen as a model peptide. The model tetrapeptide, H-Ser-Lys-Cys-Phe-OH was synthesized by standard solid-phase methods, cleaved with HF, and purified by reverse-phase HPLC. Reaction of the unprotected peptide with 1.3 equiv of various alkylating agents in saturated ammonia in methanol at 0 °C proceeded cleanly to yield single alkylation products within one hour as shown by HPLC analysis. In most cases acidic, basic, and neutral side chains were introduced by this method in over 80% yield. The methodology is also applicable to the synthesis of cyclic peptides by intramolecular cysteine alkylation and provides a useful alternative to cyclizations that occur through disulfide or amine bond-forming reactions as illustrated by the synthesis of a carbavasopressin.

Introduction

The derivatization of natural products such as steroids and alkaloids is a well-developed and widely used approach in medicinal chemistry. However, selective modification of amino acid side chain functional groups in protected or unprotected peptides has been much less frequently reported. Instead, the unnatural amino acids or side chain modified amino acids are frequently prepared by separate syntheses and assembled into peptides. The synthesis of many unnatural amino acids can often be rather difficult and time consuming. We became interested in selective side chain derivatization of unprotected peptides because it allows the expedient preparation of many peptide analogues for structure–activity relationship studies. Selective modification of cysteine in unprotected peptides is most compelling since a considerable amount of thiol chemistry has been developed and extensively used in protein chemistry and affinity labeling.[1,2] Selective alkylation of the thiol functionality is possible due to its high nucleophilic reactivity relative to other amino acid side chains. Although much of the thiol chemistry applied to protein derivatization should also be applicable to cysteine in small peptides, derivatization of cysteine in unprotected peptides has not found widespread use. In this paper we report the selective thiol alkylation of an unprotected model tetrapeptide with various alkylation agents in good yields. The methodology is also applicable to the synthesis of cyclic peptides through intramolecular cysteine alkylation and provides a useful alternative to cyclizations that occur through disulfide or amide bond-forming reactions.[3] As an illustration of the cyclization methodology, we report the synthesis of a carbavasopressin.

Results and Discussion

In order to test the general applicability of the cysteine alkylation methodology, an unprotected cysteine-containing peptide possessing several potentially competing nucleophilic functionalities such as amino, hydroxy, and carboxyl groups was chosen as a model peptide. The model tetrapeptide, H-Ser-Lys-Cys-Phe-OH–2 trifluoroacetic acid (TFA), **1**, was synthesized by standard solid-phase methods using Merrifield resin, cleaved with anhydrous hydrogen fluoride (HF), and purified by reverse-phase high-performance liquid chromatography (RPHPLC). After lyophilization, the purified peptide was obtained as a white amorphous powder and could be stored under nitrogen in the freezer (−20 °C) for more than 6 months without any sign of disulfide formation by RPHPLC analysis.

For a typical alkylation, reaction of unprotected peptide **1** with 1.3 equiv of various alkylating agents in methanol saturated with ammonia at 0 °C proceeded cleanly to yield single monoalkylation products within 1 h as shown by RPHPLC analysis. For the less reactive alkylating agent ethyleneimine, a large excess of reagent was used in dimethylformamide (DMF) saturated with ammonia at room temperature. Basic, acidic, and neutral side chains were introduced by this method in over 80% isolated yield. All the alkylation products were characterized by NMR, FABMS, elemental, and amino acid analyses. The indication of selective thiol alkylation was provided by exam-

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