Phosphonate Diester and Phosphonamide Synthesis. Reaction Coordinate Analysis by ^{31}P NMR Spectroscopy: Identification of Pyrophosphonate Anhydrides and Highly Reactive Phosphonylammonium Salts[1]

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Abstract: A series of phosphonochloridates was prepared from the corresponding phosphonate monoesters, and their reactions with alcohols, amines, and the bisnucleophile 4-aminobutan-1-ol have been investigated using ^{31}P NMR spectroscopy. In the conversion of phosphonate monoesters to phosphonochloridates via the addition of thionyl chloride or oxalyl chloride, pyrophosphonate anhydrides were found to be formed readily as byproducts. The anhydrides reacted readily with alcohols, but more slowly than the corresponding phosphonochloridates, and only sluggishly, if at all, with amines. Therefore, when phosphonamides are prepared, anhydride formation must be suppressed. This is accomplished when the monoester is added to the chloridating agent. Unhindered phosphonochloridates reacted predominantly with the amino function of 4-aminobutan-1-ol to furnish the phosphonamidates, whereas a sterically hindered phosphonochloridate demonstrated a preference for O-coupling. This result indictes that the energy gained during P−O bond formation surmounts the kinetic barrier resulting from steric hindrance more effectively than formation of the weaker P−N bond. Importantly, treatment of the phosphonochloridates with tertiary amines *prior* to addition of the nucleophile resulted in the formation of hitherto unrecognized phosphonylating agents, which we formulated as phosphonyltrialkylammonium salts. The latter, unlike the anhydrides, are more reactive than the phosphonochloridates toward both alcohols and amines, affording improved yields of phosphonate esters and amides. *These improved yields are not obtained when triethylamine is added simultaneously with the nucleophile merely to neutralize acid rather than as a deliberate step to generate the phosphonyltrialkylammonium salts*. Use of these novel phosphonylating agents proceeded without concomitant racemization at stereogenic centers α to phosphorous. Interestingly, reaction of even an unhindered phosphonyltriethylammonium salt with 4-aminobutan-1-ol favored O-phosphonylation over *N*-phosphonylation by a factor of 8, demonstrating that both the charge transfer in the transition state and steric hindrance affect the propensity for P−O *vis a vis* P−N bond formation. In marked contrast, simultaneous addition of this bisnucleophile and triethylamine, like coupling in the absence of tertiary amine, afforded the phosphonate and phosphonamide in nearly equal amounts.

Organophosphorus(V) derivatives are stable surrogates of high-energy tetrahedral transition states common to many enzyme-catalyzed reactions and thus are useful both in the elucidation of enzyme mechanisms and as enzyme inhibitors.[3] Such transition state analogs have been exploited as potent inhibitors of serine and aspartic acid proteases such as chymotrypsin,[4] pepsin,[5] and HIV protease[6] and of the metalloproteases carboxypeptidase A,[7] angiotensin-converting enzyme,[8] thermolysin,[9] leucine aminopeptidase,[10] endothelin converting enzyme,[11] and human collagenase.[12] Similarly, class C β-lactamase,[13] HMG-CoA reductase,[14] and D-alanyl-D-alanine ligase[15] are effectively inhibited by P(V)-based transition state analogs. Also of interest is the fact that several phosphonopeptides have shown potent antibacterial activity.[16] More recently the transition state

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(1) A preliminary account of this work has been published, see: Hirschmann, R.; Yager, K. M.; Taylor, C. M.; Moore, W.; Sprengeler, P. A.; Witherington, J.; Phillips, B. W.; Smith, A. B., III. *J. Am. Chem. Soc.* **1995**, *117*, 6370.

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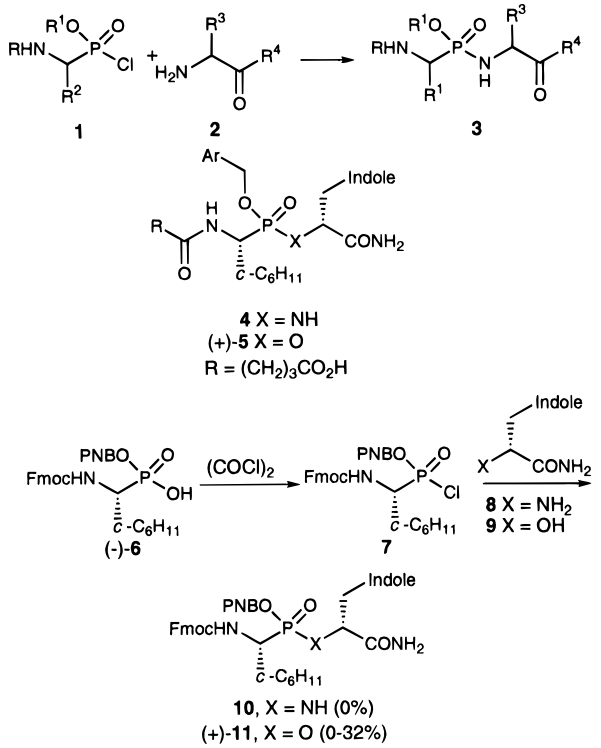
analog concept of Pauling[3] has been successfully applied to hapten design, giving rise to antibodies catalyzing diverse reactions,[17] including the recently reported formation of dipeptides[18] and of larger peptides.[18c] Because of their important, diverse chemical and biological properties, we report herein new understanding of the chemistry relating to the synthesis of phosphonate esters and phosphonamides.[1]

Background. Generally, phosphonate esters and phosphonamides are prepared by the reaction of phosphonochloridates or phosphonodichloridates[19] with alcohols or amines respectively, as typified in Scheme 1. Monochloridates have been prepared by reaction of phosphonate diesters with 1 equiv of phosphorus pentachloride,[20] by treatment of monoesters with thionyl chloride or oxalyl chloride,[21] and by oxidative chlorination of phosphinate esters with carbon tetrachloride.[22] The phosphonochloridate strategy has also been extended to the solid phase synthesis of phosphonopeptides.[23] In addition, the synthesis of phosphonopeptides from hydroxybenzotriazole esters and phosphonochloridates exploiting silver ion catalysis has been reported,[24] as have methods for preparing complex phosphonate diesters using mixed BOP−phosphonate esters,[25] di-*p*-nitrophenyl phosphonate esters,[26] and modified Mitsunobu[27] reactions. Our interest in the synthesis of complex phosphonate esters and amides stems from a continuing program to design and synthesize haptens (e.g., **4** and **5**) for the generation of catalytic antibodies possessing peptide ligase activity as reported by Hirschmann, Benkovic, and Smith and their collaborators[18a,b] and by Jacobsen and Schultz[18c] (Scheme 1).[18a,b]

Scheme 1



Although several publications have alluded to the instability of phosphonamides at acidic and even physiological pH,[22,28] Janda and co-workers[6a] observed less than 2% decomposition of a phosphonamide at pH 3.5 after 1 week,[29] encouraging us to undertake the preparation of **4**. However, efforts to couple D-tryptophanamide (**8**) with phosphonochloridate **7** failed to yield the desired phosphonamide **10** even in the presence of silver ion (see below). Attempts to couple monoester (−)-**6** with **8** using a variety of condensing reagents such as diphenyl phosphorylazide and BOP reagents were also unsuccessful. We were able, however, to couple chloridate **7** with (*R*)-(+)-β-indolyllactamide **9**[30] in the presence of silver ion[31,32] to afford phosphonate diester (+)-**11** in yields that initially varied unpredictably from 0 to 32%, but could be improved to a reproducible 40% via the new procedure described herein.[33] Phosphonate diester (+)-**11** was subsequently converted into hapten **5**, which generated useful catalytic antibodies.[18a,b]

^{31}P NMR Analysis of Phosphonochloridate Formation. In order to provide some insight into the observed preference for alcoholysis of the activated phosphonate monoesters, we studied the formation and subsequent reactions of phosphonochloridates using ^{31}P NMR. To simplify the study, we chose **16** and **18** as substrates, because the resulting stereogenic center at phosphorus would result in enantiomers rather than diastereomers, simplifying spectral interpretation. Treatment of diethyl (phthalimidomethyl)phosphonate (**13**),[19b] obtained either commercially or by bromination (PBr_3, 140 °C, 1 h) of *N*-(hydroxymethyl)-phthalimide (**12**) and subsequent Arbuzov reaction [$P(OEt)_3$, 120 °C, 1 h] with hydrazine hydrate (EtOH, 25 °C, 72 h), provided diethyl (aminomethyl)phosphonate (**14**). Because of

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(29) While the stability of phosphonamides is thus not a major concern, the lack of (or minimal) double-bond character of the P−N bond of phosphonamides negates a potential plus of phosphonamide haptens over their diester counterparts.

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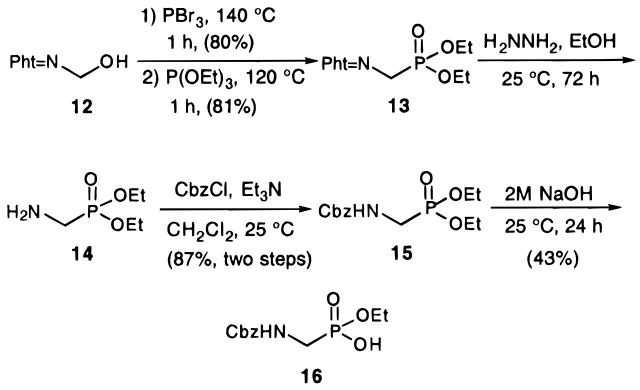
(33) Smith, A. B., III; Taylor, C. M.; Benkovic, S. J.; Hirschmann, R. *Tetrahedron Lett.* **1994**, *35*, 6853.

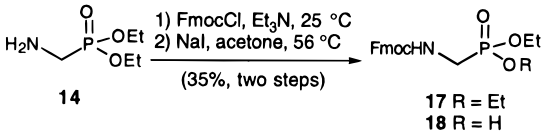
its instability, the crude amine **14** was converted directly to the stable *N*-carbobenzyloxy (Cbz) derivative **15** (CbzCl, Et_3N, CH_2Cl_2, 0 → 25 °C, 15 h) in 87% yield from **13**. Basic hydrolysis[6a] (2 M NaOH, 25 °C, 24 h) afforded **16** in 43% yield (Scheme 2).

Scheme 2



Alternatively, protection of amine **14** as its (fluorenylmethoxy)carbonyl (Fmoc) carbamate (FmocCl, Et_3N, tol, 25 °C) and subsequent hydrolysis of the resulting diester **17** afforded monoester **18** in 35% overall yield (Scheme 3).

Scheme 3



The ^{31}P NMR spectra (202.5 MHz, 0.05 M, $CDCl_3$) of the starting materials, the monoesters **16** (spectrum a) and **18** (spectrum c, respectively) (Figure 1), displayed major resonances at 24.8 and 24.9 ppm (relative to 85% H_3PO_4, external standard). Each resonance was accompanied by a minor upfield signal at

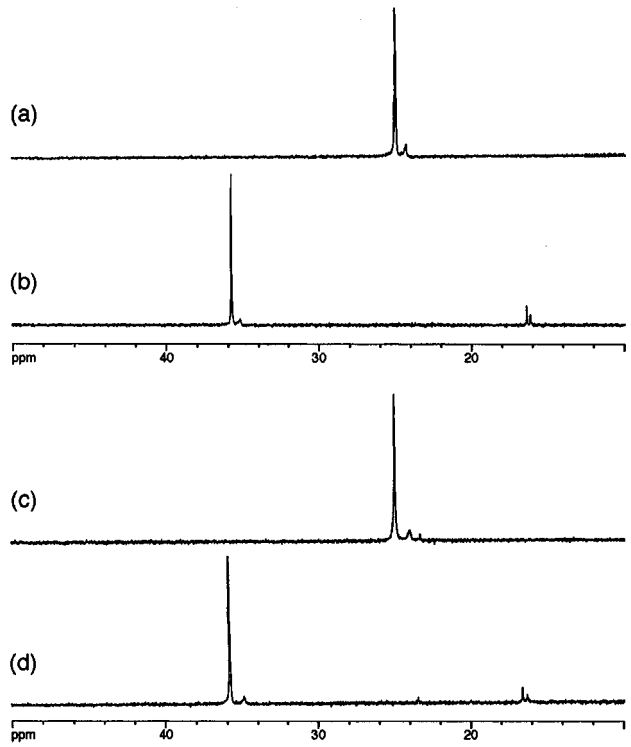


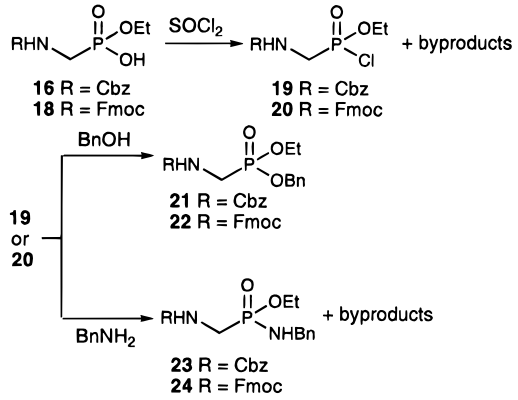
Figure 1. ^{31}P NMR spectra: (a) Cbz-protected monoester **16**; (b) phosphonochloridate **19**; (c) Fmoc-protected monoester **18**; (d) phosphonochloridate **20**.

24.2 or 23.9 ppm, which were assigned to carbamate rotamers on the basis of temperature-dependent ^{31}P NMR studies (reversible coalescence observed at 325K). Indeed, similar minor rotamers were observed in the spectra of all phosphorus-containing compounds described herein. Treatment of either **16** or **18** (0.05 M, $CDCl_3$) with thionyl chloride led, within 30 min, to their complete consumption, as revealed by ^{31}P NMR (spectra b and d) (Figure 1). In addition to the expected phosphonochloridates **19** (spectrum b; 35.6 ppm, R = Cbz) and **20** (spectrum d; 35.7 ppm, R = Fmoc), a pair of upfield singlets (byproducts) at 16.4 and 16.1 ppm (R = Cbz) or 16.5 and 16.2 ppm (R = Fmoc) were also observed.

The upfield byproducts proved to be active phosphonylating agents, as shown by the fact that on addition of benzyl alcohol (5 equiv, 32 °C) both of the phosphonochloridates and the new upfield intermediates were consumed, affording the mixed diesters **21** and **22** (23.6 ppm for both compounds) as the major products (Scheme 4). In contrast, treatment of a similar mixture with benzylamine (5 equiv, 32 °C) led to selective reaction of the phosphonochloridates, furnishing the benzyl phosphonamides **23** and **24** (27.2 ppm for both compounds), but leaving the upfield signals unchanged (Figure 2).

The above alcoholysis and aminolysis experiments demonstrated that the upfield byproducts are less reactive than

Scheme 4



phosphonochloridates **19** and **20** and that even the latter couple less readily with benzylamine than with benzyl alcohol. This result, which is in marked contrast to the well-known greater reactivity of amines compared to alcohols toward activated carboxylic acids, serves as a reminder that a comparison of the relative reactivity of two or more nucleophiles depends on the electrophile.[34]

Structure of the Upfield Byproducts. We had initially considered the possibility that at least one of the upfield signals might correspond to the mixed P−O−S anhydride **25**, which might then react with chloride ion to generate the phosphonochloridate (Scheme 5). However, the fact that the same upfield signals appear in the ^{31}P NMR spectra when **18** is treated with oxalyl chloride or oxalyl bromide disproved this interpretation, since one would expect the mixed P−O−C (**26** and **27**) and P−O−S anhydrides **25** to be spectroscopically distinct.

It was attractive to attribute the appearance of *two* upfield phosphorus resonances for each byproduct to the presence of diastereomeric phosphorus atoms; this in turn strongly suggested the formation of pyrophosphonate anhydride diastereomers:

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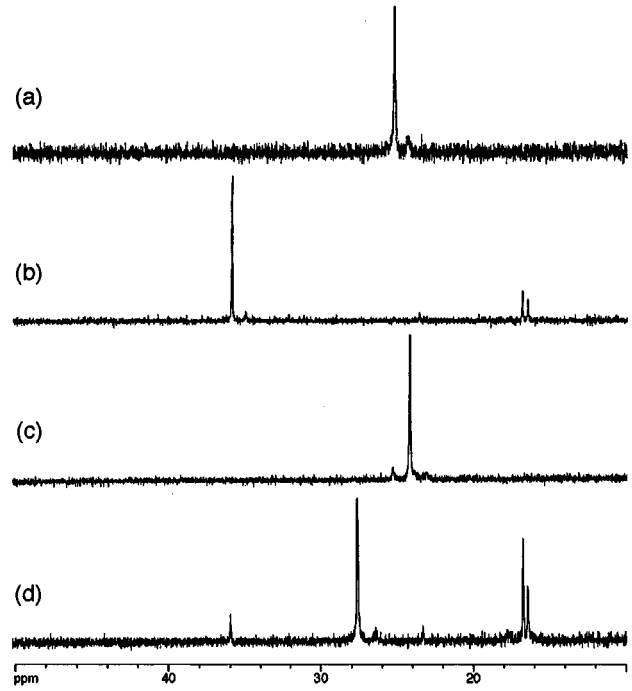
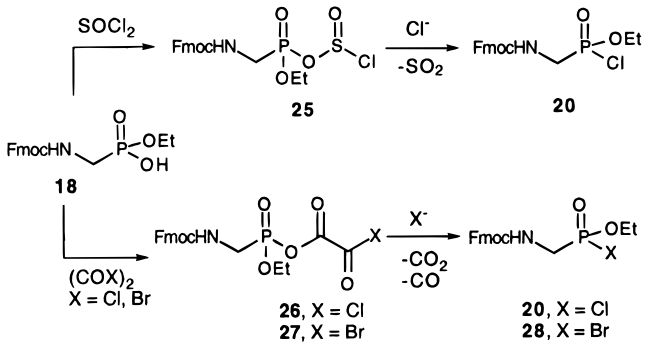


Figure 2. ^{31}P NMR spectra: (a) Fmoc-protected monoester **18**; (b) phosphonochloridate **20** and upfield byproducts; (c) reaction of line b with benzyl alcohol (5 equiv); (d) reaction of a mixture similar to line b with benzylamine (5 equiv).

Scheme 5



meso-**29** and *meso*-**31**, and (*R,R*)- and (*S,S*)-**30** and -**32** Figure 3).

Although phosphonic acid anhydrides have been described in the literature,[35,36] they have not been reported as side products of phosphonochloridate preparation. It has, however, been reported that the conversion of phosphinic acids to phosphinic chlorides with phosgene proceeds via pyrophosphinic anhydrides, the latter being converted to the halide with additional phosgene.[37] In addition, Bartlett and co-workers concluded, on both chemical and spectral grounds, that the active phosphonylating agent in the dicyclohexylcarbodiimide (DCC)-mediated couplings of phosphonate monoesters is the corresponding pyrophosphonate anhydride.[4] Similarly, Campbell had reported the formation of a pyrophosphonate anhydride as a byproduct

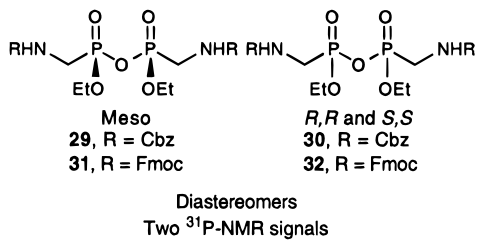
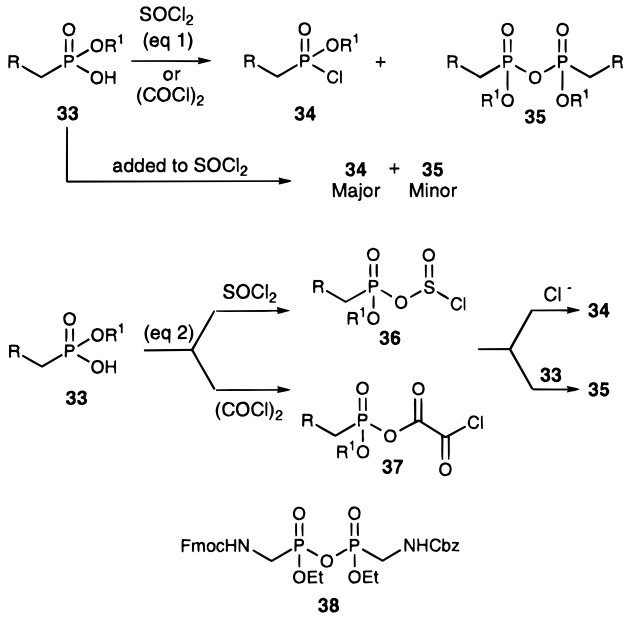


Figure 3.

via condensation of an alkylphosphonic acid with an electrophilic phosphorus species.[27b]

A plausible mechanism for the formation of pyrophosphonate anhydrides is illustrated for a generic monoester **33** and phosphonochloridate **34** in Scheme 6 (eq 1). When **33** is mixed with the chlorinating agent, there is partial conversion to phosphonochloridate **34**. Suprisingly, **34** competes effectively

Scheme 6



with the chlorinating agents for **33**, to give a mixture also containing the diastereomeric anhydrides **35**. The ^{31}P NMR spectrum supports this interpretation since the relative amount of anhydride formed is initially very high and decreases with time. As expected, addition of monoester to a solution of thionyl chloride suppresses the formation of the anhydrides, the chlorinating agent now always being present in excess. As shown below, this procedure should be employed especially when the nucleophile is an amine. A reviewer of the initial communication kindly suggested an alternative explanation, *viz.*, that monoester **33** is in competition with chloride ion for the mixed P−O-S anhydride **36**, leading to phosphonochloridate as illustrated in Scheme 6 (eq 2). This suggestion is attractive because monoester concentration is high at the beginning of the reaction and chloride ion concentration is low. However, pretreatment of monoester **16** with an excess of *tert*-butylammonium chloride (10 equiv), ensuring a high initial chloride ion concentration, does not affect the ratio of anhydrides and phosphonochloridates and therefore argues against this mechanism. Although we do not exclude the possibility that some of the anhydride arises via the pathway suggested by the referee, taken together our observations support a mechanism in which the anhydrides arise preponderantly via successful competition by the phosphonochloridates with the chlorinating agent for monoester.

To provide additional support for the structures assigned to the pyrophosphonate anhydrides **29**−**32**, the Cbz-protected monoester **16** was added to a solution of thionyl chloride (3 equiv, 32 °C, 1 h, evaporation at ≤1 mmHg) furnishing primarily phosphonochloridate **19**, accompanied by a small amount of the symmetrical anhydrides **29** and **30** (Figure 4, spectrum a). Addition of 1 equiv of the Fmoc-protected monoester **18** generated indeed the diastereomeric unsym-

(37) *Phosphorus; An Outline of its Chemistry, Biochemistry and Technology*; Corbridge, D. E. C., Ed.; Studies in Inorganic Chemistry 10; Elsevier: New York, 1990; p 340.

metrical anhydrides **38** (16.5 and 16.2 ppm; line b). A reciprocal experiment was performed by treatment of the Fmoc-protected phosphonochloridate **20** with **16**, which led to an analogous mixture of three pyrophosphonate anhydrides. The elemental compositions of the anhydrides were confirmed by electrospray mass spectroscopy, yielding molecular ions corresponding to the sodium-complexed symmetrical anhydrides **29** and **31** (R = Cbz, *m/z* calcd 550.4, found 550.8; R = Fmoc, *m/z* calcd 726.7, found 726.8) and the unsymmetrical anhydride **38** (R = Cbz, Fmoc, *m/z* calcd 639.5, found 638.9).

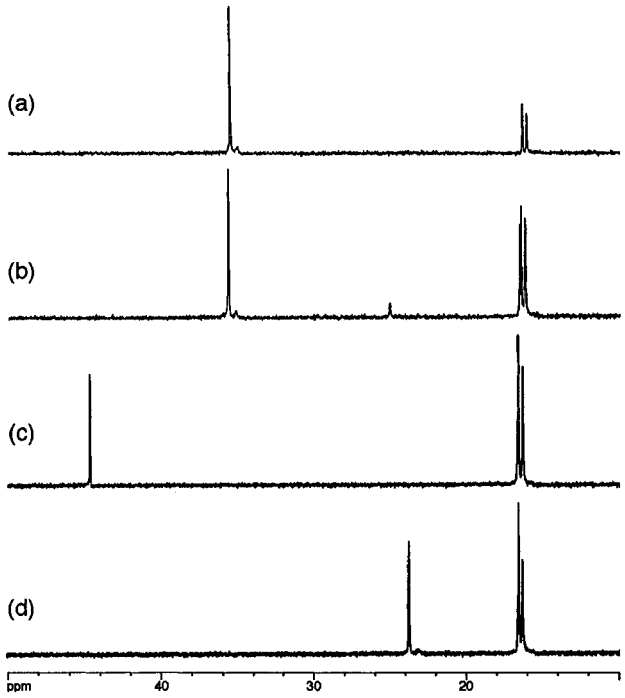


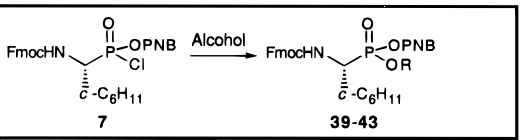
Figure 4. ^{31}P NMR spectra: (a) phosphonochloridate **19** and symmetrical anhydrides **29** and **30**; (b) reaction of line a with monoester **18** giving unsymmetrical anhydrides **38** and unreacted **19**; (c) reaction of line b with triethylamine affording **76** (*vide infra*) and unreacted **38**; (d) reaction of line c with benzyl alcohol (5 equiv) to give diester **21** and unreacted **38**.

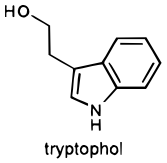
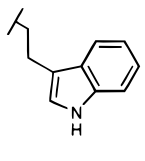
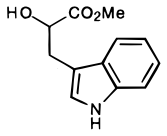
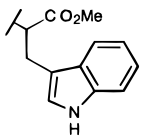
To the best of our knowledge, the ability of phosphonochlorides to compete effectively with reagents such as thionyl chloride and oxalyl chloride for phosphonic acids has not been appreciated in the prior literature. This surprising observation has important synthetic consequences, because the resulting anhydrides differ significantly in their reactivity from the phosphonochloridates, reacting slower with alcohols and not at all with amines. When phosphonamide formation is desired, formation of anhydrides must be suppressed.

The Role of Steric Factors. The center undergoing nucleophilic attack during coupling is markedly more hindered in (−)-**7** than in **19**. Methanol reacted with chloridate **7** to give the mixed ester **39** in near quantitative yield. Indeed, as shown in Table 1, most alcohols gave very good yields of mixed diesters, and even *tert*-butyl alcohol gave **41** in 48% yield. Importantly, this latter result shows that steric hindrance alone is not likely to be responsible for the failure of **7** to react with D-tryptophanamide.[38]

To gain a better understanding of the role of steric factors, we investigated a series of electrophiles that were intermediate in steric hindrance between **19** and **7**. We first studied the Fmoc-protected *p*-nitrobenzyl monoester **47**, which lacks the α-cyclohexyl substituent of **7** (Scheme 7). Dimethyl (aminomethyl)phosphonate (**44**)[39] was dephthalylated followed by reprotection with FmocCl to furnish **45**. Acid hydrolysis then

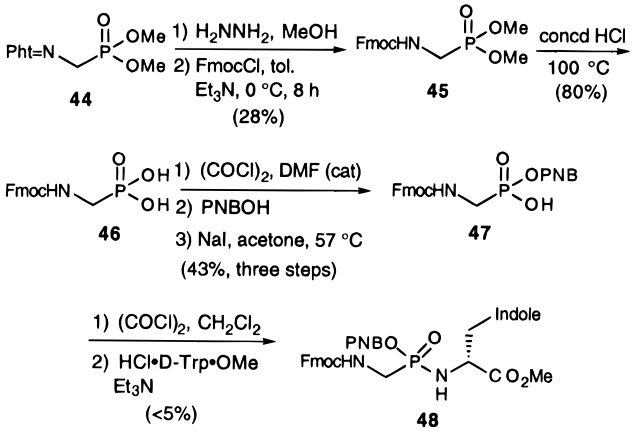
Table 1



Entry	Alcohol	Product #	Product R	Yield (%)
1	MeOH	**39**	Me	96
2	BnOH	**40**	Bn	72
3	*t*-BuOH	**41**	*t*-Bu	48
4	 tryptophol	**42**		58
5	 (±)-methyl β-indolyllactate	**43**		0

furnished diacid **46**, which was converted to the dichloridate [$(COCl)_2$, DMF, CH_2Cl_2] and allowed to react with *p*-nitrobenzyl alcohol. Hydrolysis of the resulting diester using sodium iodide in acetone afforded monoester **47** in 43% overall yield from **46**. The coupling of monoester **47** with D-tryptophan methyl ester was attempted three times; only a trace amount of what was believed to be the desired product (**48**) was ever obtained.

Scheme 7



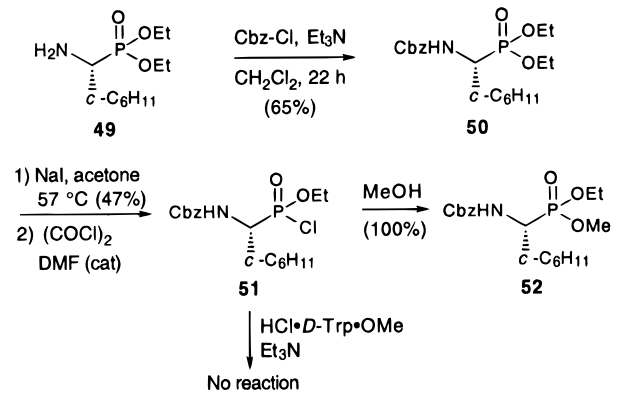
We also investigated the reactivity of chloridate **51** in which the *p*-nitrobenzyl ester is replaced by the less-hindered ethyl ester (Scheme 8). Chloridate **51** was prepared by carbamoylation of amine **49**[40] to afford Cbz-protected ester **50**, which was converted directly to **51** by heating at reflux in acetone with sodium iodide followed by chlorination [$(COCl)_2$]. The resulting chloridate **51** reacted smoothly with methanol to give

(38) Notably (±)-methyl β-indolyllactate,[30] unlike tryptophol, failed to furnish **43** under the standard reaction conditions (ROH, 2 equiv, CH_2Cl_2, 25 °C, 3 h). This difference may in part reflect reduced nucleophilicity as a result of hydrogen bonding between the hydroxyl and the C-terminal carboxyl moiety.

(39) Seyferth, D.; Marmor, R. S.; Hilbert, P. *J. Org. Chem.* **1971**, *36*, 1379.

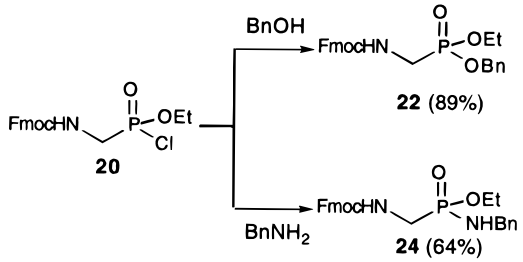
a quantitative yield of the mixed diester **52**, but again no coupling was observed with D-tryptophan methyl ester.

Scheme 8



Because the aminolysis conditions used by us are more vigorous than those employed in peptide synthesis, we considered that the failure to obtain the desired coupling products might be due to premature loss of the Fmoc protecting group. However, when the chloridate **20** was allowed to react with either benzyl alcohol or benzylamine under identical conditions (5 equiv of nucleophile, 25 °C, 0.5 h), the expected diester **22** and phosphonamide **24** were obtained in 89 and 64% yield (Scheme 9), respectively.

Scheme 9

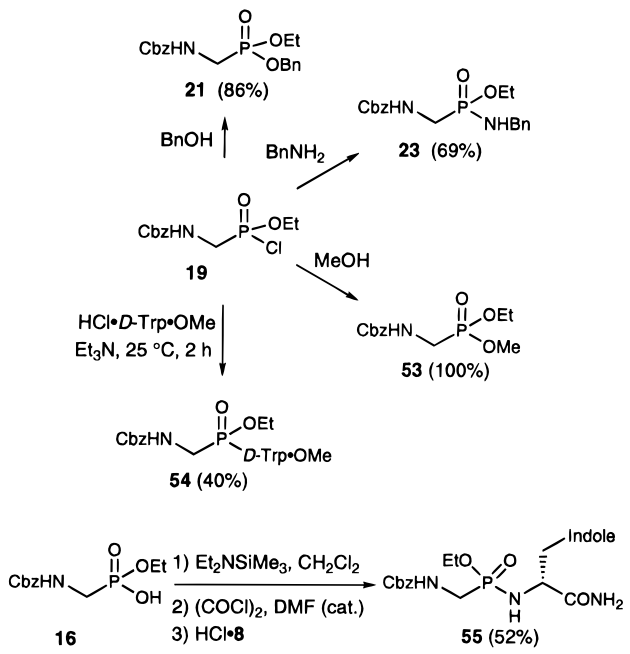


Taken together, our results suggest that the reasons for the failure of chloridate **7** to couple with derivatives of D-tryptophan are complex and not due solely to steric hindrance generated by the cyclohexyl or the *p*-nitrobenzyl substituents nor to the instability of the Fmoc protecting group. We therefore investigated more fully the effect of changes in the nucleophiles on the coupling reactions.

The Role of Electronic and Steric Properties of the Nucleophile. Treatment of chloridate **19** with anhydrous methanol afforded mixed diester **53** in quantitative yield (Scheme 10). Similarly, treatment of chloridate **19** with benzyl alcohol furnished **21** in 86% yield. In contrast, chloridate **19** gave the phosphonamide **23** in 69% yield, and the coupling of **19** with the more hindered D-tryptophan methyl ester afforded **54** in only 40% yield. To ensure that the lower yields obtained in the aminolyses were not due to acid-catalyzed hydrolysis of the products, we avoided acidic conditions via the procedure of Patel[41] and Biller,[42] using *N*,*N*-diethyltrimethylsilylamine for phosphonochloridate generation. When this protocol [Et_2-$NSiMe_3$, CH_2Cl_2, $(COCl)_2$, DMF (cat.)] was employed, the coupling of **16** with **8** provided **55** in only a slightly improved yield of 52%.

In two important publications, Greenhalgh and co-workers provided analyses of the effects of the structure of phosphylating

Scheme 10



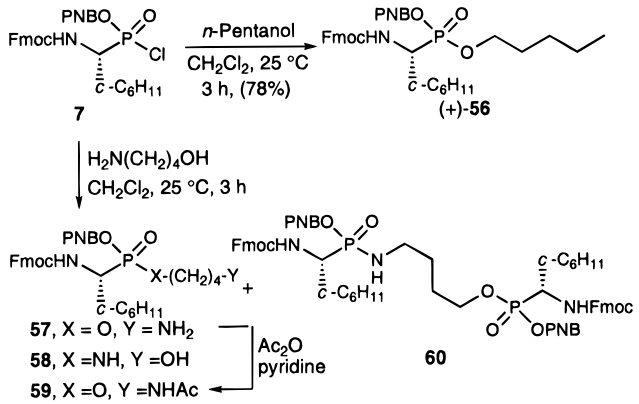
agents on their reaction with oxygen and amine nucleophiles.[35,43] Their results are briefly summarized. Employing ethanolamine as a bisnucleophile to measure alcoholysis vs. aminolysis of activated phosphylating agents, they interpreted their results in terms of the semiempirical treatment of Hudson,[44] which assumes that for small charge transfer in the transition state there is a preference for easily polarizable nucleophiles (amino), but as the charge transfer in the transition state increases, the energy obtained from bond formation becomes more important and a faster reaction is observed with less easily polarizable nucleophiles (hydroxyl). This is consistent with the fact that the P−O bond is ca. 20 kcal stronger than the P−N bond.[45−48] Greenhalgh concluded, therefore, that when the leaving group of the phosphylating agent is kept constant, the preference for the less-polarizable nucleophile increases in the series from phosphorodiamides to phosphinates. When the leaving group is varied within the series, *O*-phosphylation is observed in the order Cl < pyro anhydride < CN < F. Thus, chloro compounds represent a region of the reactivity curve where maximum selectivity for the more polarizable amino functionality should be expected, suggesting that the chlorophosphonate should have optimized the formation of the phosphonamide.

The results of Greenhalgh and co-workers were fundamental to understanding the reactivity patterns of unhindered phosphylating agents, but their studies did not address steric hindrance. We extended Greenhalgh's studies via the addition of a bisnucleophile to sterically diverse chloridates. When *n*-pentanol was allowed to react with chloridate **7**, the diester (+)-**56** was obtained in good yield (70%) (Scheme 11). When chloridate **7** was treated with 4-aminobutan-1-ol (3 equiv, CH_2-

(40) Yager, K. M.; Taylor, C. M.; Smith, A. B., III. *J. Am. Chem. Soc.* **1994**, *116*, 9377.
(41) Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E. *Tetrahedron Lett.* **1990**, *39*, 5591.
(42) Biller, S. A.; Forster, C. *Tetrahedron* **1990**, *46*, 6645.
(43) Greenhalgh, R.; Weinberger, M. A. *Can. J. Chem.* **1967**, *45*, 495.
(44) Hudson, R. F. *Chimia* **1962**, *16*, 173. (b) Hudson, R. F. *Structure and Mechanisms in Organophosphorus Chemistry*; Academic: London, 1965.
(45) Hartley, S. B.; Holmes, W. S.; Jacques, J. K.; Mole, M. F.; McCoubrey, J. C. *Quart. Rev. Loundon* **1963**, *17*, 216.
(46) Earlier, Dostrovsky and Halmann[47] and Hudson and Keay[48] established that alcoholysis and aminolysis of phosphonochloridates proceed by the same mechanism involving an S_N2 process in which the rate-determining step involves approach of the nucleophile to the electrophilic phosphorus center. These workers had also shown that basicity of the nucleophile, steric hindrance, and the relative energies of the bonds formed and broken influence the rate-determining step.
(47) (a) Dostrovsky, I.; Halmann, M. *J. Chem. Soc.* **1953**, 511. (b) Dostrovsky, I.; Halmann, M. *J. Chem. Soc.* **1953**, 516.
(48) Hudson, R. F.; Keay, L. *J. Chem. Soc.* **1960**, 1859.

Cl_2, 25 °C, 3 h), three products were isolated. The major product **57** was highly polar and gave a positive ninhydrin test indicating the presence of a free amine. Because **57** was too polar to be purified by flash chromatography and decomposed during RP-HPLC, it was characterized as the acetylated derivative **59**. Compound **59** was also prepared by coupling **7** with *N*-acetyl-4-aminobutan-1-ol in 68% yield. The two minor products, phosphonamides **58** and **60**, were formed in trace (<5%) amounts. Structure assignments are based on mass spectrometry and ^{31}P NMR analysis and are made by analogy with the model system **16** *(vide infra)*.

Scheme 11



The ^{31}P NMR spectra (202.5 MHz) of monoester (−)-**6** (spectrum a) and **58**−**60** (spectra b, c and d, respectively) are shown in Figure 5. Compounds **57**−**59** exist as mixtures of two diastereomers and **60** as four diastereomers which could not be resolved in the ^{31}P NMR spectrum. It is reasonable to assume that the ^{31}P chemical shift of **57** would be similar to that of **59**, since acetylation of the nitrogen six bonds away from phosphorus would be expected to have only a minor effect. As is demonstrated in spectrum e of Figure 5, *O*-coupling predominates in the reaction of chloridate **7** with 4-aminobutan-1-ol. This observation is consistent with our results described above (i.e., coupling with a large number of alcohols, but little or no coupling with hindered amines). *Importantly, this result is inconsistent with the hypothesis of Greenhalgh that the chlorophosphonate should optimize phosphonamide formation.*

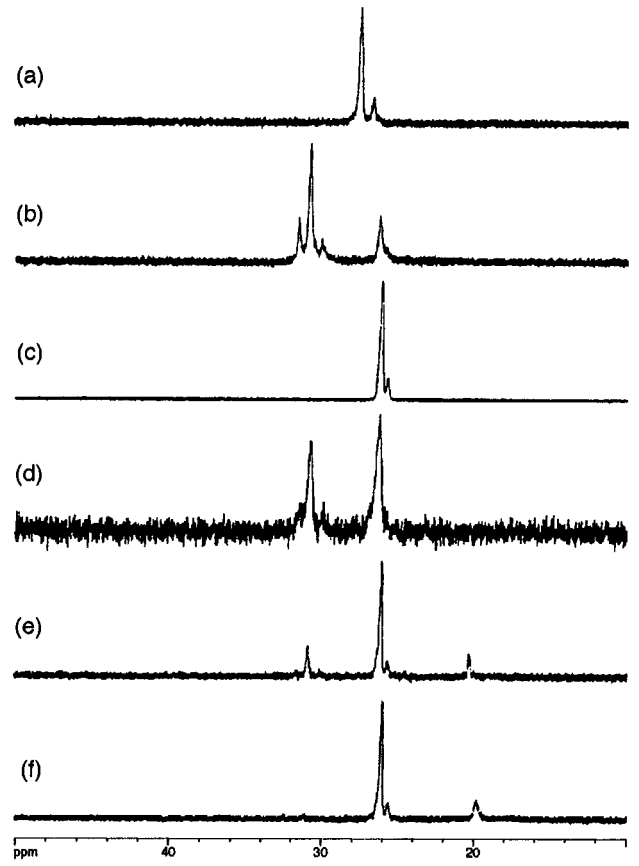
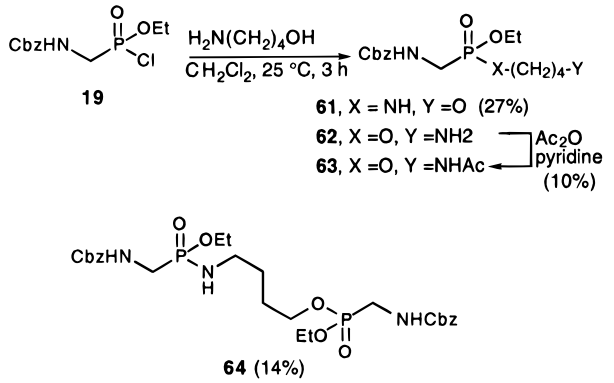


Figure 5. ^{31}P NMR spectra: (a) monoester (−)-**6**; (b) phosphonamide **58**; (c) phosphonate ester **59**; (d) bisadduct **60**; (e) reaction of phosphonochloridate **7** with 4-aminobutan-1-ol; (e) reaction of phosphonochloridate **7** with 4-aminobutan-1-ol and triethylamine.

4-Aminobutan-1-ol was also allowed to react with the unhindered chloridate **19** as shown in Scheme 12. Significantly, the ratio of the three products was different from that observed for chloridate **7**: with **19**, *N*-coupling predominates (Figure 6; spectrum e), whereas treatment of chloridate **7** with 4-aminobutan-1-ol led to selective *O*-coupling.

Scheme 12



In accord with Greenhalgh's studies, these results indicate that unhindered phosphonochloridates, such as **19**, exhibit a preference for more polarizable nucleophiles (amines). However, our results with the more-hindered phosphonochloridate **7** clearly illustrate that steric factors must also be considered. Successful coupling between sterically hindered partners requires surmounting a large energy barrier as the reactants approach in the transition state. We surmise that the energy gained as the stronger phosphonate P−O bond forms (≥20 kcal per mol more stable than a P−N bond), reduces this barrier enough to facilitate coupling with alcohol **9**. In coupling with amine **8**, too little bond energy is gained as the weaker P−N bond forms to overcome the steric repulsion, and decomposition of chloridate **7** occurs more rapidly than coupling with the amine. Consequently, when preparing complex phosphonates and phosphonamides, the sterics of the phospylating agent must be considered along with its polarizablity in determining relative preference for amine vs. alcohol nucleophiles.

By the same logic, the greater stability of the P−O bond should also lower the thermodynamic energy of product phosphonate **11** relative to phosphonamide **10**, but our failure to observe formation of **10** prevents any conclusions based on thermodynamic control. Nonetheless, experiements with the simple phosphonamide **23** failed to reveal any signs of reversibility.

While these experiments were in progress, we explored an alternate explanation for the fact that we could generate **11** but not **10**. It is a well-known fact that *N*-acylated and even urethane-protected amino acids and peptides undergo cyclization by tertiary amines to form oxazolones,[49] which are themselves reactive acylating agents (c.f., **65** to **66**, Scheme 13, eq 1). We hypothesized that the lack of amine coupling with chloridate **7** might be due to analogous cyclization of **7** to give the

(49) Benoiton, N. L. in *The Peptides*; Udenfriend, S., Meienhofer, J., Eds.; Academic Press: San Diego, CA, 1983; Vol. 5, Chapter 4.

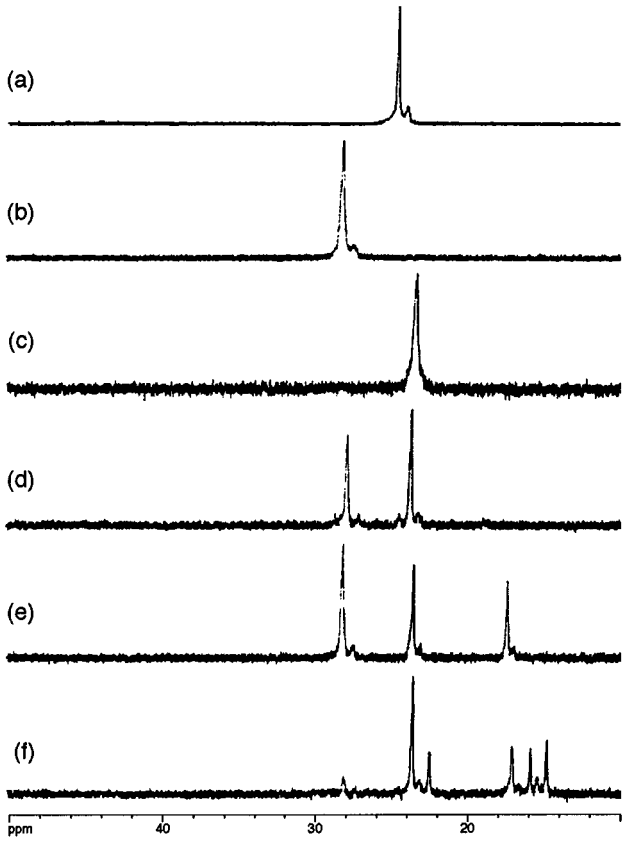
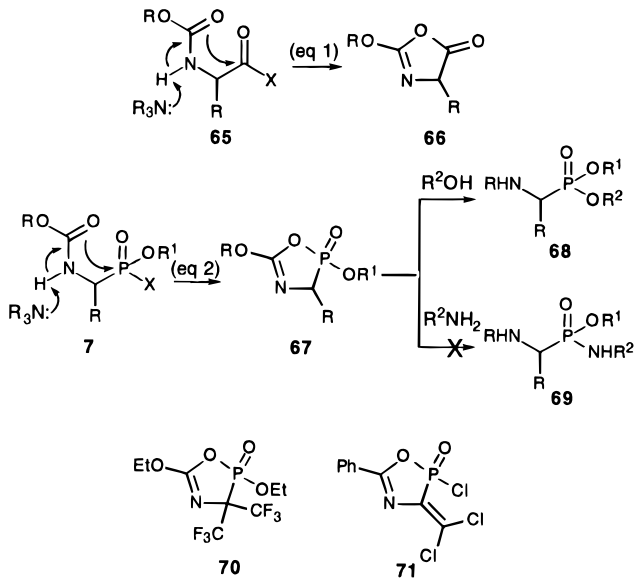


Figure 6. ^{31}P NMR spectra: (a) monoester **16**; (b) phosphonamide **61**; (c) phosphonate ester **62**; (d) bisadduct **64**; (e) reaction of phosphonochloridate **19** with 4-aminobutan-1-ol; (f) reaction of phosphonochloridate **19** with 4-aminobutan-1-ol and triethylamine.

oxazaphospholine **67**. Oxazaphospholines such as **70** and **71**, substituted at the α-position, had been prepared previously by alternate routes.[50,51] Indeed, **70** was reported to undergo ethanol-induced ring opening to afford the diethyl ester, but not to react with aniline. We speculated, therefore, that oxazaphospholines might similarly react with alcohols to furnish the diester (**68**) but fail to undergo a similar ring opening phosphonylation of amines (Scheme 13, eq 2).

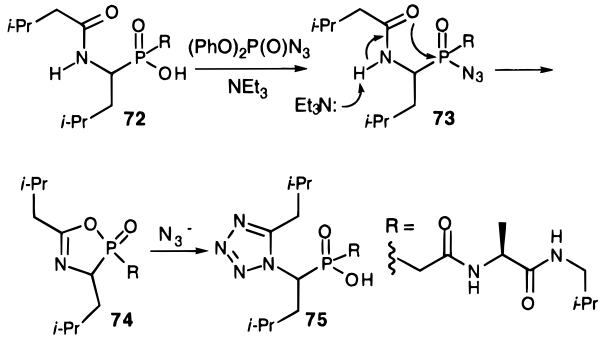
Additionally, Bartlett and Acher have proposed such a heterocycle as an undetected intermediate in the rearrangement

Scheme 13



of phosphinyl azide **74** to tetrazole phosphinic acid **75** (Scheme 14).[52]

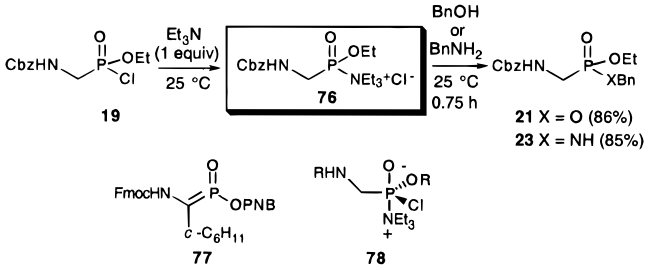
Scheme 14



However, as will be shown below, cyclization does not occur when α-aminophosphonochloridates are allowed to react with amines.

Reaction of Phosphonochloridates with Tertiary Amines. Formation of a Novel Reactive Species. In the hope of generating an oxaphospholine, the phosphonochloridate **16**, containing some of the diastereomeric anhydrides, was allowed to react with triethylamine. This resulted in the conversion of **16** into a new species displaying a dramatic downfield shift of the ^{31}P NMR resonance (44.7 ppm); the anhydrides remained unchanged (see Figure 4). We propose that the product corresponding to the low-field resonance is not the anticipated oxazaphospholine (c.f., **67**, Scheme 14), but rather phosphonyltriethylammonium salt **76** (Scheme 15).[53,54] Our assignment

Scheme 15



is based upon the following considerations. The IR spectrum of **70** displays a characteristic absorption at 1625 cm^{-1} (C═N), which is absent in the spectrum of **76**. Moreover, the reported ^{31}P NMR chemical shifts of **70** and **71** (23 and 24.6 ppm, respectively) are considerably upfield of the observed 44.7 ppm resonance. The "P-ketene" **77** and trigonal bipyramidal (TBP) species **78** were considered as alternate structures for the new reactive intermediate. The former possibility has been ruled out (*vide infra*), while the TBP structure (**78**), although not rigorously excluded, seems unlikely in light of both the known lability of phosphorus derivatives with this ligand array (phosphorus pentahalides excluded) and their proclivity toward reorganization to the more stable tetrahedral coordination

(50) Korenchenko, O. V.; Aksinenko, A. Y.; Sokolov, V. B.; Martynov, I. V. *Heteroatom Chem.* **1992**, *3*, 147.

(51) (a) Drach, B. S.; Lobanov, O. P. *J. Gen. Chem. USSR* **1974**, *44*, 2730. (b) Lobanov, O. P.; Drach, B. S. *J. Gen. Chem. USSR* **1982**, *52*, 980.

(52) Bartlett, P. A.; Acher, F. *Bull. Soc. Chim. Fr.* **1986**, 771.

(53) A structure analogous to **76** was proposed by Mucha et al. for a compound which displayed a ^{31}P shift at 15.3 ppm; however, our earlier results suggest that this species is actually the anhydride: Mucha, A.; Kafarski, P.; Plenat, F.; Cristau, H.-J. *Tetrahedron* **1994**, *50*, 12743.

(54) Yamazaki and co-workers have proposed that an acyloxy *N*-phosphonium salt with pyridine was formed an intermediate in an Arbuzov reaction but the species was uncharacterized: Yamazaki, N.; Niwano, M.; Kawabata, J.; Higashi, F. *Tetrahedron* **1975**, *31*, 665.

environment.[55] Though quaternary ammonium salts have been suggested as intermediates in acyl phosphonate couplings, this is the first conclusive identification of such a species.

Importantly, intermediate **76** reacted more rapidly with benzyl alcohol than phosphonochloridate **19**, although both afforded the mixed diester **21** in high yield. The increased reactivity of **76** relative to **19** was even more pronounced in the coupling with amines. When a 1:1 mixture of **76** and **16**, generated with 0.5 equiv of triethylamine, was treated with a limiting amount of benzylamine, the amine reacted exclusively with **76** to give **23** (X = NH), with no detectable consumption of the phosphonochloridate as indicated by ^{31}P NMR.

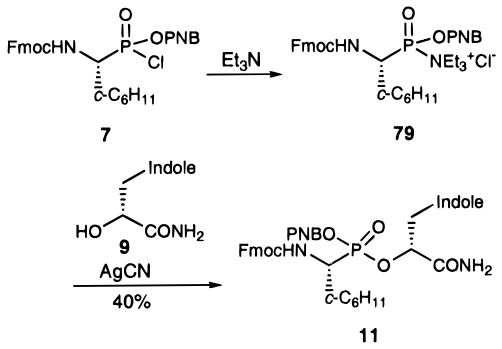
Intermediate **76** also displayed a markedly greater affinity for alcohols than did phosponocloridate **19**. As mentioned above, treatment of **19** with 4-aminobutan-1-ol led to a 1.5-fold preference for *N*-coupling (Figure 6). In striking contrast, when **19** is allowed to first react with 1 equiv of triethylamine to generate **76**, and then allowed to react with 4-amino-1-butanol, *O*-coupling dominates over *N*-coupling by a factor of 8, as evidenced by RP-HPLC and ^{31}P NMR (Figure 6f). Such a change in selectivity indicates a shift to greater charge transfer in the transition state. The strong preference for coupling with O suggests that formation of **76** is the procedure of choice for preparation of phosphonate esters.

In many conventional phosphonate syntheses, triethylamine is added along with the nucleophile as an acid scavenger. The suggestion has been made,[56] in response to our previous publication,[1] that intermediate **76** could be the actual intermediate for all such couplings. However, we believe that the experimental results cited in the previous paper and those reported in this paper favor the view that, in such conventional procedures, the triethylamine acts only as an acid scavenger. For example in several ^{31}P NMR experiments in which the nucleophile and triethylamine were added simultaneously to the chloridate **19**, no evidence for the formation of **76** was seen, nor were any noticeable changes in reaction rates or product composition in comparison to reactions carried out in the absence of triethylamine. On the other hand, as reported previously, both yields and reaction rates were improved when **19** was allowed to react first with triethylamine, generating **76**.

The marked difference in selectivity between phosphonochloridate **19** and phosphonyltriethylammonium species **76** toward the bisnucleophile 4-aminobutan-1-ol allowed us to address this question directly. In couplings with this bisnucleophile, **19** displayed a 1.5-fold preference for *N*-coupling, while **76** displayed an 8-fold preference for *O*-coupling. Therefore, the product ratio of a conventional coupling procedure in which the bisnucleophile and triethylamine are added simultaneously will reveal which species is the reaction intermediate. As we anticipated, treatment of chloridate **19** with a mixture of 4-aminobutan-1-ol and 1 equiv of triethylamine yielded a 1.2:1 mixture of *N*-coupled to *O*-coupled products, as determined by RP-HPLC. Thus, simultaneous addition of a tertiary amine had no effect on the coupling ratio to within expeimental error. These results demonstrate that while **76** may play a minor role in this system during a conventional coupling, the triethylamine acts primarily as an acid scavenger. *Thus, the phosphonyltriethylammonium species **76** must be preformed to affect the outcome of the reactions.*

Eager to exploit the increased reactivity of the triethylammonium salts, we returned to the synthesis of hapten (+)-**5**. Previously, we had observed coupling of chloridate **7** with (*R*)-(+)-*β*-indolyllactamide (**9**)[30] in the presence of silver ion to afford phosphonate diester (+)-**11** in yields that varied unpredictably from 0 to 32%.[57] As we had hoped, conversion of phosphonochloridate **7** to the phosphonyltriethylammonium intermediate **79** *prior* to the addition of silver cyanide *reproducibly* furnished diester (+)-**11** in 40% yield (Scheme 16).[58] Addition of triethylamine *after* the addition of **9** and silver cyanide gave yields below 10%. Thus, our protocol both improved the yield of (+)-**11** over the conventional procedure and made the reaction reproducible. Unfortunately, **79** failed to form the desired phosphonamide **10** even in the presence of silver ion, as demonstrated by ^{31}P NMR studies. This result is consistent with the phophonyltriethylammonium species' preference for oxygen over amine nucleophiles.

Scheme 16



Despite the increased reactivity of **76** toward both alcohols and amines, the α-carbon of the phosphonylammonium species is not prone to racemization, as is evidenced by the formation of only two diastereomers of (+)-**11** (diastereomeric at phosphorus) in the coupling of **79** with **9**. Moreover, enantiomeric purity is retained upon an aqueous quench of **79**; a result that also rules out formation of **77**. Additional support derives from the observation that deuterium is not incorporated (^{2}H NMR, HRMS) at the α-center during coupling reactions of **76** with excess benzylamine-*N*,*N*-d_2. We have also observed the formation of phosphonylammonium salts of **19** with other tertiary amines including diisopropylethylamine, *N*-methyl piperidine, *N*-methyl-2,6-tetramethylpiperidine, 4-(dimethylamino)pyridine (DMAP), and Dabco, but not with pyridine or 2,6-lutidine. Reaction of **19** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) lead to decomposition.[19c,59−61]

Summary. We have demonstrated that pyrophosphonate anhydrides are readily formed in the preparation of phosphonochloridates from phosphonate monoesters with thionyl chloride and oxalyl chloride and that these anhydrides are less-reactive toward nucleophiles, particularly toward amines than

(55) Van Wazer, J. R. *Phosphorus and its Compounds*; Interscience Publishers: New York, 1964; Vol. 1, Chapter 3, pp 74−75.

(56) Fernandez, M. F.; Vlaar, C. P.; Fan, H.; Liu, Y.; Froczek, F. R.; Hammer, R. P. *J. Org. Chem.* **1995**, *60*, 7390.

(57) Smith, A. B., III; Taylor, C. M.; Benkovic, S. J.; Hirschmann, R. *Tetrahedron Lett.* **1994**, *35*, 6853.

(58) Numerous attempts to employ ^{31}P NMR to probe the effects of silver ion have not, to date, been enlightening. There are no obvious changes in the ^{31}P NMR spectrum of **77** after treatment with silver cyanide at room temperature, and heating in the absence of a nucleophile leads to decomposition as evidenced by a complex upfield region in the ^{31}P NMR spectrum.

(59) Since the standard protocol for phosphonopeptide (amide) formation involves the addition of tertiary amines to convert the amine salt to the free base, an excess of tertiary amine in these cases would be expected to form a phosphonylammonium salt.[53] 1*H*-Tetrazole-assisted phosphonate diester synthesis from phosphonodichloridates has been reported.[60] In particular reaction of phosphonodichloridates with 1*H*-tetrazole leads sequentially and selectively to the replacement of the chloride substituents with two different alcohols to give the product mixed diesters in good yield. This reaction was not, however, studied with alkylamine nucleophiles. Amine-catalyzed coupling and hydrolysis of phosphate derivatives is also well-known;[61] here, ^{1}H NMR and IR spectroscopic evidence for *N*-phosphorylated adducts has been provided.[51b] To our knowledge, however, the presumed P−N adducts in many studies have not been identified.[62]

(60) Zhao, K.; Landry, D. W. *Tetrahedron* **1993**, *49*, 363.

the corresponding phosphonochloridates. Unlike their carboxylic acid counterparts, the phosphonochloridates do not cyclize to oxazaphospholines upon treatment with a tertiary amine, but afford instead the hitherto unrecognized phosphonylammonium salts. These phosphonylammonium salts are highly reactive phosphonylating agents, superior to phosphonochloridates, affording higher yields of phosphonate esters and amides.[62] *These improved yields are not obtained when triethylamine is added merely to neutralize acid rather than as a deliberate step to generate the phosphonyltrialkylammonium salts.*[63] We have also shown that the phosphonochloridates differ markedly in their reactivities toward amines and alcohols. The preference for oxygen- vs. nitrogen-coupling varies and depends on both the steric and electronic environment surrounding the electrophilic phosphorus center and the structure of the nucleophile. For example, with the chloridate derived from acid **47** or chloridates **7** and **51**, the steric congestion imparted by the cyclohexyl and/or *p*-nitrobenzyl groups hindered, and in many cases precluded, formation of phosphonamides. Our results indicate that successful coupling of phosphonochloridate **7** with hindered alcohols was due largely to the added strength of the forming P−O ester bond. On the other hand, when steric requirements of the phosphonochloridate are less demanding (i.e., **19** and **20**), phosphonamide formation tends to dominate. Alteration of the electronic properties of the electrophilic phosphorous center by conversion of phosphonochloridates into the phosphonylammonium salts resulted in a dramatic increase in oxygen selectivity, as demonstrated in coupling reactions with the bisnucleophile 4-aminobutan-1-ol.

Experimental Section

Materials and Methods. Except as otherwise indicated, reactions were carried out under argon with dry, freshly distilled solvents, in glassware flame-dried under vacuum, with magnetic stirring. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium and benzophenone. Benzene was distilled from sodium. Dichloromethane, triethylamine, and benzylamine were distilled from calcium hydride. Thionyl chloride and oxalyl chloride were distilled immediately prior to use.

All reactions were monitored by thin-layer chromatography (TLC) using 0.25 mm E. Merck precoated silica gel plates. Flash chromatography was performed with E. Merck silica gel 60 (particle size 0.040−0.063 mm). Yields refer to chromatographically and spectroscopically pure compounds, except as noted.

Proton, carbon-13, and phosphorus-31 NMR spectra were recorded on a Bruker AM-500 spectrometer. Proton and ^{13}C chemical shifts are reported in δ values relative to internal tetramethylsilane. Phosphorus-31 spectra were acquired with broad-band proton decoupling; shifts are reported in δ values relative to external 85% phosphoric acid. Optical rotations were measured with a Perkin-Elmer Model 241 polarimeter. High-resolution mass spectra were obtained with a VG Micromass 70/70H or VG ZAB-E spectrometer.

Microanalyses were performed by Robertson Labs, Madison, N.J.

Phosphonate Diesters 11. A solution of monoester (−)-**6** (40.0 mg, 0.073 mmol) in CH_2Cl_2 (2 mL) was cooled to 0 °C, and dry dimethylformamide (6 μl, 0.010 mmol) and oxalyl chloride (13 μL, 0.147 mmol) were added. The mixture was stirred for 0.5 h at 0 °C, diluted with benzene (5 mL), and concentrated. The residue was redissolved in benzene (2 mL) and treated with Et_3N (20 μL, 0.147 mmol) followed by silver cyanide (29 mg, 0.217 mmol). After 5 min at room temperature, (*R*)-β-indolyllactamide (**9**) (22.4 mg, 0.011 mmol) was introduced, and the mixture was heated at reflux for 2 h, cooled to room temperature, filtered and concentrated. Flash chromatography (2% MeOH/CH_2Cl_2) gave diesters **11** (19.8 mg, 37% yield) as a white solid. The diastereomers were separated by RP-HPLC. For the minor diastereomer: amorphous white solid (4.5 mg); $[\alpha]^{25}_D$ +15° (*c* 0.47, EtOH); IR ($CHCl_3$) 3480 (m), 3430 (w), 3005 (m), 2930 (s), 2860 (m), 1710 (br, s), 1610 (w), 1525 (s), 1455 (m), 1350 (s), 1320 (w), 1290 (m), 1230 (m), 1010 (s), 955 (m), 855 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, J = 8.5 Hz, 2 H), 7.96 (br s, 1 H), 7.78 (dd, J = 7.5, 2.0 Hz, 2 H), 7.60 (d, J = 7.9 Hz, 2 H), 7.53 (dd, J = 10.8, 7.6 Hz, 1 H), 7.40 (t, J = 7.5 Hz, 2 H), 7.33 (d, J = 8.5 Hz, 2 H), 7.28 (t, J = 7.5 Hz, 1 H), 7.25 (d, J = 7.9 Hz, 1 H), 7.15 (t, J = 7.5 Hz, 1 H), 7.08 (t, J = 7.5 Hz, 1 H), 7.00 (d, J = 1.8 Hz, 1 H), 6.12 (br s, 1 H), 5.54 (br s, 1 H), 5.11−4.90 (m, 3 H), 4.60 (dd, J = 10.8, 6.0 Hz, 1 H), 4.35 (dd, J = 10.8, 6.0 Hz, 1 H), 4.12 (t, J = 6.0 Hz, 1 H), 3.95 (ddd, J = 18.5, 10.7, 4.5 Hz, 1 H), 3.33 (m, 2 H), 1.85−0.65 (m, 11 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 156.1, 147.8, 143.6, 143.5, 142.7, 141.4, 141.3, 135.9, 128.1, 127.9, 127.8, 127.5, 127.2, 127.1, 124.8, 124.6, 123.7, 122.3, 120.1, 120.0, 119.8, 118.7, 111.2, 109.3, 66.8 (d, J_{CP} = 7 Hz), 66.6, 53.3 (d, J_{CP} = 154 Hz), 47.2, 38.1, 38.0, 30.4, 30.3, 29.7, 29.2, 27.8, 25.8, 25.7, 25.6; high-resolution mass spectrum (CI, NH_3) *m/z* 737.2740 [$(M + H)^+$; calcd for $C_{40}H_{42}N_4O_8P$ 737.2740].

For the major diastereomer: amphous white solid (15 mg); $[\alpha]^{25}_D$ +25° (*c* 0.44, EtOH); IR ($CHCl_3$) 3420 (w), 3000 (m), 2950 (s), 2930 (s), 2860 (m), 1720 (s), 1605 (w), 1520 (w), 1505 (w), 1455 (m), 1345 (m), 1250 (s), 1125 (s), 1035 (s), 855 (w), 550 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, J = 8.7 Hz, 2 H), 7.84 (dd, J = 19.0, 7.5 Hz, 2 H), 7.58 (d, J = 17.7, 7.4 Hz, 2 H), 7.55−7.30 (m, 10 H), 7.03 (ddd, J = 7.9, 5.2, 2.5 Hz, 1 H), 6.76 (d, J = 2.2 Hz, 1 H), 6.71 (br s, 1 H), 5.50 (br s, 1 H), 4.93 (m, 1 H), 4.82 (dd, J = 12.8, 7.1 Hz, 1 H), 4.71 (dd, J = 11.0, 5.3 Hz, 1 H), 4.67 (dd, J = 12.9, 6.9 Hz, 1 H), 4.44 (dd, J = 10.9, 5.1 Hz, 1 H), 4.18 (t, J = 5.1 Hz, 1 H), 4.13 (d, J = 10.5 Hz, 1 H), 3.81 (ddd, J = 17.5, 11.0, 6.2 Hz, 1 H), 3.39 (d, J = 15.0 Hz, 1 H), 3.18 (dd, J = 15.0, 9.2 Hz, 1 H), 1.71−0.40 (m, 11 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 156.2, 147.7, 143.9, 143.5, 142.6, 142.5, 141.5, 141.3, 135.7, 128.1, 127.9, 127.7, 127.3, 124.9, 124.6, 123.7, 122.8, 122.4, 120.2, 120.1, 119.9, 118.6, 111.3, 110.0, 66.5, 66.0, 52.8 (d, J_{CP} = 151 Hz), 47.4, 38.0, 30.4, 30.3, 29.0, 28.1, 28.0, 25.8, 25.7; high-resolution mass spectrum (CI, CH_4) *m/z* 614.2343 [$(M-p\text{-}NO_2C_6H_4)^+$; calcd for $C_{34}H_{37}N_3O_6P$ 614.2420].

Phthalimide (13). A mixture of *N*-(hydroxymethyl)phthalimide (**12**) (31.46 g, 0.180 mol) and phosphorus tribromide (48.45 g, 0.180 mol) was heated at 140 °C for 1 h. The homogeneous orange solution was cooled to room temperature and poured into ice water, and the resultant pale yellow crystals were collected by filtration, dried over P_2O_5 under vacuum (<1 mmHg), and recrystallized from $CHCl_3$−hexanes (1:1) to give *N*-(bromomethyl)phthalimide (34.4 g, 80% yield) as colorless needles: mp 148−150 °C (lit.[19b] 149−150 °C);[64,65] IR ($CHCl_3$) 3050 (w), 1790 (s), 1730 (s), 1470 (m), 1425 (s), 1385 (s), 1350 (s), 1305 (m), 1065 (s), 915 (s), 705 (w), 590 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.94−7.30 (m, 4 H), 5.50 (s, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 134.7, 131.8, 123.9, 31.2; high-resolution mass spectrum (CI, NH_3) *m/z* 239.9638 [$(M + H)^+$; calcd for $C_9H_7NO_2Br$ 239.9660].

The bromide and triethyl phosphite (27.69 g, 0.170 mol) were heated at 120 °C; the ethyl bromide byproduct was collected via a distillation apparatus. After 1 h, the mixture was cooled to room temperature and diluted with $CHCl_3$ (100 mL). The solution was washed with water (3 × 100 mL), dried ($CaSO_4$), and concentrated to give a yellow solid. Crystallization from hexanes−Et_2O (1:1) gave **13** (40.12 g, 81% yield) as colorless needles: mp 67−68 °C (lit.[20b] 67 °C); IR ($CHCl_3$) 3000 (w), 1780 (m), 1730 (s), 1405 (m), 1395 (m), 1310 (w), 1240 (m), 1060 (m), 1020 (m), 975 (w), 905 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.9−7.7 (m, 4 H), 4.22 (dd, J_{HP} = 14.0 Hz, J_{HH} = 7.0 Hz,

(61) (a) Wagner-Jauregg, T.; Hackley, B. E., Jr. *J. Am. Chem. Soc.* **1953**, *75*, 2125. (b) Jencks, W. P.; Gilchrist, M. *J. Am. Chem. Soc.* **1965**, *87*, 3199. (c) Kirby, A. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1965**, *87*, 3209. (d) Kirby, A. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1965**, *87*, 3217. (e) Kirby, A. J.; Varvoglis, A. G. *J. Am. Chem. Soc.* **1967**, *89*, 415. (f) Jameson, G. W.; Lawlor, J. M. *J. Chem. Soc. B* **1970**, 53. (g) Wakselman, M.; Guibé-Jampel, E. *Tetrahedron Lett.* **1970**, 1521. (h) Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569. (i) Kirby, A. J.; Varvoglis, A. G. *J. Chem. Soc. B* **1968**, 135.

(62) Studies are underway in our laboratory which will explore the synthetic potential and mechanistic aspects of the phosphonylammonium salts more fully.

(63) Attempts to monitor the simultaneous addition of a nucleophile and triethylamine to chloridates employing ^{31}P NMR could not be carried out because the triethylammonium salts are converted instananeously to product on addition of the nucleophile.

(64) Davidson, S. K.; Phillips, G. W.; Martin, S. F. *Org. Synth.* **1987**, *65*, 119.

(65) Pucher, G. W.; Johnson, T. B. *J. Am. Chem. Soc.* **1922**, *44*, 817.

4 H), 4.12 (d, J = 11.4 Hz, 2 H), 1.34 (t, J = 7.0 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 133.8, 131.5, 123.0, 62.3, 32.9 (d, J_{CP} = 156 Hz), 15.9; high-resolution mass spectrum (CI, NH_3) *m/z* 298.0871 [$(M + H)^+$; calcd for $C_{13}H_{16}NO_5P$ 298.0844].

Diester (15). A solution of phthalimide **13** (13.74 g, 0.046 mol) in absolute ethanol (90 mL) was treated with hydrazine hydrate (2.43 g, 0.049 mol) and stirred at ambient temperature for 3.5 days. The white phthalyl hydrazide precipitate was removed by vacuum filtration, and the filtrate was concentrated at reduced pressure without heating to provide primary amine **14** as a pale yellow oil. Without purificataion, **14** was dissolved in $CHCl_3$ (155 mL), and the solution was cooled to 0 °C, treated with benzyl chloroformate (8.67 g, 0.051 mol) and Et_3N (7.02 g, 0.069 mol), warmed to room temperature, and stirred for 15 h. The resultant mixture was diluted with CH_2Cl_2 (100 mL), washed with 2 N aqueous H_2SO_4 (2 × 170 mL), dried ($MgSO_4$), filtered, and concentrated to furnish **15** (12.11 g, 87% yield) as a pale yellow, viscous oil: IR ($CHCl_3$) 3450 (m), 3000 (s), 1725 (s), 1515 (s), 1450 (w), 1390 (w), 1305 (m), 1240 (s), 1150 (m), 1025 (s), 975 (s), 820 (w), 690 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (m, 5 H), 5.35 (br s, 1 H), 5.12 (s, 2 H), 4.11 (q, J = 7.3 Hz, 4 H), 3.61 (dd, J_{HP} = 11.2 Hz, J_{HH} = 6.0 Hz, 2 H), 1.29 (t, J = 7.1 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.1, 136.2, 128.4, 128.1, 128.0, 123.4, 102.2, 67.1, 32.5, 36.6 (d, J_{CP} = 157 Hz), 16.3; high-resolution mass spectrum (CI, NH_3) *m/z* 302.1133 [$(M + H)^+$; calcd for $C_{13}H_{21}NO_5P$ 302.1157].

Anal. Calcd for $C_{13}H_{20}NO_5P$: C, 51.83; H, 6.69. Found: C, 51.92; H, 6.79.

Monoester (16). A mixture of diester **15** (5.32 g, 0.018 mol) and 2 N aqueous NaOH (30 mL) was stirred vigorously for 18 h at ambient temperature and then washed with CH_2Cl_2 (2 × 70 mL) and acidified with 2 N H_2SO_4 (85 mL). The resultant solution was extracted with CH_2Cl_2 (160 mL) and EtOAc (2 × 160 mL), and the combined organic solutions were dried ($MgSO_4$), filtered, and concentrated to give the crude product (4.74 g, 100% yield) as a white solid. Crystallization from hot benzene afforded **16** (2.03 g, 43% yield) as white needles: mp 101−103 °C; IR ($CHCl_3$) 2990 (w), 1732 (s), 1510 (m), 1450 (w), 1305 (w), 1230 (m), 1145 (m), 1044 (s), 995 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (br s, 1 H), 7.33 (s, 5 H), 5.11 (s, 2 H), 4.10 (p, J = 7.2 Hz, 2 H), 3.61 (d, J = 11.5 Hz, 2 H), 1.28 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.3, 136.1, 128.5, 128.2, 128.1, 67.3, 62.7, 37.0 (d, J_{CP} = 159 Hz), 16.2; ^{31}P NMR (202.5 MHz, $CDCl_3$) δ 24.8; high-resolution mass spectrum (CI, NH_3) *m/z* 274.0829 [$(M + H)^+$; calcd for $C_{11}H_{17}NO_5P$ 274.0844].

Anal. Calcd for $C_{11}H_{16}NO_5P$: C, 48.35; H, 5.90; N, 5.13. Found: C, 48.16; H, 5.94; N, 5.03.

Benzyl Ethyl [(*N*-Benzyloxycarbonyl)aminomethyl]phosphonate [(±)-21]. At ambient temperature, a solution of monoester **16** (66 mg, 0.242 mmol) in CH_2Cl_2 (1.9 mL) was treated with thionyl chloride (53 μL, 0.725 mmol). After 30 min, the mixture was concentrated and the resultant opaque oil was exposed to high vacuum (≤1 mmHg) for 3 h. The crude chloridate (±)-**19** was dissolved in CH_2Cl_2 (1.9 mL), Et_3N (37 μL, 0.266 mmol) and then benzyl alcohol (125 μL, 1.208 mmol) were added, and the solution was stirred for 45 min. Concentration and flash chromatography (33% hexanes/EtOAc) afforded (±)-**21** (71.1 mg, 81% yield) as a colorless oil: IR ($CHCl_3$) 3460 (m), 3000 (m), 1735 (s), 1520 (s), 1460 (w), 1315 (m), 1240 (s), 1150 (m), 1020 (s), 695 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (m, 10 H), 5.08 (s, 2 H), 5.06 (d, J_{HP} = 9 Hz, 2 H), 4.05 (m, 2 H), 3.62 (dd, J_{HP} = 11.2 Hz, J_{HH} = 6.1 Hz, 2 H), 1.25 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.9, 136.2, 135.9, 128.7, 128.6, 128.5, 128.3, 128.1, 128.0, 68.0 (d, J_{CP} = 7 Hz), 67.3, 62.7, (d, J_{CP} = 7 Hz), 36.8 (J_{CP} = 157 Hz), 16.3 (d, J_{CP} = 6 Hz); ^{31}P NMR (202.5 MHz, $CDCl_3$) δ 23.6; high-resolution mass spectrum (CI, CH_4) *m/z* 364.1318 [$(M + H)^+$; calcd for $C_{18}H_{23}NO_5P$ 364.1315].

Anal. Calcd for $C_{18}H_{22}NO_5P$: C, 59.50; H, 6.10; N, 3.85. Found: C, 59.59; H, 5.99; N, 3.74.

Phosphonamide [(±)-23]. Following the procedure described above for **21**, chloridate **19** was prepared from monoester **16** (51.6 mg, 0.189 mmol) and thionyl chloride (41.0 μL, 0.567 mmol) in CH_2Cl_2 (1.5 mL). The crude chloridate was dissolved in CH_2Cl_2 (1.5 mL), Et_3N (29 μL, 0.208 mmol) and then benzylamine (103 μL, 0.944 mmol) were added, and the solution was stirred for 1 h at ambient temperature. Concentration and flash chromatography (7.5% MeOH/CH_2Cl_2) afforded (±)-**23** (57.9 mg, 85% yield) as a pale yellow wax: IR ($CHCl_3$) 3420 (w), 3250 (w), 3000 (m), 1725 (s), 1515 (s), 1460 (m), 1410 (m), 1305 (m), 1250 (s), 1195 (m), 1145 (m), 1095 (m), 1070 (m), 1035 (s), 960 (s), 910 (w), 880 (w), 690 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.22 (m, 10 H), 5.77 (br s, 1 H), 5.07 (d, J = 5.1 Hz, 2 H), 4.13−4.00 (m, 3 H), 3.92 (m, 1 H), 3.68 (ddd, J = 15.8, 10.5, 6.0 Hz, 1 H), 3.45 (ddd, J = 15.8, 10.8, 5.1 Hz, 1 H), 3.34 (dd, J = 16.8, 7.0 Hz, 1 H), 1.22 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2, 139.6, 136.3, 128.5, 128.1, 128.0, 127.3, 127.2, 67.0, 60.6 (d, J_{CP} = 7 Hz), 44.6, 37.9 (d, J_{CP} = 145 Hz), 16.3 (d, J_{CP} = 6 Hz); ^{31}P NMR (202.5 MHz, $CDCl_3$) δ 27.2; high-resolution mass spectrum (CI, CH_4) *m/z* 363.1472 [$(M + H)^+$; calcd for $C_{18}H_{24}N_2O_4P$ 363.1474].

Anal. Calcd for $C_{18}H_{23}N_2O_4P$: C, 59.66; H, 6.40; N, 7.73. Found: C, 59.86; H, 6.33; N, 7.59.

Diester (17). Following the procedure described above for **15**, amine **14** was prepared from **13** (7.0 g, 0.024 mol) and hydrazine hydrate (1.26 g, 0.025 mol) in absolute ethanol (47 mL). A solution of fluorenylmethyl chloroformate (6.7 g, 0.026 mol) in toluene (20 mL) was cooled to 0 °C, and a solution of crude amine **14** in toluene (40 mL) was added via a pressure-equalizing addition funnel over 30 min. After an additional 30 min, the solution was treated dropwise with Et_3N (4.9 mL, 0.035 mol), warmed to room temperature, and stirred for 9 h. The mixture was then diluted with CH_2Cl_2 (10 mL), filtered, and concentrated. Flash chromatography (5% MeOH−CH_2Cl_2) furnished **17** (3.08 g, 33% yield) as a pale yellow oil: IR ($CHCl_3$) 3420 (w), 3000 (m), 1725 (s), 1510 (m), 1445 (w), 1305 (m), 1240 (s), 1145 (w), 1025 (s), 970 (m), 795 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, J = 7.5 Hz, 2 H), 7.62 (d, J = 7.6 Hz, 2 H), 7.42 (t, J = 7.4 Hz, 2 H), 7.32 (t, J = 7.4 Hz, 2 H), 5.27 (br s, 1 H), 4.40 (d, J = 7.0 Hz, 2 H), 4.25 (t, J = 6.9 Hz, 1 H), 4.17 (m, 4 H), 3.66 (dd, J_{HP} = 10.1 Hz, J_{HH} = 5.9 Hz, 2 H), 1.35 (t, J = 7.0 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2, 143.8, 141.3, 134.1, 127.8, 127.1, 125.0, 123.5, 120.0, 67.3, 62.6 (d, J_{CP} = 6.9 Hz, 2 C), 47.2, 36.7 (d, J_{CP} = 158 Hz), 16.4 (d, J_{CP} = 5.7 Hz, 2 C); high-resolution mass spectrum (CI, CH_4) *m/z* 390.1467 [$(M + H)^+$; calcd for $C_{20}H_{25}NO_5P$ 390.1470].

Monoester (18). Sodium iodide (200 mg, 1.33 mmol) was added to a solution of diester **17** in acetone (8 mL), and the resultant mixture was heated at reflux for 48 h, cooled, and concentrated. The concentrate was diluted with water (50 mL) and washed with EtOAc (2 × 50 mL). The aqueous layer was then acidified to pH with 2 N H_2SO_4 and extracted with EtOAc (3 × 50 mL), and the combined extracts were dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (25% MeOH−$CHCl_3$) gave **18** (168 mg, 35% yield) as a colorless foam: IR ($CHCl_3$) 3420 (br, w), 3000 (br, w), 1725 (s), 1510 (m), 1450 (w), 1310 (w), 1230 (m), 1035 (s), 800 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.09 (br s, 1 H), 7.77 (d, J = 7.5 Hz, 2 H), 7.60 (d, J = 7.5 Hz, 2 H), 7.41 (t, J = 7.3 Hz, 2 H), 7.31 (t, J = 7.3 Hz, 2 H), 5.40 (br s, 1 H), 4.43 (d, J = 6.9 Hz, 2 H), 4.23 (t, J = 6.6 Hz, 1 H), 4.16 (p, J = 7.2 Hz, 2 H), 3.67 (d, J_{HP} = 11.4 Hz, 2 H), 1.35 (qd, J_{HH} = 7.0, J_{HP} = 2.7 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2, 143.7, 141.3, 127.7, 127.1, 125.1, 120.0, 67.4, 62.7, 47.1, 37.1 (d, J_{CP} = 157 Hz), 16.3 (d, J_{CP} = 7 Hz); ^{31}P NMR (202.5 MHz, $CDCl_3$) δ 24.2; high-resolution mass spectrum (CI, CH_4) *m/z* 361.1168 [$(M + H)^+$; calcd for $C_{18}H_{21}NO_5P$ 361.1157.

Phosphonate [(±)-22]. Following the procedure described above for **21**, chloridation of **18** (31.4 mg, 0.087 mmol) with thionyl chloride (11.4 mg, 0.096 mmol) followed by reaction with Et_3N (13.3 μL, 0.208 mmol) and benzyl alcohol (46.9 mg, 0.434 mmol) furnished (±)-**22** (35.0 mg, 89% yield) as a colorless oil after flash chromatography (50% EtOAc−hexanes): IR ($CHCl_3$) 3440 (m), 3220 (m), 3000 (br, w), 1725 (s), 1515 (s), 1450 (m), 1310 (m), 1240 (s), 1150 (m), 1025 (m), 910 (s), 710 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, J = 7.5 Hz, 2 H), 7.60 (d, J = 7.5 Hz, 2 H), 7.45−7.30 (m, 9 H), 5.17 (br s, 1 H), 5.13 (d, J_{HP} = 8.6 Hz, 2 H), 4.41 (d, J = 6.8 Hz, 2 H), 4.22 (t, J= 7.1 Hz, 1 H), 4.13 (m, 2 H), 3.66 (dd, J_{HP} = 11.1 Hz, J_{HH} = 8.0 Hz, 2 H), 1.31 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2, 143.8, 141.3, 136.0, 128.7, 128.6, 128.1, 127.8, 127.1, 125.0, 120.0, 68.0 (d, J_{CP} = 6.2 Hz), 67.3, 62.7 (d, J_{CP} = 5.5 Hz), 47.1, 36.9 (d, J_{CP} = 158 Hz), 16.3 (d, J_{CP} = 5.8 Hz); ^{31}P NMR (202.5 MHz, $CDCl_3$) δ 23.6; high-resolution mass spectrum (CI, CH_4) *m/z* 452.1621 [$(M + H)^+$; calcd for $C_{25}H_{27}NO_5P$ 452.1626].

Phosphonamide [(±)-24]. Following the procedure described above for **21**, chloridation of **18** (33.0 mg, 0.091 mmol) with thionyl chloride (11.9 mg, 0.100 mmol) followed by reaction with benzylamine (48.9

mg, 0.457 mmol) furnished (±)-**24** (26.4 mg, 64% yield) as a pale yellow oil after flash chromatography (gradient elution, 50% EtOAc−hexanes to 7% MeOH−$CHCl_3$): IR ($CHCl_3$) 3405 (w), 3000 (m), 1720 (s), 1510 (m), 1450 (m), 1300 (w), 1235 (m), 1030 (m), 955 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, J = 7.5 Hz, 2 H), 7.60 (d, J = 7.2 Hz, 2 H), 7.41 (t, J = 6.4 Hz, 2 H), 7.32 (m, 7 H), 5.48 (br s, 1 H), 4.40 (m, 2 H), 4.21 (t, J = 6.9 Hz, 1 H), 4.15 (m, 2 H), 4.03 (p, J = 8.2 Hz, 1 H), 3.71 (p, J = 6.3 Hz, 1 H), 3.52 (m, 1 H), 3.14 (m, 1 H), 1.73 (br s, 1 H), 1.30 (t, J = 7.9 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5, 143.8, 141.3, 139.6, 128.7, 128.6, 127.8, 127.4, 127.2, 127.1, 125.1, 120.0, 67.2, 60.8 (d, J_{CP} = 6.5 Hz), 47.2, 44.8, 38.0 (d, J_{CP} = 145 Hz), 16.4 (d, J_{CP} = 6.0 Hz); ^{31}P NMR (202.5 MHz, $CDCl_3$) δ 27.2; high-resolution mass spectrum (CI, CH_4) *m/z* 451.1779 [(M + H)$^+$; calcd for $C_{25}H_{28}N_2O_4P$ 451.1786].

Phosphonamide (54). At room temperature, a solution of monoester **16** (112.3 mg, 0.411 mmol) in CH_2Cl_2 (0.50 mL) was treated with thionyl chloride (58.7 mg, 0.493 mmol), and the resultant mixture was stirred for 30 min and then concentrated. The residue was dissolved in THF (1 mL) and added dropwise over 10 min to a solution of HCl·D-Trp·OEt (99.5 mg, 0.390 mmol) and Et_3N (124.8 mg, 1.23 mmol) in CH_2Cl_2 (1 mL) at 0 °C. The mixture was gradually warmed to room temperature, stirred for 2 h and concentrated. Flash chromatography (2% MeOH−$CHCl_3$) furnished **54** (66.6 mg, 36% yield), a mixture of diastereomers, as a colorless oil: IR ($CHCl_3$) 3490 (w), 3400 (w), 3000 (m), 1735 (s), 1515 (m), 1460 (w), 1420 (w), 1380 (m), 1305 (m), 1250 (s), 1135 (w), 1095 (w), 1040 (s), 965 (w), 910 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.30 (br s, 1 H), 7.54 (dd, J = 13.0, 8.0 Hz, 1 H), 7.38−7.28 (m, 6 H), 7.16 (q, J = 7.5 Hz, 1 H), 7.10 (t, J = 7.5 Hz, 1 H), 7.01 (d, J = 15.9 Hz, 1 H), 5.04 (m, 2 H), 4.38−4.27 (m, 1 H), 3.99−3.94 (m, 1 H), 3.83−3.71 (m, 1 H), 3.67 (s, 3 H), 3.64−3.29 (m, 3 H), 3.25 (d, J = 6.0 Hz, 1 H), 3.17 (d, J = 5.5 Hz, 1 H), 1.14 (q, J = 7.1 Hz, 3 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 174.2, 173.9, 156.2, 136.2, 136.1, 128.5, 128.1, 127.5, 127.2, 123.4, 123.0, 122.2, 119.6, 118.4, 118.3, 111.4, 109.7, 67.0, 60.8, 60.7, 54.3, 54.2, 52.4, 38.5 (d, J_{CP} = 148 Hz), 38.2 (d, J_{CP} = 145 Hz), 30.4, 30.3, 29.9, 29.8, 16.2 (m): high-resolution mass spectrum (CI, NH_3) *m/z* 474.1821 [(M + H)$^+$; calcd for $C_{23}H_{29}N_3O_6P$ 474.1797].

Anal. Calcd for $C_{23}H_{28}N_3O_6P$: C, 58.35; H, 5.96. Found: C, 58.44; H, 5.69.

Ester (39). A solution of monoester (−)-**6** (37.8 mg, 0.069 mmol) and sodium methoxide (3.7 mg, 0.069 mmol) in MeOH (1 mL) was stirred at room temperature for 4 h, diluted with toluene (1 mL), and concentrated. The residue was suspended in CH_2Cl_2 (2 mL), DMF (1 drop) was added, and the mixture was cooled to 0 °C and treated with oxalyl chloride (10.5 mg, 0.082 mmol). After 15 min at 0 °C, MeOH (0.5 mL) was added and the mixture was stirred at room temperature for 3 h. Concentration and flash chromatography (67% EtOAc−hexanes) gave **39** (40.0 mg, 96% yield), a mixture of diastereomers as a colorless glass: IR ($CHCl_3$) 3420 (w), 3005 (w), 2950 (m), 2865 (m), 1735 (s), 1620 (w), 1535 (s), 1520 (s), 1460 (m), 1360 (s), 1330 (w), 1295 (m), 1255 (s), 1175 (m), 1050 (s), 1020 (s), 865 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.07 (t, J = 8.2 Hz, 2 H), 7.75−7.65 (m, 2 H), 7.50−7.45 (m, 2 H), 7.40 (dd, J = 8.6, 16.2 Hz, 2 H), 7.35−7.30 (m, 2 H), 7.25−7.20 (m, 2 H), 5.1−4.9 (m, 3 H), 4.45−4.35 (m, 2 H), 4.27 (dd, J = 6.8, 10.8 Hz, 1 H), 4.15−4.00 (m, 2 H), 3.66 (d, J = 10.8 Hz, 1.5 H), 3.63 (d, J = 10.8 Hz, 1.5 H), 1.85−1.5 (m, 5 H), 1.3−0.8 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.1, 147.8, 147.7, 143.6, 143.5, 143.2, 143.1, 141.3, 128.0, 127.9, 127.8, 127.0, 124.9, 124.8, 124.7, 123.7, 120.1, 120.0, 67.0 (d, J_{CP} = 6 Hz), 66.4 (d, J_{CP} = 7 Hz), 66.2 (d, J_{CP} = 6 Hz), 53.1, 52.4 (d, J_{CP} = 136 Hz), 52.3 (d, J_{CP} = 142 Hz), 47.2, 47.1, 38.6, 38.5, 38.4, 30.5, 30.4, 30.3, 28.2, 28.1, 28.0, 26.0, 25.9, 25.8; ^{31}P NMR (202.5 MHz, $CDCl_3$) δ 27.4; high-resolution mass spectrum (CI, NH_3) *m/z* 587.1978 [(M + NH_4)$^+$; calcd for $C_{30}H_{37}N_3O_7P$ 587.1923].

Anal. Calcd for $C_{30}H_{33}N_2O_7P$: C, 63.82; H, 5.89; N, 4.96. Found: C, 63.63; H, 5.89; N, 5.14.

Phosphonate (40). A solution of monoester (−)-**6** (81.4 mg, 0.140 mmol) and sodium methoxide (7.7 mg, 0.14 mmol) in MeOH (2 mL) was stirred at room temperature for 4 h, diluted with toluene (2 mL), and concentrated. The residue was suspended in CH_2Cl_2 (2 mL), DMF (2 drops) was added, and the mixture was cooled to 0 °C and treated with oxalyl chloride (21.7 mg, 0.170 mmol). After 15 min at 0 °C, benzyl alcohol (1 μL, 30.8 mg, 0.28 mmol) was added dropwise and the mixture was stirred at room temperature for 3 h. Concentration and flash chromatography (50% EtOAc−hexanes) afforded **40** as a mixture of diastereomers which were separated via RP-HPLC. For the minor diastereomer (15.2 mg, 17% yield): colorless oil; $[\alpha]^{25}_D$ +3.1° (*c* 0.98, acetone); IR ($CHCl_3$) 3415 (w), 3005 (w), 2940 (m), 2860 (w), 1725 (s), 1610 (w), 1525 (s), 1510 (s), 1450 (m), 1350 (s), 1330 (w), 1290 (m), 1230 (s), 1040 (s), 1010 (s), 1000 (s), 855 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, J = 8.5 Hz, 2 H), 7.76 (d, J = 7.5 Hz, 2 H), 7.53 (dd, J = 14.4, 7.4 Hz, 2 H), 7.31 (s, 5 H), 7.40−7.20 (m, 6 H), 5.10−4.95 (m, 5 H), 4.43 (dd, J = 10.7, 6.8 Hz, 1 H), 4.36 (dd, J = 10.7, 6.8 Hz, 1 H), 4.20−4.14 (m, 1 H), 4.12 (t, J = 6.5 Hz, 1 H), 1.95−1.91 (m, 5 H), 1.4−0.93 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2, 147.7, 143.7, 143.6, 143.1, 141.3, 135.8, 128.6, 128.1, 127.9, 127.8, 127.0, 124.9, 124.8, 123.7, 120.1, 120.0, 68.1 (d, J_{CP} = 7 Hz), 66.1 (d, J_{CP} = 5 Hz), 67.1, 52.8 (d, J_{CP} = 151 Hz), 47.2, 38.6, 30.5, 28.2, 28.1, 26.0, 25.9, 25.8; high-resolution mass spectrum (CI, NH_3) *m/z* 641.2457 [(M + H)$^+$; calcd for $C_{36}H_{38}N_2O_7P$ 641.2416]. For the major diastereomer (51.3 mg, 56% yield): colorless oil; [α]o(^{25},$_D$) +3.1° (*c* 0.75, acetone); IR ($CHCl_3$) 3440 (w), 3080 (w), 3010 (m), 2940 (m), 2860 (m), 1730 (s), 1610 (w), 1530 (s), 1455 (m), 1380 (w), 1355 (s), 1320 (w), 1290 (m), 1250 (s), 1220 (s), 1110 (w), 1045 (s), 1010 (s), 860 (m), 690 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, J = 8.7 Hz, 2 H), 7.75 (d, J = 7.5 Hz, 2 H), 7.51 (dd, J = 7.4, 0.7 Hz, 2 H), 7.31 (s, 5 H), 7.40−7.20 (m, 6 H), 5.08 (d, J = 9.2 Hz, 1 H), 5.07 (d, J = 8.9 Hz, 2 H), 4.97 (d, J = 8.0 Hz, 2 H), 4.46 (dd, J = 10.7, 6.7 Hz, 1 H), 4.31 (dd, J = 10.7, 6.8 Hz, 1 H), 4.20−4.15 (m, 2 H), 1.95−1.60 (m, 5 H), 1.31−1.11 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2, 147.6, 143.6, 143.5, 143.2, 143.1, 141.3, 135.7, 128.7, 128.6, 128.1, 127.7, 127.0, 124.9, 124.7, 123.6, 120.0, 119.9, 68.1 (d, J_{CP} = 7.0 Hz), 67.0, 66.2 (d, J_{CP} = 6.8 Hz), 52.7 (d, J_{CP} = 153 Hz), 47.1, 38.6, 38.5, 30.5, 30.4, 28.1, 28.0, 25.9, 25.8, 25.7; high-resolution mass spectrum (CI, NH_3) *m/z* 641.2439 [(M + H)$^+$; calcd for $C_{36}H_{38}N_2O_7P$ 641.2416].

Anal. Calcd for $C_{36}H_{37}N_2O_7P$: C, 67.94; H, 5.82; N, 4.37. Found: C, 66.94; H, 6.11; N, 4.19.

Phosphonate (42). A solution of monoester (−)-**6** (110.1 mg, 0.200 mmol) and sodium methoxide (10.8 mg, 0.200 mmol) in MeOH (5 mL) was stirred at room temperature for 4 h and concentrated. The residue was suspended in CH_2Cl_2 (2 mL), and DMF (4 drops) was added. The mixture was then cooled to 0 °C and treated with oxalyl chloride (30.6 mg, 0.24 mmol). After 15 min at 0 °C, a solution of tryptophol (48.6 mg, 0.300 mmol) in CH_2Cl_2 (1 mL) was introduced dropwise. The resultant mixture was stirred for 1 h at room temperature and concentrated. Flash chromatography (3% MeOH−CH_2Cl_2) provided **42** (79.8 mg, 58% yield), a mixture of diastereomers, as a yellow oil: IR ($CHCl_3$) 3395 (w), 3335 (w), 3000 (w), 2940 (m), 2860 (w), 1725 (s), 1610 (w), 1520 (s), 1450 (m), 1350 (s), 1320 (w), 1250 (m), 1210 (m), 1060 (m), 1010 (s), 910 (s), 860 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.20 (br s, 1 H), 7.98 (d, J = 8.7 Hz, 2 H), 7.74 (d, J = 7.6 Hz, 2 H), 7.54 (d, J = 7.5 Hz, 1 H), 7.51 (d, J = 7.6 Hz, 1 H), 7.35 (t, J = 7.5 Hz, 2 H), 7.29−7.21 (m, 5 H), 7.15 (td, J = 7.5, 1.0 Hz, 1 H), 7.07 (td, J = 7.5, 0.9 Hz, 1 H), 6.95 (d, J = 2.1 Hz, 1 H), 5.07 (d, J = 10.7 Hz, 1 H), 4.86 (d, J = 7.9 Hz, 2 H), 4.31 (dd, J = 7.0, 3.5 Hz, 1 H), 4.35−4.25 (m, 3 H), 4.11 (t, J = 6.7 Hz, 1 H), 4.08 (m, 1 H), 3.09 (t, J = 6.5 Hz, 2 H), 1.90−1.55 (m, 6 H), 1.30−0.82 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2, 147.5, 143.6, 143.5, 143.3, 141.3, 136.1, 127.7, 127.6, 127.2, 126.9, 124.9, 124.7, 123.5, 122.4, 122.1, 120.0, 119.9, 119.5, 118.4, 111.2, 110.9, 66.9, 66.6 (J_{CP} = 7 Hz), 66.0 (J_{CP} = 7 Hz), 52.6 (J_{CP} = 154 Hz), 47.1, 38.5, 30.3, 28.0, 27.9, 26.5, 25.9, 25.8, 25.7; high-resolution mass spectrum (CI, NH_3) *m/z* 694.2631 [(M + H)$^+$; calcd for $C_{39}H_{41}N_2O_7P$ 694.2682].

Phosphonate (45). A solution of hydrazine hydrate (0.78 g, 15.5 mmol) and diester **44** (3.98 g, 14.8 mmol) in MeOH (25 mL) was stirred at room temperature for 80 h and filtered. The filtrate was concentrated without heating to give a yellow oil which was dissolved in toluene (10 mL). The resultant solution was added dropwise to a solution of fluorenylmethyl chloroformate (4.78 g, 18.5 mmol) in toluene (20 mL) at 0 °C. The reaction mixture was then treated dropwise with Et_3N (1.87 g, 18.5 mmol), warmed to room temperature and diluted with CH_2Cl_2 (5 mL). After 8 h the mixture was filtered and concentrated. Flash chromatography (50% EtOAc−hexanes) gave **45** (1.45 g, 28% yield) as a colorless wax: IR ($CHCl_3$) 3450 (w), 3005 (m), 2960 (m), 1730 (s), 1510 (s), 1450 (m), 1310 (m), 1230 (s), 1150 (m), 1060 (s),

1040 (s), 720 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, J = 7.4 Hz, 2 H), 7.58 (d, J = 7.4 Hz, 2 H), 7.37 (t, J = 7.4 Hz, 2 H), 7.28 (t, J = 7.4 Hz, 2 H), 5.72 (br s, 1 H), 4.40 (d, J = 6.8 Hz, 2 H), 4.19 (t, J = 6.8 Hz, 1 H), 3.75 (d, J = 10.7 Hz, 6 H), 3.65 (dd, J = 10.7, 6.1 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2, 143.6, 141.2, 127.6, 126.9, 124.9, 119.9, 67.1, 53.0, 47.0, 35.7 (d, J_{CP} = 158 Hz); high-resolution mass spectrum (CI, NH_3) *m/z* 362.1128 [$(M + H)^+$; calcd for $C_{18}H_{21}NO_5P$ 362.1157].

Diacid (46). A mixture of diester **45** (591.9 mg, 1.64 mmol) and concentrated HCl (10 mL) was heated at 100 °C for 4 h with vigorous stirring and then cooled, diluted with water (10 mL), and extracted with EtOAc (3 × 65 mL). The combined extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated. RP-HPLC afforded **46** (330.2 mg, 60% yield) as a colorless solid: mp 96−102 °C (dec.); IR ($CHCl_3$) 3300 (s), 3400−2000 (br), 1695 (s), 1550 (s), 1450 (w), 1400 (w), 1310 (w), 1290 (m), 1170 (m), 1110 (w), 1080 (w), 1020 (m), 1010 (m), 985 (m), 935 (m), 650 (w), 580 (w) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 7.89 (d, J = 7.4 Hz, 2 H), 7.75 (d, J = 7.4 Hz, 2 H), 7.48 (t, J = 5.3 Hz, 1 H), 7.42 (t, J = 7.4 Hz, 2 H), 7.33 (t, J = 7.3 Hz, 2 H), 4.26 (d, J = 6.5 Hz, 2 H), 4.21 (t, J = 6.5 Hz, 1 H), 3.30 (dd, J = 11.2, 5.9 Hz, 2 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 156.2, 143.9, 140.7, 127.6, 127.1, 125.4, 120.1, 65.9, 36.6, 37.7; high-resolution mass spectrum (CI, NH_3) *m/z* 333.0742 [M^+; calcd for $C_{16}H_{16}NO_5P$ 333.0766].

Monoester (47). Sodium methoxide (99.4 mg, 1.84 mmol) was added to a solution of diacid **46** (291.9 mg, 0.88 mmol) in MeOH (5 mL), and the resultant mixture was stirred at room temperature for 4 h, diluted with toluene (2 mL), and concentrated. The residue was suspended in CH_2Cl_2 (10 mL) and DMF (6 drops), and the mixture was then cooled to 0 °C and treated with oxalyl chloride (277.9 mg, 2.19 mmol). After 15 min at 0 °C, a solution of *p*-nitrobenzyl alcohol (335.3 mg, 2.19 mmol) in CH_2Cl_2 (2 mL) and THF (0.15 mL) was added dropwise. The mixture was warmed to room temperature, stirred for 15 h, and then diluted with CH_2Cl_2 (100 mL) and washed with saturated aqueous $NaHCO_3$, water, and brine (100 mL each). The organic layer was dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (gradient elution, 67−100% hexanes−EtOAc) furnished the intermediate diester (220.5 mg, 52% yield). A solution of the diester (111.2 mg, 0.23 mmol) in acetone (4 mL) was treated with sodium iodide (34.5 mg, 0.23 mmol), heated at reflux for 1 h, and then concentrated. The residue was dissolved in CH_2Cl_2 (100 mL), and the solution was washed with 2 N HCl (100 mL) and brine and concentrated. RP-HPLC gave **47** (51.6 mg, 48% yield) as an amorphous solid: IR ($CHCl_3$) 3460 (w), 3500−2000 (br), 1730 (s), 1615 (m), 1525 (s), 1480 (w), 1470 (w), 1455 (m), 1355 (s), 1315 (m), 1230 (br, s), 1150 (s), 1110 (w), 1050 (s), 1015 (s), 860 (m), 720 (w) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.18 (d, J = 8.5 Hz, 2 H), 7.89 (d, J = 7.5 Hz, 2 H), 7.70 (m, 1 H), 7.71 (d, J = 7.5 Hz, 2 H), 7.64 (d, J = 8.4 Hz, 2 H), 7.41 (t, J = 7.4 Hz, 2 H), 7.31 (t, J = 7.4 Hz, 2 H), 5.12 (d, J = 7.2 Hz, 2 H), 4.27 (d, J = 7.0 Hz, 2 H), 4.19 (t, J = 7.0 Hz, 1 H), 3.49 (dd, J = 10.1, 6.0 Hz, 2 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 156.2, 146.9, 145.1, 143.7, 140.7, 127.8, 127.6, 127.0, 125.2, 123.3, 120.0, 65.9, 64.8 (d, J_{CP} = 5 Hz), 46.6, 36.9 (d, J_{CP} = 155 Hz); high-resolution mass spectrum (CI, negative ion) *m/z* 467.1013 [$(M - H)^+$; calcd for $C_{23}H_{20}N_2O_7P$ 467.1008].

Diester 50. Benzyl chloroformate (260.5 mg, 1.53 mmol) was dissolved in CH_2Cl_2 (2 mL) and added to a solution of amine (*R*)-**49**[40] (253.8 mg, 1.02 mmol) in CH_2Cl_2 (5 mL) at 0 °C. The mixture was treated with Et_3N (175.2 mg, 1.73 mmol), stirred at room temperature for 22 h and then concentrated. Flash chromatography (67% EtOAc−hexanes) gave **50** (253.8 mg, 65% yield) as a colorless foam: IR ($CHCl_3$) 3440 (w), 3000 (m), 2940 (s), 2860 (m), 1725 (s), 1505 (s), 1450 (w), 1290 (m), 1230 (s), 1050 (s), 1025 (s), 970 (m), 550 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35 (m, 5 H), 5.16 (d, J = 12.2 Hz, 1 H), 5.11 (s, 1 H), 5.08 (d, J = 12.2 Hz, 1 H), 4.10 (m, 5 H), 3.30 (t, J = 7.0 Hz, 3 H), 2.00−1.00 (m, 11 H), 1.24 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2, 136.3, 128.4, 128.1, 128.0, 67.1, 62.2 (d, J_{CP} = 7 Hz), 52.4 (d, J_{CP} = 153 Hz), 38.7, 38.6, 30.6, 30.5, 27.9, 26.1, 25.9, 25.8, 16.3 (d, J_{CP} = 5 Hz); high-resolution mass spectrum (CI, NH_3) *m/z* 384.1931 [$(M + H)^+$; calcd for $C_{19}H_{31}NO_5P$ 384.1940].

Diester (56). Sodium methoxide (5.9 mg, 0.109 mmol) was added to a suspension of monoester (−)-**6** (60.2 mg, 0.109 mmol) in dry MeOH (3 mL), and the mixture was stirred at room temperature for 4 h and then concentrated. The residue was dissolved in CH_2Cl_2 (4 mL) containing DMF (2 drops), and the solution was cooled to 0 °C and treated with oxalyl chloride (16.7 mg, 0.131 mmol). After 15 min at 0 °C, 1-pentanol (1 μL, 14.5 mg, 0.164 mmol) was introduced, and the mixture was then stirred at room temperature for 3 h. Concentrated and flash chromatography (67% hexanes−EtOAc) provided **56** (53.2 mg, 78% yield) as a mixture of diastereomers which were separated via RP-HPLC. For the major diastereomer: colorless oil; $[\alpha]^{25}_D$ +4.3° (*c* 0.19, MeOH); IR ($CHCl_3$) 3440 (w), 3000 (w), 2860 (w), 1940 (m), 1725 (s), 1610 (w), 1525 (s), 1510 (s), 1465 (m), 1350 (s), 1320 (w), 1290 (m), 1240 (m), 1055 (m), 1010 (s), 990 (s), 860 (m), 755 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, J = 8.7 Hz, 2 H), 7.77 (d, J = 7.6 Hz, 2 H), 7.56 (dd, J = 10.7, 7.4 Hz, 2 H), 7.47 (d, J = 8.7 Hz, 2 H), 7.40 (dd, J = 12.7, 7.4 Hz, 2 H), 7.29 (m, 2 H), 5.15 (m, 2 H), 4.96 (d, J = 10.7 Hz, 1 H), 4.45 (dd, J = 10.7, 6.9 Hz, 1 H), 4.37 (dd, J = 10.7, 6.9 Hz, 1 H), 4.16 (t, J = 6.9 Hz, 1 H), 4.09 (ddd, J = 18.2, 10.7, 4.5 Hz, 1 H), 4.03 (m, 2 H), 1.89−1.59 (m, 8 H), 1.30−1.03 (m, 9 H), 0.86 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2, 147.0, 143.7, 143.6, 141.4, 128.0, 127.9, 127.0, 124.9, 124.8, 123.7, 120.1, 120.0, 67.1, 66.7 (d, J_{CP} = 7.7 Hz), 66.1, 52.6 (d, J_{CP} = 151 Hz), 47.2, 38.6, 30.6, 30.5, 30.2, 28.2, 27.6, 26.0, 25.9, 22.1, 13.9; high-resolution mass spectrum (CI, NH_3) *m/z* 621.2706 [$(M + H)^+$; calcd for $C_{34}H_{42}N_2O_7P$ 621.2729].

For the minor diastereomer: colorless oil; $[\alpha]^{25}_D$ −7.7° (*c* 1.19, MeOH); IR ($CHCl_3$) 3440 (w), 3010 (m), 2940 (s), 2870 (m), 1730 (s), 1615 (w), 1530 (s), 1480 (w), 1470 (w), 1455 (m), 1355 (s), 1320 (m), 1290 (br, s), 1250 (s), 1110 (w), 1030 (br, s), 900 (w), 860 (s), 560 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, J = 8.7 Hz, 2 H), 7.75 (d, J = 7.5 Hz, 2 H), 7.54 (dd, J = 15.5, 7.5 Hz, 2 H), 7.44 (d, J = 8.7 Hz, 2 H), 7.38 (t, J = 7.5 Hz, 2 H), 7.29−7.25 (m, 2 H), 5.14−5.03 (m, 3 H), 4.47 (dd, J = 10.7, 6.8 Hz, 1 H), 4.31 (dd, J = 10.7, 6.8 Hz, 1 H), 4.14−3.97 (m, 6 H), 1.91−1.63 (m, 8 H), 1.33−1.02 (m, 9 H), 0.87 (m, 3 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 156.1, 147.6, 143.5, 141.3, 127.7, 127.0, 124.9, 124.7, 123.7, 120.0, 66.9, 66.6 (d, J_{CP} = 7.4 Hz), 66.3 (d, J_{CP} = 6.5 Hz), 52.6 (d, J_{CP} = 153 Hz), 47.1, 38.6, 30.5, 30.3, 30.1, 30.0, 28.0, 27.9, 27.5, 26.0, 25.9, 25.8, 22.1, 13.9; high-resolution mass spectrum (CI, NH_3) *m/z* 621.2711 [$(M + H)^+$; calcd for $C_{34}H_{42}N_2O_7P$ 621.2729].

Coupling of (−)-6 with 4-Aminobutan-1-ol. A suspension of monoester (−)-**6** (157.4 mg, 0.286 mmol) in dry MeOH (4 mL) was treated with sodium methoxide (15.4 mg, 0.286 mmol), stirred at room temperature under argon for 4 h, and concentrated. The residue was dried azeotropically with benzene and dissolved in CH_2Cl_2 (6 mL), and the solution was cooled to 0 °C. DMF (20 μL) was added followed by oxalyl chloride (43.5 mg, 0.343 mmol). After 15 min at 0 °C, the solution was concentrated, the residue was redissolved in CH_2Cl_2 (6 mL), and 4-aminobutan-1-ol (76.5 mg, 0.858 mmol) was introduced. The resultant mixture was stirred at room temperature for 3 h and then concentrated. Flash chromatography (gradient elution, 5−50% MeOH−CH_2Cl_2) gave two fractions. The first contained **58** and **60**, separable by flash chromatography (gradient elution, 1−2% MeOH−CH_2Cl_2). For **58**: colorless oil; ^{31}P NMR (202.5 MHz, $CDCl_3$) δ 30.8; high-resolution mass spectrum (FAB) *m/z* 622.2690 [$(M + H)^+$; calcd for $C_{33}H_{40}N_3O_7P_1$ 622.2682]. Analytical data for **60**: colorless oil; ^{31}P NMR (202.5 MHz, $CDCl_3$) δ 30.7, 26.2; high-resolution mass spectrum (FAB) *m/z* 1154.4521 [$(M + H)^+$; calcd for $C_{62}H_{69}N_5O_{13}P_2$ 1154.4445]. The second fraction consisted of unreacted (−)-**6** and the major reaction product **57**. This mixture was dissolved in pyridine (0.5 mL) containing acetic anhydride (0.50 mL), and the solution was stirred at room temperature for 3 h and concentrated. Flash chromatography (2% MeOH−CH_2Cl_2) furnished **59** as a colorless oil: IR ($CHCl_3$) 3450 (w), 3005 (m), 2940 (m), 1725 (s), 1675 (m), 1530 (s), 1455 (m), 1350 (s), 1325 (w), 1290 (w), 1240 (m), 1155 (w), 1065 (s), 1030 (s), 860 (w), 560 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.16−8.13 (m, 2 H), 7.78−7.75 (m, 2 H), 7.60−7.25 (m, 8 H), 5.84−5.77 (m, 1 H), 5.45 (d, J = 10.7 Hz, 1 H), 5.22−5.10 (m, 2 H), 4.51−4.46 (m, 1 H), 4.35−4.29 (m, 1 H), 4.15 (t, J = 6.3 Hz, 1 H), 4.11−4.01 (m, 3 H), 3.23−3.18 (m, 2 H), 1.98−1.94 (s, 3 H), 1.89−1.53 (m, 9 H), 1.33−0.88 (m, 6 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 170.1, 156.3, 147.7, 143.6, 143.2, 141.3, 128.0, 127.0, 127.8, 127.0, 125.0, 124.9, 124.8, 124.7, 123.7, 120.1, 120.0, 77.2, 67.0 (d, J_{CP} = 9 Hz), 66.1 (d, J_{CP} = 7 Hz), 63.9, 52.6 (d J_{CP} = 151 Hz), 47.1, 39.1, 38.8, 38.6, 38.5, 38.4, 38.3,

30.6, 30.5, 30.4, 30.3, 28.2, 28.1, 27.8, 27.7, 27.5, 27.4, 26.2, 26.0, 25.9, 25.6, 23.2; ^{31}P NMR (202.5 MHz, $CDCl_3$) δ 26.1; high-resolution mass spectrum (FAB) *m/z* 664.2753 [(M + H)$^+$; calcd for $C_{35}H_{43}N_3O_8P$ 664.2787].

Coupling of (−)-6 with 4-(*N*-Acetylamino)butan-1-ol. A suspension of monoester (−)-**6** (94.2 mg, 0.171 mmol) in dry MeOH (3 mL) was treated with sodium methoxide (9.2 mg, 0.171 mmol), and the mixture was stirred at room temperature for 4 h and then concentrated. The residue was dried azeotropically with benzene (5 mL) and dissolved in CH_2Cl_2 (4 mL). The solution was cooled to 0 °C, and DMF (2 drops) and oxalyl chloride (23.9 mg, 0.188 mmol) were sequentially introduced. After 15 min at 0 °C, a solution of 4-(*N*-acetylamino)-butan-1-ol (50.0 mg, 0.381 mmol) in CH_2Cl_2 (2 mL) was added, and the mixture was stirred at room temperature for 5 h. Concentration and flash chromatography (2% MeOH−CH_2Cl_2) gave **59** (77.6 mg, 68% yield), a mixture of diastereomers, as a colorless oil.

Coupling of 16 with 4-Aminobutan-1-ol. A solution of monoester **16** (63.1 mg, 0.235 mmol) in dry MeOH (2 mL) sodium methoxide (12.7 mg, 0.235 mmol), stirred at room temperature for 4 h and then concentrated. The residue was dissolved in CH_2Cl_2 (2 mL), the solution was cooled to 0 °C, and DMF (2 drops) and oxalyl chloride (35.8 mg, 0.282 mmol) were introduced sequentially. After 15 min at 0 °C, toluene (1 mL) was added and the mixture was concentrated. The residue was taken up in CH_2Cl_2 (2 mL) and treated with 4-aminobutan-1-ol (62.9 mg, 0.706 mmol), and the resultant mixture was stirred at room temperature for 1 h and concentrated. An aliquot of the crude reaction mixture was analyzed by analytical RP-HPLC. The following relative ratios were obtained: (±)-**61** (1.49), (±)-**62** (1.00). Flash chromatography (gradient elution, 3−50% MeOH−CH_2Cl_2) afforded (±)-**61** (21.9 mg, 27% yield) and (±)-**64** (9.5 mg, 13.5% yield). For (±)-**64**: colorless oil; IR ($CHCl_3$) 3470 (m), 3280 (br), 3000 (m), 1725 (s), 1515 (s), 1455 (w), 1400 (w), 1345 (w), 1305 (m), 1240 (br, s), 1150 (m), 1100 (w), 1035 (s), 970 (s), 840 (w), 690 (w), 500 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.27 (m, 10 H), 5.57 (br d, J = 2.9 Hz, 1 H), 5.41 (br s, 1 H), 5.11 (s, 2 H), 5.10 (s, 2 H), 4.15−3.97 (m, 6 H), 3.62 (m, 3 H), 3.43 (m, 1 H), 2.93 (m, 2 H), 1.65 (p, J = 6.8 Hz, 2 H), 1.51 (p, J = 7.0 Hz, 2 H), 1.29−1.24 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5, 156.2, 136.2, 128.4, 128.2, 128.1, 67.2, 67.1, 65.8 (d, J_{CP} = 6 Hz), 62.8 (d, J_{CP} = 6 Hz), 60.6 (d, J_{CP} = 6 Hz), 40.2, 37.9 (d, J_{CP} = 144 Hz), 36.5 (dd, J_{CP} = 158, 8.0 Hz), 28.1, 27.2, 16.4; ^{31}P NMR (202.5 MHz, $CDCl_3$) δ 23.5, 27.7; high-resolution mass spectrum (FAB) *m/z* 600.2210; [(M + H)$^+$; calcd for $C_{26}H_{40}N_3O_9P_2$ 600.2240]. For (±)-**61**: colorless oil; IR ($CHCl_3$) 3430 (m), 3300 (br, m), 3000 (s), 2940 (s), 1725 (s), 1520 (s), 1460 (w), 1410 (w), 1305 (m), 1250 (br, s), 1150 (m), 1100 (m), 1040 (s), 965 (m), 910 (w), 850 (w), 690 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39−7.29 (m, 5 H), 5.79 (m, 1 H), 5.11 (s, 2 H), 4.10−3.97 (m, 2 H), 3.67 (ddd, J = 15.8, 10.8, 7.1 Hz, 1 H), 3.61 (t, J = 5.7 Hz, 2 H), 3.41 (ddd, J = 15.7, 10.8, 5.0 Hz, 1 H), 3.14 (br s, 1 H), 2.92 (m, 2 H), 2.50 (br s, 1 H), 1.53 (m, 4 H), 1.28 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 156.5, 136.2, 128.5, 128.1, 128.0, 67.1, 62.0, 60.4 (d, J_{CP} = 6 Hz), 40.5, 37.7 (d, J_{CP}= 145 Hz), 29.4, 28.4, 28.3, 16.4, 16.3; ^{31}P NMR (202.5 MHz, $CDCl_3$) δ 28.1; high-resolution mass spectrum (CI, NH_3) *m/z* 344.1477 [(M + H)$^+$; calcd for $C_{15}H_{25}N_2O_5P$ 344.1501].

For acetylation of the *O*-coupled adduct **63**, a mixture of **64** and **62** was dissolved in pyridine (1 mL) and acetic anhydride (0.5 mL). The resultant solution was stirred at room temperature for 1 h and concentrated. Flash chromatography (2% MeOH−CH_2Cl_2) furnished (±)-**63** (8.8 mg, 10% yield) as a colorless oil: IR ($CHCl_3$) 3450 (m), 3350 (br, w), 3005 (m), 1725 (s), 1760 (s), 1515 (s), 1450 (w), 1370 (w), 1310 (m), 1235 (br, s), 1145 (m), 1020 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40−7.31 (m, 5 H), 5.90 (br s, 1 H), 5.33 (m, 1 H), 5.12 (s, 2 H), 4.16−4.01 (m, 4 H), 3.63 (ddd, J = 10.5, 6.0, 3.5 Hz, 2 H), 3.25 (q, J = 7.0 Hz, 2 H), 1.96 (s, 3 H), 1.67 (m, 2 H), 1.57 (q, J = 7.0 Hz, 2 H), 1.31 (t, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 170.3, 156.2, 136.1, 128.5, 128.3, 128.0, 67.2, 66.0 (d, J_{CP} = 7 Hz), 62.7 (d, J_{CP} = 6 Hz), 38.9, 36.6 (d, J_{CP} = 158 Hz), 27.7, 27.6, 25.5, 23.2, 16.4 (d, J_{CP} = 5 Hz); high-resolution mass spectrum (CI, NH_3) *m/z* 387.1658 [(M + H)$^+$; calcd for $C_{17}H_{28}N_2O_6P$ 387.1685].

Coupling of 16 with 4-Aminobutan-1-ol via 76. A solution of monoester **16** (105.2 mg, 0.392 mmol) in dry MeOH (3 mL) sodium methoxide (21.1 mg, 0.392 mmol), stirred at room temperature for 4 h and then concentrated. The residue was dissolved in CH_2Cl_2 (3 mL), the solution was cooled to 0 °C, and DMF (2 drops) and oxalyl chloride (59.6 mg, 0.47 mmol) were introduced sequentially. After 15 min at 0 °C, toluene (1.5 mL) was added and the mixture was concentrated. The residue was taken up in CH_2Cl_2 (3 mL), cooled to 0 °C, and treated with triethylamine (TEA 43.5 mg, 0.429 mmol). After 15 min, the reaction was warmed to room temperature and treated with 4-aminobutan-1-ol (104.2 mg, 1.17 mmol). The resultant mixture was stirred at room temperature for 1 h and concentrated. An aliquot of the crude reaction mixture was analyzed by analytical RP-HPLC. The following relative ratios were obtained: (±)-**61** (0.11), (±)-**62** (1.00). Flash chromatography (gradient elution, 3−50% MeOH−CH_2Cl_2) afforded (±)-**61** (7.0 mg, 5%) and (±)-**64** (12.3mg, 13%). Isolation of (±)-**62** as its N-acyl derivative gave (±)-**63** (50 mg, 35%).

Coupling of 16 with 4-Aminobutan-1-ol and Triethylamine. A solution of monoester **16** (101.2 mg, 0.375 mmol) in dry MeOH (3 mL) sodium methoxide (20.3 mg, 0.375 mmol) was stirred at room temperature for 4 h and then concentrated. The residue was dissolved in CH_2Cl_2 (3 mL), the solution was cooled to 0 °C, and DMF (2 drops) and oxalyl chloride (57.3 mg, 0..452 mmol) were introduced sequentially. After 15 min at 0 °C, toluene (1.5 mL) was added and the mixture was concentrated. The residue was taken up in CH_2Cl_2 (3 mL) and treated with a mixture of 4-aminobutan-1-ol (100.2 mg, 1.13 mmol) and TEA (41.8 mg, 0.413 mmol) in CH_2Cl_2 (0.5 mL), and the resultant mixture was stirred at room temperature for 1 h and concentrated. An aliquot of the crude reaction mixture was analyzed by analytical RP-HPLC. The following relative ratios were obtained: (±)-**61** (1.22), (±)-**62** (1.00). Flash chromatography (gradient elution, 3−50% MeOH−CH_2Cl_2) afforded (±)-**61** (34 mg, 23%) and (±)-**64** (21 mg, 18%). Isolation of (±)-**62** as the *N*-acyl derivative gave (±)-**63** (21.5 mg, 15%)

Reaction Monitoring via ^{31}P NMR Spectroscopy: A Representative Experiment. An oven-dried NMR tube was charged with monoester **16** (10 mg, 0.037 mmol) and dry chloroform-*d* (0.7 mL) under argon. Following acquisition of the ^{31}P NMR spectrum, the mixture was treated with a solution of freshly distilled thionyl chloride (2 M in $CDCl_3$, 37 μL, 0.073 mmol). The tube was shaken periodically over 30 min, and the solution was then concentrated with a stream of dry argon. The resultant oil was exposed to high vacuum (≤1 mmHg) for 1 h and dissolved in dry chloroform-*d* (0.7 mL). A ^{31}P NMR spectrum was acquired, and the Fmoc monoester **18** (13 mg, 0.037 mmol) was then added. After 2.4 h, a ^{31}P NMR spectrum showed the presence of unreacted **18** and the anhydrides **29**, **30**, and **38**. After treatment of the reaction mixture with dry triethylamine (5 μL, 0.037 mmol), the NMR spectrum was consistant with formation of the phosphonyl triethylammonium salt **76**, accompanied by anhydrides **29**, **30**, and **38**. This mixture was then allowed to react with dry benzyl alcohol (11 μL, 0.11 mmol). After 10 min the ^{31}P NMR spectrum revealed complete conversion of **76** to **21** (X = O); **29**, **30**, and **38** did not react.

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