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Optically Active Alkyl Phenyl Phosphoramidates: Preparation and Stereochemistry of Acid-catalyzed Alcoholysis[1]

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Both enantiomers of methyl (or ethyl) phenyl phosphoramidate (**8**, **13**) were prepared from the corresponding diastereomeric amidates of L-phenylalanine ester (**5**, **10**), *via* a transaminative reaction involving the following sequence: N-chlorination, treatment with sodium methoxide, and mild acid-catalyzed hydrolysis of the resulting amino acetal (**7**, **12**). Stereochemical studies of H^+- and BF_3-catalyzed alcoholyses of **8** and **13** indicated that the nature of the acid catalyst had a profound effect on the steric course of the reaction. Complete stereospecificity observed in H^+ catalysis was ascribed to direct displacement with inversion of configuration at phosphorus (A-2 mechanism). On the other hand, BF_3 catalysis, which produced both inversion (70%) and retention product (30%), was explained in terms of (1) a pentacoordinate intermediate mechanism for retention product formation and (2) a dual mechanism, pentacoordinate intermediate and direct displacement A-2 mechanisms, for inversion product formation.

Keywords——N-phosphoryl phenylalanine ethyl ester; optically active phosphoramidate; transamination; chiral alkyl phenyl phosphoramidate; alcoholysis of phosphoramidates; direct displacement A-2 mechanism; pentacoordinate intermediate mechanism; optically active dialkyl phenyl phosphates

Previously we investigated the stereochemistry of acid-catalyzed methanolysis of various phosphinamides,[3] and showed that the mechanism of the reaction could be classified into three categories: 1) direct displacement mechanism (A-2), 2) unimolecular dissociative mechanism (A-1), and 3) associative pentacoordinate intermediate mechanism (Westheimer's mechanism), depending on the structure of the substrate, the nature of the leaving amino groups, and the acidity of the reaction medium.

Our continuing interest in the chemistry of phosphorus amides in general led us next to a stereochemical investigation of the acid-catalyzed solvolysis of phosphoramidates. Despite their chemical and biological importance, the stereochemical course of acid-catalyzed P–N bond cleavage of phosphoramidates has not been studied systematically. An A-2 mechanism with inversion of configuration at phosphorus has been accepted without any stereochemical evidence; Garrison and Boozer[4] suggested an A-2 mechanism based on a kinetic study of the hydrolysis of 2,4-dichlorophenyl methyl N-alkylphosphoramidates.

As our initial investigation in this field, we have recently studied the acid-catalyzed methanolysis of the *cis*-(and *trans*)-2-amino-1,3,2-dioxaphosphorinane-2-oxide system and found that the reaction certainly proceeded with complete inversion of configuration when H^+ was employed, whereas under BF_3 catalysis both inversion and retention products were formed.[5] The most reasonable explanation for the latter result was the participation of a pentacoordinate intermediate mechanism. However, another possibility, which involves ring

1) This work was presented in part at the 46th Hokuriku Branch Meeting of the Pharmaceutical Society of Japan, Kanazawa, June 1978.
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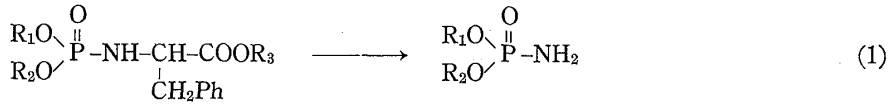
3) *a*) T. Koizumi, Y. Kobayashi, and E. Yoshii, *J. Chem. Soc. Chem. Commun.*, **1974**, 678; *b*) *Idem*, *Chem. Pharm. Bull.* (Tokyo), **24**, 834 (1976); *c*) *Idem*, *Tetrahedron Lett.*, **1976**, 2853; *d*) T. Koizumi, *Yukigosei Kagaku Kyokaishi*, **34**, 137 (1976).
4) A.W. Garrison and C.E. Boozer, *J. Am. Chem. Soc.*, **90**, 3486 (1968).
5) T. Koizumi, Y. Kobayashi, and E. Yoshii, *Heterocycles*, **9**, 1723 (1978).

opening and subsequent ring closure, could not be completely ruled out.[6] In order to eliminate this possibility, it seemed desirable to investigate the stereochemistry of acid-catalyzed solvolysis of acyclic amidates which are chiral only at phosphorus. We report in this paper the first practical preparative method for optically pure alkyl phenyl phosphoramidates[7] through a transaminative process, and describe stereochemical aspects of their acid-catalyzed alcoholysis.

Preparation of optically Active Alkyl Phenyl Phosphoramidates

For the preparation of simple optically active phosphorus amides, a nucleophilic displacement reaction of chiral phosphorus esters with lithium amides has generally been employed.[8] The method however, is not really applicable to the preparation of phosphotriesters, since in this case the reaction may lead to a mixture of diester monoamide, monoester diamide, and triamide even under controlled reaction conditions. Furthermore, the stereochemistry of the reaction is not well established. With these factors in mind, we sought to develop a new and facile synthesis of chiral phosphoramidates which embodied two key processes: preparation and separation of diastereomeric phosphoramidates of L-phenylalanine esters and subsequent C–N bond fission (eq. 1).



(1)

In a preliminary experiment on the latter chiral transfer step, a transaminative procedure developed by Yamada *et al.*[9] for the preparation of chiral alkyl amines was tested on a model compound, N-(diphenyl phosphoryl) phenylalanine methyl ester (**1**). N-Chlorination of **1** with *tert*-butyl hypochlorite was found to be rather sluggish in ether but proceeded rapidly in methanol in the presence of borax at room temperature to give the N-chloride (**2**) as crystals in 91% yield. Attempted dehydrochlorination of **2** with triethylamine in chloroform unexpectedly yielded the amide **1** as a sole product. On the other hand, treatment of **2** with 1 equivalent of sodium methoxide at 0° gave the amino acetal (**3**) in fair yield; the structure was confirmed by the spectral data. The formation of **3** could be interpreted as a result of the addition of methanol to an intermediate N-phosphorylimine. Compound **3** was easily hydrolyzed by 5% H_2SO_4–MeOH to afford diphenyl phosphoramidate (**4**) in 50% yield.

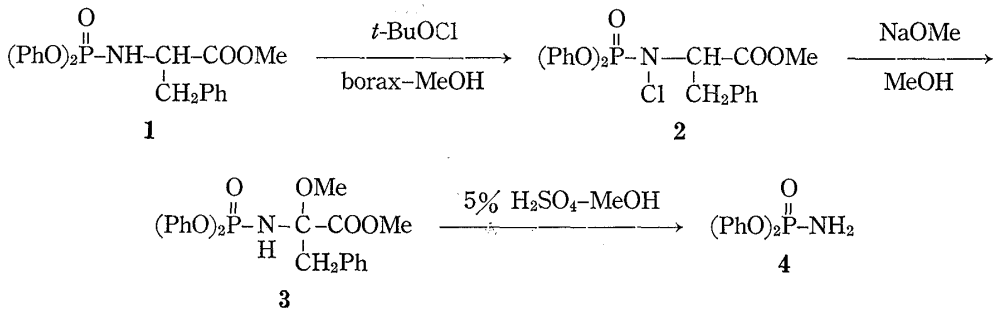
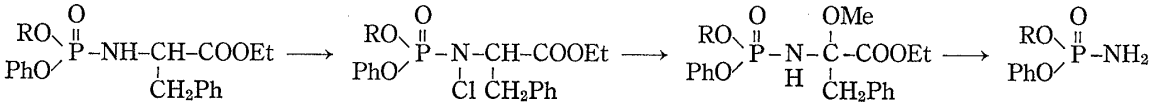


Chart 1

Based on the success of this model experiment, we then attempted to prepare (+) and (−) methyl phenyl phosphoramidates (**8**). The reaction of phenyl phosphorodichloridate

6) Methanolysis with ring opening and subsequent P-N bond cleavage might afford dimethyl phosphoryl derivatives which could yield both *cis* and *trans* 2-methoxy-1,3,2-dioxaphosphorinane-2-oxides.
7) Inch *et al.* recently reported the preparation of chiral dialkyl phosphoramidates, although the enantiomeric purity was low: C.R. Hall and T.D. Inch, *Tetrahedron Lett.*, **1977**, 3765.
8) A. Nudelman and D.J. Cram, *J. Org. Chem.*, **36**, 335 (1971).
9) *a*) S-i. Yamada and S-i. Hashimoto, *Tetrahedron Lett.*, **1976**, 997; *b*) S-i. Yamada, N. Ikota, and K. Achiwa, *ibid.*, **1976**, 1001.

with L-phenylalanine ethyl ester followed by *in situ* treatment with excess methanol afforded the methyl phenyl phosphoryl derivative in 70% yield as a mixture of diastereomers (**5a, 5b**) (ratio=*ca.* 1:1 as determined by integration of a pair of P–OMe doublets in nuclear magnetic resonance (NMR)). Separation of the diastereoisomers obtained here could not be achieved by chromatography under various conditions, in contrast to the case of proline derivatives.[10] Only one isomer (**5a**, mp 60—61°) was obtained in very poor yield after careful column chromatography on silica gel followed by crystallization from diisopropyl ether.

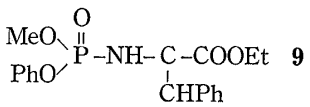


5a, 5b: R=Me **6a, 6b:** R=Me **7a, 7b:** R=Me **8:** R=Me
10a, 10b: R=Et **11a, 11b:** R=Et **12a, 12b:** R=Et **13:** R=Et

Chart 2

In the expectation that separation might be possible at a later stage of the reactions, the mixture was subjected to N-chlorination. A mixture of N-chloro derivatives (**6a, 6b**) showed two distinct spots on a silica gel plate (benzene–ethyl acetate, 5:1), suggesting that chromatographic separation of the isomers would be possible. However, instability of the N–Cl bond induced considerable decomposition of the compounds during the usual chromatographic procedure, affording dechlorinated amidates (**5a, 5b**) and unidentified products. Although such decomposition could be largely suppressed by employing the technique of flash chromatography[11] or rapid preparative thin-layer chromatography (TLC), giving analytically pure diastereomers (**6a** and **6b**) both in *ca.* 40% yield, complete resolution was only successful on a small scale (less than 2 mmol) that made the whole operation possible in a relatively short time. Experimental difficulty encountered again in the separation of diastereomers was finally overcome by taking advantage of the facile reductive dechlorination of N-chloro phosphoramidate observed in the model experiment (*vide supra*). An N-chloride mixture was subjected to flash chromatography and two major fractions contaminated with small amounts of the other isomer were separately treated with triethyl amine in chloroform. Each crystalline product was purified by recrystallization from a mixture of diisopropyl ether and *n*-hexane to furnish pure diastereomer, **5a** (mp 59—60°, 28% yield) or **5b** (mp 58—59°, 26% yield).[12]

With both diastereomers (**5a** and **5b**) in hand, transaminative cleavage of the C–N bond was carried out according to the method established in the model experiment. The N-chloro compound **6a** obtained from **5a** in a stereochemically homogeneous state was directly subjected to treatment with sodium methoxide in dry methanol. The reaction was found to be sensitive to temperature. Above 15°, both amino acetal (**7a**) and a cinnamate (**9**) were produced.



9

Formation of the latter product could be minimized by lowering the reaction temperature. Only a trace amount of **9** was formed at 7° for 5 min. The NMR spectra of **7a** indicated that it was a mixture of epimers at the carbon bearing the ethoxycarbonyl group. Crude **7a** was smoothly hydrolyzed to give (+) methyl phenyl phosphoramidate, (+)-**8**, $[\alpha]_D$ +13.5°, in an overall yield of 50% based on **5a**. Employing the same reaction sequence, the isomer **5b** could be transformed to (—)-isomer, (—)-**8**, $[\alpha]_D$ —13.6°. The enantiomeric purities of

10) T. Koizumi, Y. Kobayashi, H. Amitani, and E. Yoshii, *J. Org. Chem.*, **42**, 3459 (1977).
11) W.C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, **43**, 2923 (1978).
12) Yields were calculated on the basis of phenyl phosphorodichloridate employed.

the amidates thus obtained were shown to be over 96% by NMR determination using a chiral shift reagent $Eu(hfc)_3$.

Optically active ethyl phenyl phosphoramidates, (+)-**13** (mp 63—64° $[\alpha]_D$ +6.5°) and (−)-**13** (mp 64—65°, $[\alpha]_D$ −6.2°) were prepared essentially by the procedure described above for methyl analogs (**8**). In this case, one of the diastereomeric phosphoryl phenylalanine esters (**10a**) could be obtained by recrystallization of the mixture from diisopropyl ether and the other isomer (**10b**) was isolated from the mother liquor by performing the N-chlorination-dechlorination sequence. The optical purities of (+)- and (−)-**13** should be as high as those of **8** since it has been shown here that the transaminative procedure did not affect the chirality of the phosphoryl center.

Our synthetic method for chiral alkyl phenyl phosphoramidates presented in this section requires relatively few operations and gives optically pure samples in good yields. Further application of this method to the preparation of other phosphorus amides is in progress in this laboratory.

Stereochemistry of Acid-catalyzed Alcoholysis of Alkyl Phenyl Phosphoramidates

As mentioned briefly in the introductory part of this paper, acid-catalyzed alcoholysis of phosphoramidates has been considered to proceed by an A-2 mechanism with complete inversion of configuration. This stereospecificity of P–N bond cleavage enabled us to establish an effective route to optically pure dialkyl phenyl phosphates from phosphoramidates of proline ethyl ester.[10] Inch *et al.* also reported the preparation of various chiral phosphorus derivatives by means of acid-catalyzed alcoholysis of amidates derived from (−)-ephedrin or amino sugars.[13]

Recently, however, examples that violate this stereochemical course have appeared: BF_3-catalyzed alcoholysis of phosphorinane amidates[5] and hydrogen chloride-catalyzed alcoholysis of phosphoramidothioates.[7] Therefore, it was of considerable interest to investigate the stereochemistry of alcoholysis of the chiral phosphoramidates described in the above section.

First, methanolysis of (−) ethyl phenyl phosphoramidate (**13**) was carried out at reflux temperature in various concentrations of sulfuric acid. The isolation yields and optical rotations of the product, ethyl methyl phenyl phosphate (**14**), are shown in Table I. Stereospecificity of the reaction, irrespective of acid concentration used, is evident from the constant rotational values within experimental error and also from NMR determination of the optical purity, which appeared to be 100%.

Table I. H_2SO_4-Catalyzed Methanolysis of (−) Ethyl Phenyl Phosphoramidate (**13**)

Molar concentration of H_2SO_4	Ethyl methyl phenyl phosphate	
	Yield (%)	$[\alpha]_D$ (c, °C)
0.1	60	−3.3° (2.61, 26)
0.1	53	−3.6° (2.29, 21)
1	63	−3.5° (1.78, 20)
1	52	−3.7° (2.49, 21)
3	53	−3.6° (2.74, 20)
3	34	−3.5° (1.36, 20)

The effect of the structure of the alcohol on the stereochemistry was then investigated for both enantiomers of methyl phenyl phosphoramidate (**8**) using ethanol, *n*-propanol, and

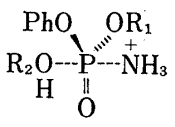
13) *a*) C.R. Hall, T.D. Inch, G.J. Lewis, and R.A. Chittenden, *J. Chem. Soc. Chem. Commum.*, **1975**, 720; *b*) D.B. Cooper, C.R. Hall, and T.D. Inch, *ibid.*, **1975**, 721.

n-butanol with 1 M sulfuric acid. Although the results shown in Table II indicate some decrease in yield compared with the previous experiment (Table I), the optical purities of the product esters were again determined by NMR to be 100%, except in the case of *n*-butyl methyl phenyl phosphate.[14] Because of the low yield of the product, racemization during butanolysis might be a result of unknown secondary reactions and therefore this result may be exceptional.

Table II. H_2SO_4-Catalyzed Alcoholysis of optically Active Methyl Phenyl Phosphoramidate (**8**)

Amidate	Alcohol	Methyl alkyl phenyl phosphate		
		Alkyl	Yield (%)	$[\alpha]_D$ (c, °C)
(+)-**8**	EtOH	Et	44	−3.2° (1.09, 21)
(−)-**8**	EtOH	Et	30	+3.5° (1.05, 27)
(+)-**8**	*n*-PrOH	*n*-Pr	26	−4.4° (2.56, 25)
(−)-**8**	*n*-PrOH	*n*-Pr	31	+4.6° (2.46, 25)
(+)-**8**	*n*-BuOH	*n*-Bu	10	−4.2° (1.22, 27)
(+)-**8**	*n*-BuOH	*n*-Bu	20	−4.4° (1.96, 25)

In summary, hydrogen ion-catalyzed alcoholyses of **8** and **13** proceeeded with complete stereospecificity, independent of the acidity of the medium and the kind of alcohol. This is best interpreted as being due to the operation of an inversion process, not a retention process, taking account of our previous experiments on H^+-catalyzed solvolysis of phosphinamides.[3] Thus the most reasonable mechanism at present seems to be a direct displacement A-2 mechanism which involves a pentacoordinated transition state of the N-protonated form (**15**).



R_1=Me, Et
R_2=Me, Et, *n*-Pr, *n*-Bu

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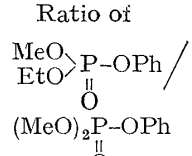
In order to investigate the effect of the nature of the acid catalyst on the steric course of the alcoholysis, we next examined BF_3 catalysis. Treatment of (−) ethyl phenyl phosphoramidate (**13**) with 2% BF_3 in methanol under reflux for 5.5 hr unexpectedly gave two

Table III. BF_3-Catalyzed Methanolysis of (−) Ethyl Phenyl Phosphoramidate (**13**)

BF_3 concentration (%) in MeOH	Reflux time (hr)	Ethyl methyl phenyl phosphate			Ratio of 
		Yield (%)	$[\alpha]_D$ (c, °C) in CCl_4	Retention % determined by $[\alpha]_D$ (NMR)[a]	
2	5.5	23	−2.5° (2.48, 27)	14(15)	6.3
2	5.5	31	−2.7° (3.11, 19)	12(13)	6.9
5	2.5	34	−2.5° (3.67, 19)	14(14)	7.5
5	2.5	34	−2.7° (3.31, 21)	11(15)	9.6
10	2	40	−2.7° (3.88, 19)	12(11)	11.2
10	2	37	−2.7° (3.53, 21)	11(14)	12.6

a) Eu(hfc)$_3$ shift method.

14) The Eu(hfc)$_3$ method indicated contamination by the (+)-enantiomer to the extent of *ca.* 5%.

phosphates after usual work-up. These compounds, which were formed in a ratio of 1: 6.3 (by GLC determination), were isolated by preparative TLC followed by distillation, and identified as dimethyl phenyl phosphate (minor product) and ethyl methyl phenyl phosphate (**14**, major product). The major product **14** obtained in 23—30% yield showed an optical rotation of $[\alpha]_D$ −2.5° or −2.7°, indicating that partial racemization had occurred in this particular alcoholysis to the extent of 24 to 28%. The presence of the retention product (+)-**14** was also confirmed by the $Eu(hfc)_3$ method, and the amount estimated was essentially the same as that calculated from the optical rotation. The use of higher concentrations of the acid had no effect on the optical purity of the product **14**, and dimethyl phenyl phosphate was always co-produced (Table III). The by-product formation is of particular interest, since the P–OR bond is known to resist cleavage under acidic conditions. Ethanolyses of (+) and (−) methyl phenyl phosphoramidates (**8**) at various BF_3 concentrations afforded comparable results, as shown in Table IV; *i.e.*, formation of diethyl phenyl phosphate, and ethyl methyl phenyl phosphate (**14**) which contained inversion and retention products in a ratio of *ca.* 3: 1 (Table IV).

Table IV. BF_3-Catalyzed Ethanolysis of optically Active Methyl Phenyl Phosphoramidate (**8**)

BF_3 concentration (%) in EtOH	Amidate	Reflux time (hr)	Ethyl methyl phenyl phosphate			Ratio of $\frac{MeO}{EtO}>P(=O)-OPh$ / $(EtO)_2P(=O)-OPh$
			Yield (%)	$[\alpha]_D$ (*c*, °C) in CCl_4	Retention % determined by $[\alpha]_D$ (NMR)[a]	
2	(+)-**8**	2.5	11	−2.3° (1.28, 19)	18(21)	1.3
3.8	(−)-**8**	2	11	+1.8° (1.05, 25)	25(27)	3
5	(+)-**8**	1	21	−1.7° (2.56, 19)	25(23)	2.3
5	(−)-**8**	1	13	+1.7° (1.20, 19)	26(25)	2.0
10	(+)-**8**	1	17	−1.9° (1.46, 19)	22(27)	2.4
19	(−)-**8**	0.75	17	+1.5° (2.03, 25)	29(27)	3.5

a) $Eu(hfc)_3$ shift method

In order to determine how the retention product and dialkyl phenyl phosphate were formed under BF_3 catalysis, a control experiment with optically pure (−) ethyl methyl phenyl phosphate was carried out under the same reaction conditions. Neither decrease in the optical purity of the sample nor production of a dialkyl derivative was observed (Table V). Therefore, the formation of partially racemized ethyl methyl phenyl phosphate and dialkyl phenyl phosphate could not be ascribed to a transesterification reaction of ethyl methyl phenyl phosphate with solvent alcohol.

Table V. Reaction of BF_3-Alcohol with optically Active Ethyl Methyl Phenyl Phosphate (**14**)

$[\alpha]_D$ (*c*, °C) of **14** in CCl_4	BF_3 concentration in alcohol	Reflux time (hr)	Recovered phosphate (**14**)	
			Yield (%)	$[\alpha]_D$ (*c*, °C) in CCl_4
−3.6° (1.95, 17)	19% BF_3-EtOH	4	80	−3.5° (3.18, 17)
−3.5° (3.18, 17)	10% BF_3-EtOH	8	73	−3.6° (2.35, 16)
+3.0° (4.46, 27)	2% BF_3-MeOH	12	92	+3.0° (3.77, 27)

In order to obtain further insight into the formation of dialkyl phenyl phosphate and the observed racemization, the BF_3-catalyzed ethanolysis of (−)-**8** was interrupted before

completion of the reaction and the products were isolated by preparative TLC. In addition to diethyl phenyl phosphate and ethyl methyl phenyl phosphate ($[\alpha]_D$ +1.7°), optically pure starting material and a trace amount of ethyl phenyl phosphoramidate[15] were obtained. The recovery of pure(−)-**8** ruled out the possibility of racemization of the amidate (−)-**8** prior to the P–N bond cleavage, supporting the view that the partial racemization occurred in the course of displacement of the amino group by ethanol. The formation of ethyl phenyl phosphoramidate may well explain the concomitant formation of diethyl phenyl phosphate.

Based on the above experimental results, the following mechanism can be considered for the racemization: a dissociative A-1 mechanism or a pentacoordinate intermediate mechasism. Of the two possibilities, we suggest that the former one can be eliminated for the following reasons: 1) If there was participation of an A-1 mechanism, one would expect an acidity dependence, as in the case of phosphinamides;[3a] 2) An A-1 mechanism does not provide any rational explanation for the transesterification of alkyl phenyl phosphoramidate; 3) To our best knowledge there have been no reports suggesting the formation of an $(RO)_2\overset{+}{P}{=}O$ cation. On the other hand, the pentacoordinate intermediate mechanism illustrated in Chart 3 may well explain the experimental results. Although the formation of the major inversion product can be explained by the pentacoordinate intermediate mechanism, some contribution of a direct displacement A-2 mechanism could not be ruled out. Therefore we consider at present that a dual mechanism[16]—pentacoordinate intermediate and direct displacement mechanisms—may be responsible for the inversion process observed in BF_3-catalyzed solvolyses. To identify the mechanism conclusively and account for the role of H^+ and BF_3, more experimental data (both kinetic and stereochemical) are required from other types of phosphoramidates.[17]

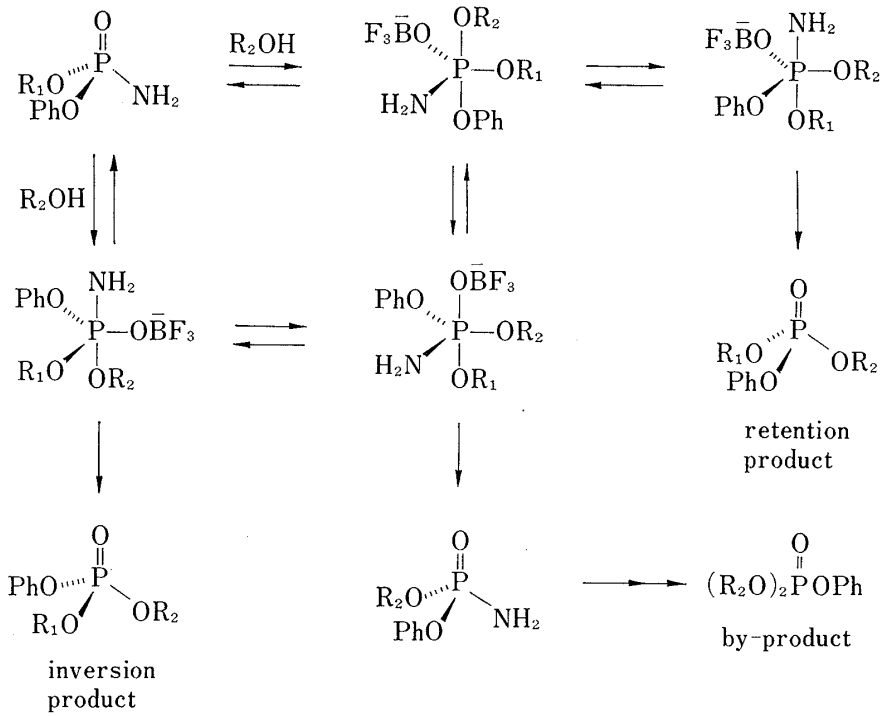


Chart 3

15) It showed $[\alpha]_D$ of around −6°, though this value is not reliable because only a very small amount of the sample was used.
16) Wadsworth similarly proposed a dual mechanism for displacement reactions in the 1,3,2-dioxaphosphorinane system: W.S. Wadsworth. Jr., *J. Org. Chem.*, **38**, 2921 (1973).
17) Inch *et al.* have made the same suggestion in their study on phosphoramidothioates (ref. 7).

Experimental

All melting points were determined on a Yanagimoto micro melting point apparatus, and are uncorrected. All boiling points correspond to bath temperatures, and are uncorrected. Infrared (IR) spectra were taken on a JASCO IRA-1 spectrometer. ^{1}H NMR spectra were recorded on JEOL PMX-60, and Varian EM-360 and EM-390 spectrometers. Chemical shifts are reported in δ (ppm) units from internal tetramethylsilane. Mass spectral data were obtained on a JEOL-01SG-2 instrument at an ionization potential of 75 eV. Optical rotations were measured at 589 nm with a 1 dm cell using a JASCO DIP-4 automatic polarimeter. Analytical GLC analyses were carried out with a Shimadzu 4AIT gas chromatograph using a column (3 mm × 1 m) packed with 5% SE-30 on Chromosorb W 80/100 mesh and a column temperature of 150°. Column chromatography was performed using Merck silica gel (0.06—0.20 mm) and flash chromatography using Merck silica gel (0.040—0.063 mm). Preparative TLC was done using Merck silica gel $PF_{254+366}$. The chiral shift reagent, tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III) Eu(hfc)$_3$, was purchased from Aldrich Chemical Co. Inc.

N-Chloro-N-(diphenyl phosphoryl)-L-phenylalanine Methyl Ester (2)——N-(Diphenyl phosphoryl)-L-phenylalanine methyl ester (**1**, mp 93—94°) was prepared from diphenyl phosphorochloridate and L-phenylalanine methyl ester as described in the literature.[18] A solution of 70 mg of *tert*-butyl hypochlorite in 3 ml of 4% methanolic borax was added to a solution of 240 mg of **1** in 7 ml of 4% methanolic borax. After stirring at room temperature for 20 min, the mixture was diluted with $CHCl_3$, washed with H_2O, and dried with $MgSO_4$. Removal of the solvent by evaporation afforded a crystalline mass, which was recrystallized from CH_2Cl_2–*n*-hexane to give 236 mg of **2**, mp 80—81°. MS *m/e*: 447, 445, 410, 388, 386, 356, 354. *Anal.* Calcd. for $C_{22}H_{21}ClNO_5P$: C, 59.27; H, 4.75; N, 3.14. Found: C, 59.06; H, 4.64; N, 3.29. IR (KBr) cm^{-1}: 1738, 1280, 958. NMR (CCl_4) δ: 3.0 (2H, m, methylene), 3.50 (3H, s, OMe), 4.83 (1H, t of d, J=9, 6 Hz, methine), 7.1 (10H, phenyl).

Reaction of the N-Chloro Compound 2 with Triethylamine–Chloroform——To a solution of 42 mg of **2** in 5 ml of $CHCl_3$ was added 25 mg of Et_3N at room temperature. After standing overnight the solvent was evaporated off and the residue was dissolved in ether. Precipitated Et_3N–HCl was removed and the solvent was evaporated off to give 36 mg of **1**, mp 93—94°. The NMR and IR spectra were superimposable on those of **1**.

N-(Diphenyl phosphoryl)-2-methoxy-L-phenylalanine Methyl Ester (3)——Sodium methoxide solution prepared from 3 ml of dry MeOH and 8.4 mg of Na was added at 0° to a solution of 200 mg of **2** in a few ml of methanol. The mixture was stirred at 0° for 1 hr, then diluted with $CHCl_3$, and the solution was washed with H_2O and dried with $MgSO_4$. Removal of the solvent by evaporation afforded 216 mg of **3** containing a small amount of **1**. The crude material was crystallized from iso-Pr_2O–CH_2Cl_2 to give 97 mg (43%) of **3** as colorless needles (essentially one spot on TLC, C_6H_6–AcOEt=5:1). An analytical sample was obtained by recrystallization from the same solvent mixture, mp 116—117°. *Anal.* Calcd. for $C_{23}H_{24}NO_6P$: C, 62.64; H, 5.49; N, 3.18. Found: C, 62.51; H, 5.60; N, 3.43. IR (KBr) cm^{-1}: 3235, 1742, 1260. NMR ($CDCl_3$) δ: 3.27 (1H, J=14 Hz, PhCH), 3.28 (3H, s, α-OMe), 3.75 (3H, s, COOMe), 3.83 (1H, d, J=14 Hz, PhCH), 4.78 (1H, br d, J=9 Hz, NH; exchangeable with D_2O), 7.23 (15H, phenyl).

Diphenyl Phosphoramidate (4) by Hydrolysis of 3——A solution of 56 mg of the amino acetal **3** in 7 ml of MeOH and 5 ml of 5% H_2SO_4 was stirred at 40° for 30 min. The mixture was diluted with H_2O and extracted with $CHCl_3$. The organic layer was washed with 4% $NaHCO_3$ and brine, dried with $MgSO_4$, and the solvent was evaporated off. The residue was crystallized from EtOH–CCl_4 to give 15 mg of **4**, mp 147—150° (lit.[19] mp 149°). IR (KBr) cm^{-1}: 3440, 1587, 1260, 1220, 950. The IR spectrum was identical with that of an authentic sample prepared by the reaction of diphenyl phosphorochloridate with aqueous NH_4OH.

N-(Methyl phenyl phosphoryl)-L-phenylalanine Ethyl Ester (5a and 5b)——(1) To a solution of 4.1 g of phenyl phosphorodichloridate in 60 ml of dry THF was added at 0° and with stirring a solution of 4.1 g of L-phenylalanine ethyl ester and 4.3 g of Et_3N in 50 ml of dry THF. After continued stirring of the mixture at 0° for 3 hr, precipitated Et_3N·HCl was removed by filtration. The filtrate was mixed with 10 ml of dry MeOH, refluxed for 3 hr, and then evaporated off. The residue was dissolved in $CHCl_3$ and the solution was successively washed with brine, 1 N HCl, saturated $NaHCO_3$ and brine, and dried with $MgSO_4$. Evaporation of the solvent afforded 4.9 g of a viscous oil (*ca.* 1:1 mixture of **5a** and **5b**) which showed a pair of P–OMe doublets at δ 3.43 (J=11 Hz) and 3.67 (J=11 Hz) in NMR.

To a solution of 4.9 g of the diastereomeric mixture (**5**) in 40 ml of 4% methanolic borax was added a solution of 2.1 g of *tert*-butyl hypochlorite in 40 ml of 4% methanolic borax. After stirring at room temperature for 10 min, the mixture was diluted with $CHCl_3$, washed with H_2O, dried with $MgSO_4$, and evaporated down. The residue was subjected to flash chromatography (*n*-hexane–AcOEt=3.5:1) to afford diastereomeric N-chloro compounds, **6a** and **6b**, which were each contaminated with a small amount of the other isomer as evidenced by TLC (*Rf*: **6a**=0.58, **6b**=0.67, C_6H_6–AcOEt=5:1). Each crude isomer was dissolved

18) L.J. Sciarini and J.S. Fruton, *J. Am. Chem. Soc.*, **71**, 2940 (1949).
19) R.W. Chambers and H.G. Khorana, *J. Am. Chem. Soc.*, **80**, 3749 (1958).

in 50 ml of $CHCl_3$ and 6.3 g of Et_3N. After standing at room temperature for 2 hr, the solution was washed with 1 N HCl and brine, dried with $MgSO_4$, and evaporated down. The residual solid (essentially one spot on TLC) was recrystallized from iso-Pr_2O–*n*-hexane in each case to give 1.96 g of **5a** or 1.82 g of **5b**.

5a: mp 59°. *Anal.* Calcd. for $C_{18}H_{22}NO_5P$: C, 59.55; H, 6.11; N, 3.86. Found: C, 59.27; H, 6.15; N, 4.06. $[\alpha]_D^{28}$ +33.0° (c=3.44, $CHCl_3$). IR (KBr) cm^{-1}: 3240, 1740, 1250, 1055, 930. NMR (CCl_4) δ: 1.10 (3H, t, J=7 Hz, C–Me), 2.91 (2H, br d, J=7 Hz, $PhCH_2$), 3.43 (3H, d, J=11 Hz, P–OMe), 3.97 (3H, m, O–CH_2 and N–CH), 4.57 (1H, br t, J=10 Hz, NH), 7.2 (10H, phenyl).

5b: mp 59°. *Anal.* Calcd. for $C_{18}H_{22}NO_5P$: C, 59.55; H, 6.11; N, 3.86. Found: C, 59.73; H, 5.95; N, 3.70. $[\alpha]_D^{28}$ +8.0° (c=3.07, $CHCl_3$). IR (KBr) cm^{-1}: 3240, 1740, 1240, 1050, 922. NMR (CCl_4) δ: 1.13 (3H, t, J=7 Hz, C–Me), 2.93 (2H, br d, J=7 Hz, $PhCH_2$), 3.67 (3H, d, J=11 Hz, P–OMe), 4.03 (3H, m, OCH_2 and N–CH), 4.5 (1H, br t, J=10 Hz, NH), 7.17 (10H, phenyl).

(2) A mixture of **5a** and **5b** obtained as described above from 4.1 g of phenyl phosphorodichloridate was chromatographed on 200 g of silica gel, eluting with mixtures of C_6H_6 and AcOEt (5: 1 to 3: 1). A portion of the early fractions afforded crystals on trituration with iso-Pr_2O. Recrystallization from the same solvent afforded 280 mg of pure **5a**.

N-Chloro-N-(methyl phenyl phosphoryl)-L-phenylalanine Ethyl Ester (6a and 6b)——Chromatography of 715 mg of a mixture of **6a** and **6b** which was obtained by the procedure described above afforded each isomer as an oil. Preparative TLC (C_6H_6–AcOEt=15: 4, single development): **6a**, 253 mg (36%) and **6b**, 203 mg (29%); flash chromatography (*n*-hexane–AcOEt=3.5: 1): **6a**, 287 mg (41%) and **6b**, 273 mg (39%).

6a: MS *m/e*: 399, 397, 362, 326, 324, 308, 306. IR (film) cm^{-1}: 1738, 1278, 1040, 942. NMR (CCl_4) δ: 1.25 (3H, t, J=7 Hz, C–Me), 3.1 (2H, m, $PhCH_2$), 3.80 (3H, d, J=12 Hz, P–OMe), 4.17 (2H, q, J=7 Hz, OCH_2), 4.8 (1H, t of d, J=9, 5 Hz, N–CH), 7.03 (10H, phenyl).

6b: MS *m/e*: 399, 397, 362, 326, 324, 308, 306, IR (film) cm^{-1}: 1740, 1280, 1040, 944. NMR (CCl_4) δ: 1.12 (3H, t, J=7 Hz, C–Me), 2.98 (3H, d, J=12 Hz, P–OMe), 3.2 (2H, m, $PhCH_2$), 4.0 (2H, q, J=7 Hz, OCH_2), 4.87 (1H, t of d, J=10, 5 Hz, N–CH), 7.2 (10H, phenyl).

(+) Methyl Phenyl Phosphoramidate ((+)-8)——The N-chloride (**6a**) was obtained by the reaction of 1 g of **5a** with 418 mg of *tert*-butyl hypochlorite according to the method described above. To a solution of the crude **6a** in 20 ml of dry MeOH was added at 7° with stirring a solution of NaOMe prepared from 8 ml of dry MeOH and 63 mg of Na. After stirring at the same temperature for 5 min, the reaction mixture was diluted with $CHCl_3$, washed with brine, and dried with $MgSO_4$. Removal of the solvents by evaporation yielded **7a** as an oil which was contaminated with a trace amount of the by-product **9**. The crude product was dissolved in 20 ml of MeOH and 10 ml of 5% H_2SO_4, and the solution was left to stand overnight at room temperature. It was then diluted with H_2O and extracted with $CHCl_3$. The organic layer was washed with brine, dried with $MgSO_4$, and evaporated. The residue was chromatographed on 25 g of silica gel, eluting with mixtures of C_6H_6 and AcOEt, to give 258 mg of (+)-**8**, mp 81—82°, $[\alpha]_D^{23}$ +14.0° (c=2.23, $CHCl_3$). The optical purity of (+)-**8** was determined by NMR using the Eu(hfc)$_3$ shift method: 15 mg of the sample in 0.2 ml of $CDCl_3$ exhibited a P–OMe doublet at δ 3.83, which was shifted to δ 5.5 as a single doublet by the addition of 70 mg of Eu(hfc)$_3$; addition of *ca.* 1 mg of racemic compound to the solution clearly showed a new P–OMe doublet, indicating that the optical purity of the sample is over 96%.

A sample for elemental analysis and alcoholysis experiments was obtained by recrystallization from iso-Pr_2O–*n*-hexane, mp 79—80°. *Anal.* CalCd. for $C_7H_{10}NO_3P$: C, 44.96; H, 5.39; N, 7.49. Found: C, 45.23; H, 5.29; N, 7.67. $[\alpha]_D^{26}$ +13.5° (c=2.33, $CHCl_3$). IR (KBr) cm^{-1}: 3260, 1580, 1220, 1050, 920. NMR ($CDCl_3$) δ: 3.57 (2H, br s, NH_2), 3.77 (3H, d, J=12 Hz, P–OMe), 7.3 (5H, phenyl).

(−) Methyl Phenyl Phosphoramidate ((−)-8)——From 1.76 g of **5b**, employing the procedure described for the preparation of (+)-**8**, we obtained 448 mg (50%) of pure (−)-**8**. An analytical sample was obtained by recrystallization from iso-Pr_2O–*n*-hexane, mp 79—80°, $[\alpha]_D^{26}$ −13.6° (c=2.13, $CHCl_3$). *Anal.* Calcd. for $C_7H_{10}NO_3P$: C, 44.96; H, 5.39; N, 7.49. Found: C, 45.01; H, 5.37; N, 7.37. IR (KBr) cm^{-1}: 3260, 1580, 1220, 1050, 920. NMR ($CDCl_3$) δ: 3.57 (2H, br s, NH_2), 3.77 (3H, d, J=12 Hz, P–OMe), 7.3 (5H, phenyl).

Ethyl N-(Methyl phenyl phosphoryl)-2-aminocinnamate (9)——A sample obtained by dehydrochlorination of 503 mg of **6a** with NaOMe at a temperature of 15° for 15 min was chromatographed on silica gel, eluting with mixtures of C_6H_6–AcOEt (5: 1—30: 7). After isolation of 100 mg of almost pure **7a** from the initial fractions, 42 mg of **9** was obtained: This was crystallized from *n*-hexane–CH_2Cl_2 as needles, mp 95—101° (broad range of mp since it was a mixture of geometrical isomers). *Anal.* Calcd. for $C_{18}H_{20}NO_5P$: C, 59.88; H, 5.58; N, 3.88. Found: C, 60.07; H, 5.55; N, 3.63. IR (KBr) cm^{-1}: 3131, 1720, 1630, 1592, 1250, 1050, 935. NMR (CCl_4) δ: 1.30 (3H, t, J=7 Hz, C–Me), 3.62 (3H, d, J=12 Hz, P–OMe), 4.20 (2H, q, J=7 Hz, O–CH_2), 5.35 (1H, br d, J=5 Hz, NH), 7.3 (11H, m, phenyl and vinyl).

N-(Ethyl phenyl phosphoryl)-L-phenylalanine Ethyl Ester (10a and 10b)——To a solution of 3.0 g of phenyl phosphorodichloridate in 50 ml of dry THF at 0° was added a solution of 3.0 g of L-phenylalanine ethyl ester and 1.6 g of Et_3N in 30 ml of dry THF. After stirring at 0° for 2 hr the reaction mixture was filtered and the solvent was evaporated. The residue was dissolved in 10 ml of dry EtOH followed by the addition of 1.6 g of Et_3N. The solution was then heated at 80° for 2 hr, and diluted with $CHCl_3$ after cooling. The $CHCl_3$ solution was washed with brine, 1 N HCl, saturated $NaHCO_3$ and brine, dried with $MgSO_4$, and evaporated. Fractional crystallization of the residue from iso-Pr_2O gave 1.5 g of pure **10a**, mp 88—90°,

$[\alpha]_D^{31}$ +9.9° (c=2.64, $CHCl_3$). *Anal.* Calcd. for $C_{19}H_{24}NO_5P$: C, 60.53; H, 6.42; N, 3.72. Found: C, 60.48; H, 6.16; N, 3.87. IR (KBr) cm^{-1}: 3240, 1742, 1583, 1235, 1040, 960. NMR (CCl_4) δ: 1.13 (3H, t, J=7 Hz, C–Me), 1.23 (3H, t, J=7 Hz, C–Me), 2.92 (2H, br d, J=6 Hz, $PhCH_2$), 4.03 (6H, m), 7.1 (10H, phenyl).

The mother liquor was evaporated *in vacuo* leaving 3.4 g of an oily material which was subjected to N-chlorination followed by dechlorination. To a solution of 900 mg of the sample in 7 ml of 4% methanolic borax was added 400 mg of *tert*-butyl hypochlorite in 3 ml of 4% methanolic borax at room temperature for 10 min under stirring. Usual work-up followed by preparative TLC (C_6H_6–AcOEt=5:1) gave **11b**, which was contaminated with a small amount of **11a**. The crude **11b** was dissolved in 30 ml of $CHCl_3$ followed by the addition of 1.0 g of Et_3N. After usual work-up crystallization of the product from iso-Pr_2O–*n*-hexane gave 225 mg of **10b**, mp 47—49°, $[\alpha]_D^{31}$ +34.3° (c=3.22, $CHCl_3$). *Anal.* Calcd. for $C_{19}H_{24}NO_5P$: C, 60.53; H, 6.42; N, 3.72. Found: C, 60.27; H, 6.14; N, 3.99. IR (KBr) cm^{-1}: 3240, 1745, 1592, 1258, 1035. NMR (CCl_4) δ: 1.12 (3H, t, J=7 Hz, C–Me), 1.15 (3H, t, J=7 Hz, C–Me), 2.87 (2H, br d, J=6 Hz, $PhCH_2$), 3.97 (6H, m), 7.1 (10H, phenyl).

(+) and (−) Ethyl Phenyl Phosphoramidates ((+)-13 and (−)-13)——Using the procedure described for the preparation of (+)- and (−)-**8**, (+)-**13** and (−)-**13** were prepared from **10a** and **10b** in yields of 48% and 56% respectively.

(+)-**13**: mp 63—64°, $[\alpha]_D^{27}$ +6.5° (c=1.61, $CHCl_3$). *Anal.* Calcd. for $C_8H_{12}NO_3P$: C, 47.80; H, 6.02; N, 6.97. Found: C, 47.60; H, 6.05; N, 6.82. IR (KBr) cm^{-1}: 3360, 3260, 1590, 1240, 1040, 920. NMR ($CDCl_3$) δ: 1.33 (3H, t, J=7 Hz, C–Me), 2.3 (2H, br s, NH_2), 4.13 (2H, q of d, J=8, 7 Hz, P–OCH_2), 7.2 (5H, phenyl).

(−)-**13**: mp 64—65°, $[\alpha]_D^{27}$ −6.2° (c=1.48, $CHCl_3$). *Anal.* Calcd. for $C_8H_{12}NO_3P$: C, 47.80; H, 6.02; N, 6.97. Found: C, 47.54; H, 5.81; N, 6.77. IR (KBr) cm^{-1}: 3360, 3260, 1590, 1240, 1040, 920. NMR ($CDCl_3$) δ: 1.33 (3H, t, J=7 Hz, C–Me), 3.5 (2H, br s, NH_2), 4.13 (2H, q of d, J=8, 7 Hz, P–OCH_2), 7.2 (5H, phenyl).

H_2SO_4-Catalyzed Alcoholyses of Alkyl Phenyl Phosphoramidates——An optically pure alkyl phenyl phosphoramidate (50—100 mg) was dissolved in 3—20 ml of an appropriate alcohol containing 0.1—3 M H_2SO_4. The solution was heated under reflux until the starting amidate disappeared on TLC, and diluted with $CHCl_3$ after cooling. The organic layer was successively washed with brine, 1 N NaOH and brine, dried with $MgSO_4$, and evaporated down *in vacuo*. The residue was subjected to microdistillation and the purity of the product phosphate was checked by GLC and elemental analyses (C, H: ±0.3%). The optical rotations were measured in CCl_4, and in several cases the enantiomeric purities were confirmed by NMR using the Eu(hfc)$_3$ shift method.

BF_3-Catalyzed Alcoholyses of Alkyl Phenyl Phosphoramidates——$BF_3(MeOH)_2$ (bp 76°/15 torr) or BF_3–ether (bp 122°) were used as catalysts. A concentration such as 10% BF_3–MeOH, for example, refers to a methanolic solution containing 10% (v/v) of $BF_3(MeOH)_2$. An appropriate optically pure alkyl phenyl phosphoramidate (*ca.* 100 mg) was dissolved in 5—10 ml of BF_3–ROH and refluxed until the amidate disappeared on TLC. After cooling, the mixture was diluted with $CHCl_3$, washed with brine, 1 N NaOH and brine, and dried with $MgSO_4$. Removal of the solvent gave a mixture of ethyl methyl phenyl phosphate and dialkyl phenyl phosphate. The product ratio was determined by GLC (retention times (min): ethyl methyl phenyl phosphate, 5.6; dimethyl phenyl phosphate, 4.4; diethyl phenyl phosphate, 7.0). The mixture was separated by preparative TLC (C_6H_6–AcOEt=1:1) to give pure samples, all of which were identified by comparison of the NMR and IR spectra and retention times in GLC with those of authentic samples. Optical rotations were measured with distilled samples in CCl_4 and enantiomeric composition was determined by NMR using the Eu(hfc)$_3$ shift method. As control experiments, optically active ethyl methyl phenyl phosphate (40—100 mg) was dissolved in 5—15 ml of BF_3–ROH and heated under reflux. Usual work-up provided only the starting phosphate as determined by GLC. After microdistillation, the optical rotation was measured.

Quenching Experiment in the Ethanolysis of Methyl Phenyl Phosphoramidate——A solution of 200 mg of (−)-**8** in 37 ml of 2% BF_3–EtOH was refluxed for 1 hr. The reaction mixture was cooled, diluted with $CHCl_3$, washed with brine, dried with $MgSO_4$, and the solvent was evaporated off. Preparative TLC (AcOEt) of the residual oil afforded four components: unchanged amidate **13** (12 mg), mp 80—81°, $[\alpha]_D^{12}$ −13.4° (c=1.19, $CHCl_3$); ethyl phenyl phosphoramidate **13** (4 mg), mp 62—63°, $[\alpha]_D^{12}$ −6° (c=0.46, $CHCl_3$); ethyl methyl phenyl phosphate **14** (21 mg), $[\alpha]_D^{15}$ −1.7° (c=1.43, CCl_4); and diethyl phenyl phosphate (15 mg).

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