(1*H*-Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium Hexafluorophosphate- and (1*H*-Benzotriazol-1-yloxy)tripyrrolidinophosphonium Hexafluorophosphate-Mediated Activation of Monophosphonate Esters: Synthesis of Mixed Phosphonate Diesters, the Reactivity of the Benzotriazolyl Phosphonic Esters *vs* the Reactivity of the Benzotriazolyl Carboxylic Esters

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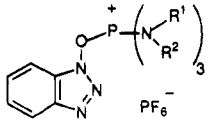
Received February 15, 1995®

A general method for synthesizing mixed phosphonate diesters from monoesters using (1*H*-benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate or (1*H*-benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate reagents is described. The reaction proceeded through a benzotriazolyl ester as shown by comparison with other reagents such as DCC, DCC/DMAP, DCC/1-hydroxybenzotriazole, bromotris(dimethylamino)phosphonium hexafluorophosphate, or *O*-(1*H*-benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate and by ^{31}P NMR analysis. This benzotriazolyl phosphonic ester intermediate was more reactive toward alcohols than toward amines, contrary to its carboxylic analogue.

Introduction

BOP (**1a**)[1,2] and PyBOP (**1b**)[3] are (benzotriazolyloxy)-phosphonium reagents commonly used in peptide synthesis. It is assumed that the first step in carboxylic acid activation by phosphonium salt reagents involves formation of an (acyloxy)phosphonium salt.[4] This initially

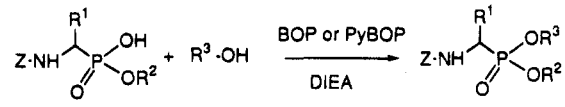


1a: $R^1 = R^2 = Me$ BOP

1b: R^1, $R^2 = (CH_2)_4$ PyBOP

formed salt is attacked by the benzotriazolyloxy anion to form the benzotriazolyl ester (Bt ester), which is considered to be the aminolyzed intermediate in coupling

Scheme 1



3a: $R^1 = CH_2Ph$; $R^2 = CH_2Ph$
(R)-**3b**: $R^1 = CH_2Ph$; $R^2 = Me$
3c: $R^1 = CH(CH_3)_2$; $R^2 = Me$

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reactions with DCC/HOBt[5] or BOP and PyBOP.[4] Castro showed that BOP-promoted activation of carboxylic acids also allows for the synthesis of phenyl esters,[6a] whereas the Bt ester of palmitic acid reacts poorly with the secondary alcohols of trehalose; in this case, the use of 1 equiv of imidazole is necessary for ester formation.[6b] The low reactivity of Bt esters of carboxylic acids with secondary alcohols has also been observed by others.[7]

In the case of phosphonic acids, the situation is very different. By using BOP, Dumy was able to form a phosphonamide linkage between an *N*-Pht-glycylphosphonic acid monoester and α-amino esters,[8] but the reaction gave moderate yields (60–65%) and failed when the Fmoc protection was used.[8b] In the case of the *Z*-protected α-amino phosphonate monoester **3b**, Musiol[9] recently reported that the reaction also failed when PyBOP was used but succeeded when the Bt or At ester was first formed from the phosphonochloridate and KOBt (or KOAt). This ester then reacted with α-amino esters

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® Abstract published in *Advance ACS Abstracts*, July 1, 1995.

(1) Nomenclature, abbreviations, and symbols follow the recommendations of: *Nomenclature of Organic Chemistry*; Pergamon: Oxford, 1979, and Sections A–F and H and of the IUPAC–IUB Joint Commission on Biochemical Nomenclature (*Eur. J. Biochem.* **1984**, *138*, 9–37). In addition, the following abbreviations are used: At ester, 7-azabenzotriazolyl ester; BOP, (1*H*-benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate; BOP-Cl, *N*,*N*-bis(2-oxo-3-oxazolidinyl)phosphinic chloride; BroP, bromotris(dimethylamino)-phosphonium hexafluorophosphate; Bt ester, benzotriazolyl ester; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DCC, dicyclohexylcarbodiimide; DCM, dichloromethane; DMF, dimethylformamide; DIEA, diisopropylethylamine; EDC, *N*-[3-(dimethylamino)propyl]-*N*′-ethylcarbodiimide hydrochloride; HBTU, *O*-(1*H*-benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate; HOAt, 1-hydroxy-7-azabenzotriazole; HOBt, 1-hydroxybenzotriazole; NMM, *N*-methylmorpholine; PyBOP, (1*H*-benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate; PyBroP, bromotripyrrolidinophosphonium hexafluorophosphate; OTP, tripyrrolidinophosphine oxide.

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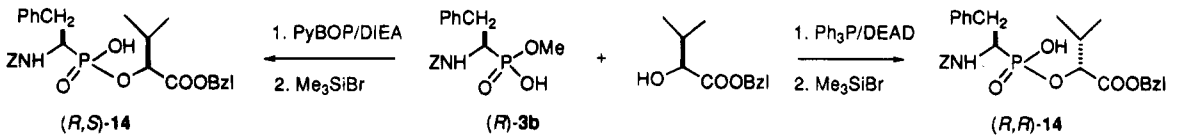
Table 1. BOP- or PyBOP-Promoted Synthesis of Mixed Phosphonate Diesters

starting material	alcohol	reaction time (h)	reagent	yield (%)	product
3a	$PhCH_2OH$	0.5	BOP	87	**4**
	i-PrOH	1.5	BOP	87	**5**
	$HOCH_2COOMe$	0.5	BOP	85	**6**
	$HOCH_2COOBzl$	0.5	BOP	85	**7**
	(*S*)-$HOCH(CH_3)COOMe$	2	BOP	82	**8**
	(*S*)-$HOCH(CH_3)COOMe$	2	PyBOP	82	**8**
	(*R*)-HOCH(*i*-Pr)COOBzl	3	PyBOP	81	**9**
(*R*)-**3b**	(*S*)-HOCH(*i*-Pr)COOBzl	2	BOP	85	**10**
	(2*S*,3*S*)-HOCH(*s*-Bu)COOBzl	2	PyBOP	81	**11**
3c	$HOCH_2COOMe$	1	PyBOP	75	**12**
	(2*S*,3*S*)-HOCH(*s*-Bu)COOBzl	2	PyBOP	65	**13**

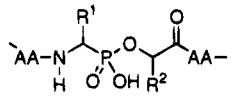
Scheme 2



in the presence of DBU. In contrast, we showed in a preliminary communication[10] that mixed phosphonate diesters of an N-protected α-amino phosphonic acid are readily formed from phosphonate monoester using BOP or PyBOP as activating agent (see Scheme 1). We present here a comprehensive study on the use of PyBOP for the synthesis of phosphonate esters. Given the marked difference in behavior between the reactivities of the BOP- or PyBOP-mediated activated carboxylic and phosphonic acids, we investigated the mechanism of the latter reaction and compared the reactivity of benzotriazolyl phosphonate *vs* that of the carboxylate analogue.

Results and Discussion

BOP- or PyBOP-Promoted Mixed Phosphonate Diester Synthesis. Phosphonopeptides **2** containing a transition state analogue from the hydrolysis of the scissile amide bond are of great interest in the development of enzyme inhibitors[11] and haptens for the production of catalytic antibodies.[12]



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To synthesize phosphonopeptides, the phosphono monoester residue (see **2**) is usually introduced in the form of a mixed diester which is selectively deprotected at the end of the synthesis.[11] These mixed phosphonates have been prepared from a monoester, in moderate yields, through phosphonochloridates.[13] They have also been obtained, but in low yield, using BOP–Cl,[14] and in good yield and under mild conditions using a Mitsunobu reaction,[15] with inversion of configuration of the hydroxyl-bearing carbon atom. Alternatively, Landry[16a] recently synthesized mixed diesters by sequential esterification from phosphonic dichlorides using tetrazole as catalyst. Similarly, Green[16b] obtained such compounds from dichlorides through bis(*p*-nitrophenyl) esters which were then sequentially transesterified in the presence of DBU.

We synthesized mixed phosphonate diesters from monoesters of phosphonic acids activated with BOP or PyBOP (Scheme 1).

Z-Protected α-amino phosphonate monoesters (racemic **3a**, **3c**, and (*R*)-**3b**) were obtained by the carbodiimide-promoted esterification of the known[17] corresponding phosphonous acids, followed by oxidation with $NaIO_4$.[18,19] The phosphonate monoesters **3a–c** were easily esterified by alcohols using BOP or PyBOP reagents to give mixed diesters as racemic or diastereomeric mixtures (Table 1). The reaction was run using 1.5 equiv of BOP or PyBOP, 1.5 equiv of alcohol, and 4 equiv of DIEA, in DMF, at room temperature. After flash chromatography, non-optimized good yields (65–87%) were obtained. This reaction was shown to be only slightly sensitive to steric hindrance, since yields were good with hindered alcohols (Table 1, compound **11**) or hindered phosphonates (Table 1, **12**) and still acceptable (65%) when both partners were hindered (Table 1, **13**).

To prepare diastereomerically pure compounds, we verified that the reaction proceeded without epimerization. (*R*)-**3b** was esterified with benzyl (*S*)-2-hydroxyisovalerate using PyBOP, and the resulting mixed phosphonate **10** (diastereomeric mixture, *R,S*-configuration at the P atom) was hydrolyzed with Me_3SiBr[15a] to obtain the monoester (*R,S*)-**14** (Scheme 2). HPLC analysis of the crude reaction product, compared with that obtained

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(19) The absolute configuration of (*R*)-**3b** was not determined in ref 17. We determined it by oxidation and comparison with the known optically pure N-unprotected phosphonic analogue (see the Experimental Section).

Table 2. PyBOP-Promoted Esterification of Methyl Phenylphosphonate (15)

alcohol	reaction time (h)	yield (%)	product
MeOH	1	90	**16**
methyl lactate	2	82	**17**
(−)-borneol	2	75	**18**
(−)-menthol	2.5	81	**19**
tert-butanol	8	0	–

for the (*R,R*)-**14** diastereoisomer prepared from benzyl (*R*)-2-hydroxyisovalerate, showed less than 0.5% epimerization. Product (*R,R*)-**14** was also obtained from (*R*)-**3b** and benzyl (*S*)-2-hydroxyisovalerate using a Mitsunobu-type reaction according to Campbell's methodology[15] (Scheme 2), since this latter reaction proceeds with inversion of the configuration of the hydroxyl-bearing carbon atom.

Starting from monomethyl phenylphosphonate (**15**), we also showed that high yields of mixed phosphonates were obtained (Table 2) with alcohols, including hindered secondary alcohols such as menthol or borneol; only *tert*-butanol failed to react. Thus, this reaction seems to be of general use.

Mechanism. This high efficiency of BOP and PyBOP for promoting mixed phosphonate diester formation contrasts with the already reported failure of the formation of *p*-nitrophenyl and thiophenyl phosphonic esters using DCC, DCC/HOBt, or DCC/DMAP.[20] Thus, it was of interest to study the mechanism of these reactions.

1. We first evaluated the esterification of **3a** with benzylglycolate using different coupling reagents such as DCC, DCC/DMAP, DCC/HOBt, BroP,[21] or HBTU[22] which are known to give specific reactive intermediates in peptide synthesis. The courses of these reactions were monitored by HPLC and are depicted in Figure 1.

With PyBOP, the best yields were obtained when the reaction was carried out under a nitrogen atmosphere (Figure 1, compare A and B); otherwise, it was necessary to use an excess of PyBOP reagent (Figure 1A; 1.5 equiv of PyBOP). This indicates that the activated species was moisture sensitive (evidence of this fact is discussed below); consequently, the different reagents were tested using 1.5 equiv of both alcohol and coupling reagent and under a nitrogen atmosphere.

With DCC, the reaction was performed under three different experimental conditions: either without additive or preactivation (Figure 1I), with 30 min of preactivation and then addition of alcohol/DIEA (Figure 1H), or without preactivation but in the presence of 20% DMAP (Figure 1G).

The DCC/HOBt reactions were carried out without preactivation (Figure 1F) or with preactivation followed by the addition of alcohol and DIEA (Figure 1D).

BroP (Figure 1E) and HBTU (Figure 1C) were used without preactivation under the same conditions as described for PyBOP.

Low to moderate yields were obtained with DCC, DCC/HOBt, or BroP. HBTU gave a good yield (70%) after reaction for 7 h. The best results were obtained with PyBOP (95%, 1 h). We noticed that increasing the reaction time did not significantly increase the yields except in the case of DCC/DMAP where a 56% yield was obtained after reaction for 48 h, instead of 15% after 7 h. Increasing the reaction time over 7 h under other experimental conditions appeared to be more detrimental than beneficial (see the Experimental Section).

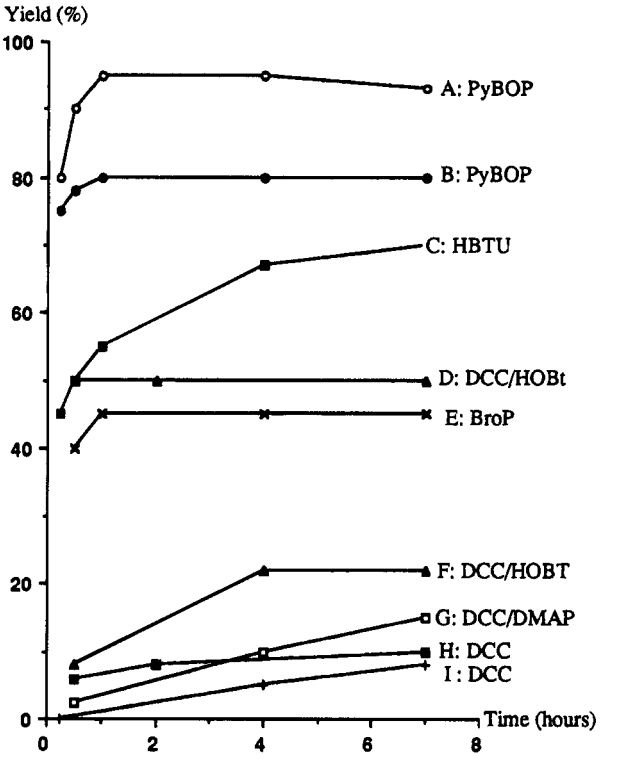

Figure 1. Synthesis of mixed phosphonate **7** with a comparison of reagents. The yields were determined by HPLC (internal standard). For A and C−I, the reactions were run under N_2 using 1.5 equiv of each reagent and benzyl glycolate. For A, an identical result was obtained using either 1.5 equiv of PyBOP in the absence of a N_2 atmosphere or 1.1 equiv of PyBOP under a N_2 atmosphere. For B, 1.1 equiv of PyBOP was used in the absence of a N_2 atmosphere. For D and H, alcohol and DIEA were added after 30 min of preactivation; time 0 corresponds to the time of the addition of benzyl glycolate and DIEA. For G, the yield was 56% after reaction for 48 h and 57% after 72 h.

2. To understand these widely dispersed results, we tried to identify the activated species formed following PyBOP-mediated activation, using ^{31}P NMR analysis. Reaction of monomethyl phenylphosphonate (**15**) with PyBOP and DIEA in $CDCl_3$ gave three signals at δ 25.8, 12.07, and 12.01 ppm, in addition to tripyrrolydinophosphine oxide (OTP) at δ 14.4 ppm. Signals at δ 12.01 and 12.07 ppm corresponded to the pyrophosphonate ester **22** (two diastereomeric pairs) which was independently prepared under the usual conditions[23] by reaction of **15** with DCC. Moreover, when HOBt/DIEA was added to the pyrophosphonate **22**, the signal at δ 25.8 ppm appeared immediately, with concomitant formation of the DIEA salt of **15** (δ 12.2 ppm).

It is known that activation of carboxylic acids by PyBOP, in the presence of a base, leads to an (acyloxy)-phosphonium intermediate that reacts with BtO^- to give a benzotriazolyl ester.[4] Similarly, the DIEA salt of

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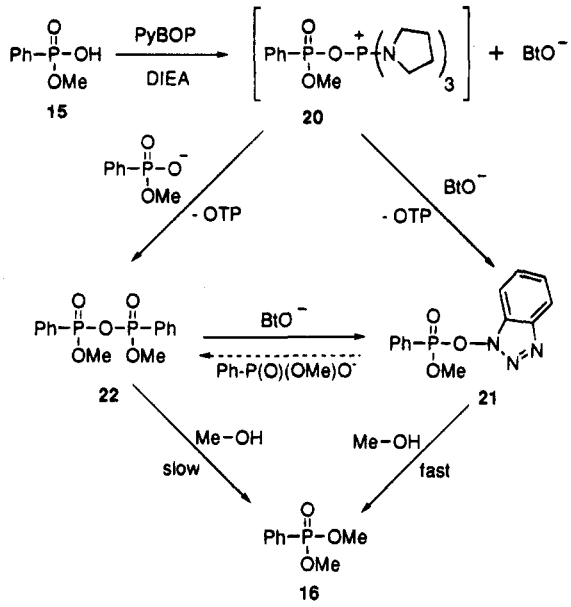
Scheme 3



phosphonate **15** should give the (phosphoryloxy)phosphonium **20** (Scheme 3).[24] Intermediate **20** could react with BtO^- to give **21** and/or with the salt of phosphonate **15** to give **22** (in both cases, with formation of OTP). Compound **21** could also be obtained by attack of BtO^- on the pyrophosphonate **22**.[25] These results are in agreement with the proposed benzotriazolyl ester structure **21** for the compound giving the signal at δ 25.8 ppm.

Similar intermediates have been reported. Dumy[8] observed such an intermediate (^{31}P NMR, δ 25.1 ppm) when the *N*-Pht-protected phosphonoglycine was activated by BOP. Moreover, van Boom obtained dibenzotriazolyl esters of phosphonic acid or a phosphoric acid monoester from the corresponding dichlorides; he used them for the synthesis of phosphonate[26] or phosphate esters.[27] Castro also observed the formation of a Bt ester during the BOP-mediated activation of phosphoric acid diester.[28]

When methanol was added to the mixture obtained by PyBOP-mediated activation of compound **15**, the ^{31}P NMR signals at δ 25.8, 12.01, and 12.07 ppm disappeared rapidly (<30 min) to give the signal of the dimethyl phenylphosphonate **16** (δ 22.0 ppm). In contrast, when the pyrophosphonate ester **22**, prepared from DCC, was treated with methanol/DIEA, formation of the diphosphonate **16** was slow (<10% after 2 h), as shown by HPLC monitoring of the reaction. These observations clearly demonstrate that, in the PyBOP-promoted reaction of **15** with methanol, the reactive species is the benzotriazolyl ester **21**.[29]

3. We have tried to relate these results to the difference in reactivity observed (Figure 1) with the coupling reagents we used.

Using DCC under one-pot conditions (Figure 1I), the pyrophosphonate ester of **3a** (**23**) was formed and reacted slowly with the alcohol; it was still present after 24 h. Addition of alcohol/DIEA after formation of the pyrophosphonate **23** did not improve the yield (Figure 1H). These results are in accord with the poor reactivity of pyrophosphonates. Addition of DMAP is commonly used in the case of the DCC-promoted esterification of carboxylic acids; in the case of **3a** (Figure 1G), the yield slowly rose to 44% in 24 h but did not exeed 56% after 48 h.

In the course of our ^{31}P NMR study (*vide supra*), we noticed that treatment of the pyrophosphonate **22** by HOBt/DIEA led immediately to the formation of the bentriazolyl ester **21**; however, in the absence of DIEA, this ester was not formed during a 30 min observation period. When monophosphonate **3a** was allowed to react with DCC/HOBt, we observed by HPLC the formation of the pyrophosphonate **23** that did not readily lead to the Bt ester because of the absence of DIEA; thus, this reaction did not give good results (Figure 1F). When the reaction was carried out with preactivation followed by the addition of alcohol/DIEA, 30 min later, HPLC analysis showed the disappearence of the pyrophosphonate and the formation of **7** (50%). However, the yield of **7** was not improved when the reaction was prolonged (Figure 1D). We deduced from that experiment that the initially formed pyrophosphonate **23** gave the benzotriazolyl ester upon reaction with HOBt/DIEA, which led rapidly to the mixed phosphonate **7**. The DIEA salt of **3a**, which was liberated from the pyrophosphonate during the HOBt/DIEA reaction, was not transformed again into **23** by DCC, probably because the DCC-mediated activation is an acid-catalyzed process[30] and the medium was now basic, thus explaining why the yield did not exceed 50% (Figure 1D). Indeed, when DCC/HOBt was used under one-pot conditions and in the presence of DIEA, the yield was only 12% after reaction for 24 h.

Results obtained with BroP (Figure 1E) can be explained as follows. With carboxylic acids, this reagent led to the formation of anhydrides.[31] Similarly, starting from **3a**, HPLC analysis showed the formation of the pyrophosphonate ester **23**. Consequently, we expected the same result as that obtained with DCC. The better yield we obtained with BroP is probably due to reaction between the alcohol and the (phosphoryloxy)phosphonium intermediate (corresponding to **20**).[32]

With HBTU, as with PyBOP, we did not detect formation of the **3a**–pyrophosphonate (**23**) by HPLC. In the case of the carboxylic acids, PyBOP and HBTU behave similarly in the formation of the peptide bond; with both reagents, benzotriazolyl esters are the reactive intermediates, and the reaction is conducted in a basic medium.[5] In the case of **3a**, the yield was significantly better with PyBOP (Figure 1, compare A and C). We do not have an explanation for this difference.

In conclusion, the PyBOP-mediated esterification of monophosphonates involves a benzotriazolyl ester. The

(24) This compound was not observed (at rt or at −40 °C) on the ^{31}P NMR spectrum of the PyBOP-mediated activation of **15**.

(25) An equilibrium between **22** and **21** could also be postulated.

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(29) In addition, to our knowledge, pyrophosphonate esters have never been used for the synthesis of phosphonodiesters; in the case of the synthesis of phosphonate monoesters from pyrophosphonates, the reaction with the alcohol was conducted for several hours under reflux.[23b]

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(32) We tried to observe this intermediate by ^{31}P NMR in the same way as we did for the intermediate obtained from 2,4,6-trimethylbenzoic acid.[4] We were unable to obtain interpretable results. Considering practical considerations (superimposition of the NMR signals), we used PyBroP[4] in these experiments. Nevertheless, in the case of the BOP-promoted activation of phophoric acid di-*tert*-butyl ester, we observed (^{31}P NMR) the (phosphoryloxy)phosphonium intermediate (unpublished results).

Table 3. Comparison of the Reactivity of Carboxylic and Phosphonic Acids

acid	alcohol or amine	reaction time (h)	yield %[a]	product
BzlCOOH	(−)-menthol	24	65[b,c]	**24**
	(*S*)-HOCH(CH$_3$)COOMe	4	72[b]	**25**
	H-Ala-OMe	0.5	90[d]	**26**
15	(−)-menthol	2.5	81[b]	**19**
	(*S*)-HOCH(CH$_3$)COOMe	2	82[b]	**17**
	H-Ala-OMe	4	64[e]	**27**

[a] Isolated yield. [b] Reaction with 1.5 equiv of PyBOP, 1.5 equiv of alcohol, and 4 equiv of DIEA. [c] With BOP, in the same conditions, the yield was 68%. [d] Reaction with 1.2 equiv of BOP, 1.2 equiv of H-Ala-OMe·HCl, and 3 equiv of DIEA. [e] Reaction with 2 equiv of BOP, 2 equiv of H-Ala-OMe·HCl and 5 equiv of DIEA.

basic medium which is necessary when using this reagent allows for the formation of this intermediate, which is particularly reactive with alcohols.

Reactivity of Benzotriazolyl Esters of Phosphonic *vs* Carboxylic Acids. The difference in reactivity between phosphonic and carboxylic Bt esters is illustrated in the following experiments.

Formation of intermediate **21** was demonstrated above by using ^{31}P NMR; we were unable to observe it however by RP-HPLC. This is probably accounted for by its high reactivity with water.[33] In contrast, benzotriazolyl esters of carboxylic acids are considerably more stable and can be isolated and purified after the usual workup,[7a,34] and observed by RP-HPLC.[4] The relative stability of Bt carboxylic esters with water is in accord with their poor reactivity with alcohols, and this explains why BOP or PyBOP are not widely used in the synthesis of carboxylic esters.

We reinvestigated the PyBOP-mediated esterification of a carboxylic acid. The reaction of phenylacetic acid with menthol in the presence of PyBOP/DIEA gave, after reaction at room temperature for 24 h, only a 65% yield of the ester **24** (Table 3), whereas under the same conditions, the monomethyl phenylphosphonate (**15**) gave an 81% yield of the menthyl ester **19**, after only 2.5 h. Similar results were obtained using methyl lactate (Table 3, compare compounds **17** and **25**).[35] In the course of the esterification reaction of phenylacetic acid, the phenylacetic Bt esters were observed (HPLC); they reacted relatively slowly with the alcohol to give esters **24** and **25**.[36]

Although the reactivity of carboxylic Bt esters with alcohols is not high, they react very well with amines since they are the reactive species formed with numerous peptide-coupling reagents (DCC/HOBt, BOP, PyBOP, and HBTU).[5] We compared this reactivity to that of phosphonic Bt esters with amines.

The reaction of **15** with Ala-OMe in the presence of BOP/DIEA gave the corresponding phosphonamidate **27**.[37] Nevertheless, the yield was only 64% despite the use of 2 equiv of BOP and Ala-OMe and reaction for 4 h, whereas in the case of phenylacetic acid, the amide **26** was obtained in 90% yield after only 0.5 h without the use of a large excess of reagents (Table 3).

To better compare the relative reactivities of the benzotriazolyl phosphonic and carboxylic esters toward amines and alcohols, we used competition reactions. One equivalent of the phosphonic acid **15** or, independently, phenylacetic acid was allowed to react with a mixture of 1 equiv of methyl lactate and 1 equiv of Ala-OMe·HCl, in the presence of PyBOP (1.5 equiv) and DIEA (4 equiv). As expected, the phenylacetic acid reacted faster with the amine than with the alcohol in a 95:05 ratio, while the reverse 20:80 ratio was obtained starting from **15**. To ensure that, in these experiments, the Bt esters were the reactive intermediates, the reactions were also conducted by PyBOP-mediated preactivation of the acids before alcohol addition. In both cases, ratios identical to those obtained under one-pot conditions were obtained.

We conclude that Bt esters of carboxylic acids were more reactive with amines than with alcohols, while the reverse situation was observed in the case of phosphonic acids. This behavior is not limited to the phosphonic acid Bt esters. In the case of carboxylic−phosphinic or carboxylic−phosphoric mixed anhydrides, amines react with the carboxylic part whereas alcohols react with the phosphorus part.[38] In addition, we have shown[39] that BOP- or PyBOP-mediated activation of a phosphinic acid does not produce the phosphinamidate, while in the presence of methanol, the methyl ester is obtained. It is also noteworthy that phosphorylated α-amino acids with an unprotected phosphoric residue have been used in peptide synthesis, using the BOP reagent, without formation of phosphoramidates.[40]

It is known that acid chlorides (or fluorides) are much more reactive with amines than with alcohols.[41] In the case of phosphorus (phosphoric, phosphonic, or phosphinic) acid chlorides, a similar reactivity has been

(33) Bt esters were never observed during the esterification of compound **3**. In contrast, the pyrophosphonate esters were visible by using the same HPLC conditions.

(34) (a) König, W.; Geiger, R. *Chem. Ber.* **1970**, *103*, 788−798. (b) Barlos, K.; Papaioannou, D.; Theodoropoulos, D. *Int. J. Pept. Protein Res.* **1984**, *23*, 300−305. (c) Katritzky, A. R.; Malhotra, N.; Fan, W.-Q.; Anders, E. *J. Chem. Soc., Perkin Trans. 2* **1991**, 1545−1547.

(35) Phenylacetic acid was used, instead of benzoic acid, for comparison with **15**, to avoid conjugation leading to a difference in reactivity; in the case of **15**, the conjugation is not effective (Hudson, R. F.; Keay, L. *J. Chem. Soc.* **1960**, 1859−1864).

(36) By reference to our previous work,[4] the Bt esters (O- and N-acylated forms) were identified by RP-HPLC, using the in flight UV spectra obtained during HPLC analysis (diode array UV detector). HPLC studies of this reaction conducted with, or without, preactivation gave the same results; in both cases, the Bt esters were observed and disappeared in favor of ester **24** or **25**. This result and others[7] are in conflict with the recent claim by Patel that Bt esters are unreactive toward alcohols (Kim, M. H.; Patel, D. V. *Tetrahedron Lett.* **1994**, *35*, 5603−5606).

(37) The fact that BOP- or PyBOP-mediated activation was effective in forming the P−N linkage in the case of *N*-phthalyl α-aminophosphonic acid[8a] and **15** and was not in the case of Fmoc- or *Z*-protected α-aminophosphonic acid[8b,9] remains to be explained. In the later case, Dumy[8b] observed (^{31}P NMR) Bt ester, pyrophosphonates, and unexpected signals, and Musiol[9] observed the transformation of the first obtained Bt ester (P−O form) into a postulated P−N form of this ester. If the transposition of the C−O form of the Bt ester into the C−N form is well-established in the case of carboxylic acids (see ref 34c and references cited therein), the same transposition in the case of phosphorus compounds seems questionable, owing to the energy difference between these two kinds of bond; for example, if, as now established by X-ray structure determination, in the HBTU reagent, the OBt rest is linked to the carbon atom with a C−N bond (Abdelmoty, I.; Albericio, F.; Carpino, L. A.; Foxman, B. M.; Kates, S. A. *Lett. Pept. Sci.* **1994**, *1*, 57−67), in the case of the BOP, OBt is linked to the phosphonium part by a P−O bond (Coste, J.; Castro, B.; Mornon, J. P. Unpublished X-ray data).

(38) (a) Ramage, R.; Hopton, D.; Parrot, M. J.; Richardson, R. S.; Kenner, G. W.; Moore, G. A. *J. Chem. Soc., Perkin Trans. 1* **1985**, 461−470. (b) Crofts, P. C. In *Organic Phosphorus Compounds*; Kosolapoff, G. M., Maier, L., Eds.; Wiley-Interscience: New York, 1973; Vol. 6, pp 51−52.

(39) Campagne, J.-M.; Coste, J.; Guillou, L.; Heitz, A.; Jouin, P. *Tetrahedron Lett.* **1993**, *34*, 4181−4184.

(40) Ottinger, E. A.; Shekels, L. L.; Bernlohr, D. A.; Barany, G. *Biochemistry* **1993**, *32*, 4354−4361.

(41) Kivinen, A. In *The chemistry of acyl halides;* Patai, S., Ed.; Interscience: London, 1972; pp 178−222. See p 210.

demonstrated.[42] In contrast, Horner[42] observed that phosphorus acid fluorides are more reactive with alcohols than with amines. The same behavior has been observed with phosphinic acid cyanide or *p*-nitrophenyl ester,[42a] and Green showed that this is also true for the bis-(*p*-nitrophenyl) phosphonates.[16b] Thus, the reactivity of the carboxylic Bt esters with alcohols and amines is analogous to that of acid chlorides, whereas that of phosphonic Bt esters is different from that of the phosphonyl chlorides. The phosphonic Bt esters behave more like phosphonic fluorides. Nevertheless, given the experimental conditions described by Horner, Bt esters are much more reactive than the corresponding fluoride analogues.

In conclusion, the method for synthesizing mixed phosphonic acid diesters by BOP- or PyBOP-mediated activation of phosphonate monoesters is efficient and racemization-free. The reaction proceeds *via* a highly reactive benzotriazolyl phosphonic ester whose formation is favored by the basic medium which is needed when using these phosphonium reagents. The reactivity of this Bt ester with alcohol and amine nucleophiles is reversed in comparison with that of the carboxylic acid Bt esters. The use of this method for solid phase synthesis of phosphonopeptides is under investigation.

Experimental Section

General. For the instrumentation used, see ref 4. "Usual workup" consists of the following: washing the organic phase with 5% $KHSO_4$, 5% $NaHCO_3$, and brine, drying over Na_2SO_4, filtration, and concentration of the solvent *in vacuo*. HPLC analyses: Column Ultrabase C8 5 μm (Société Française de Chromatographie Colonne), 150 × 4.6 mm, CH_3CN/H_2O (with 0.1% TFA), 1.5 mL/min, detection at 214 nm. Various sets of conditions were used: 1, gradient 30 to 90% CH_3CN in 20 min; 2, gradient 40 to 90% CH_3CN in 20 min; 3, gradient 30 to 100% CH_3CN in 20 min; 4, gradient 10 to 100% CH_3CN in 20 min. Commercially available compounds were used as received, unless otherwise stated. Diethyl ether and THF were distilled under argon from sodium/benzophenone. DCM was filtered, under argon, on alumina. Alcohols are commercially available or known.[43]

Benzyl (±)-[1-[(Benzyloxycarbonyl)amino]-2-phenylethyl]phosphonic Acid (3a). To a solution of (±)-[1-[(benzyloxycarbonyl)amino]-2-phenylethyl]phosphonous acid[17] (3 g, 9.4 mmol) and DMAP (115 mg, 0.94 mmol) in THF (10 mL) was added, at room temperature over a period of 20 min, a solution of DCC (2.3 g, 11.3 mmol) and benzyl alcohol (0.97 mL, 9.4 mmol) in THF (10 mL). Stirring was continued during 24 h. DCU was filtered, and THF was evaporated under reduced pressure. After dissolution of the residue in ethyl acetate (100 mL), the insoluble DCU was filtered and the solution washed with $NaHCO_3$ (3 × 10 mL) and brine (2 × 10 mL) and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The crude product was dissolved in DCM (50 mL) and the solution left overnight at 4 °C. DCU was filtered and DCM removed to furnish (±)-[1-[(benzyloxycarbonyl)amino]-2-phenylethyl]phosphonous acid benzyl ester as a oil (3.8 g) which was used in the next step without purification.

Following Karanewsky's procedure,[18] to a solution of the preceding product in dioxane (10 mL) was added $NaIO_4$ (2 g, 9.4 mmol) dissolved in H_2O (5 mL). After reaction under stirring at room temperature for 16 h, the mixture was filtered and the filtrate dissolved in ethyl acetate (100 mL). The solution was washed with 5% $KHSO_4$ (2 × 10 mL), 10% $NaHSO_3$ (10 mL), and brine (10 mL) and dried (Na_2SO_4) and the solvent removed under reduced pressure to furnish a white solid (2.5 g, 62% for the two steps): mp 130 °C; HPLC (condition 3) t_R 8.6 min; ^1H NMR (DMSO-d_6) δ 7.64 (d, J = 9.7 Hz, 1H), 7.1–7.4 (m, 15H), 5.00 (m, 2H), 4.88 and 4.93 (AB, J = 13.0 Hz, 2H), 4.08 (m, 1H), 3.10 (m, 1H), 2.81 (m, 1H); ^{31}P NMR (DMSO-d_6) δ 22.6 (22.2, rotamer, 6%); MS (FAB+, GT) m/z (relative intensity) 448 (M + Na^+, 26), 426 (M + H^+, 5). Anal. Calcd for $C_{23}H_{24}NO_5P$: C, 64.94; H, 5.69; N, 3.29. Found: C, 64.82; H, 5.98; N, 3.21.

Methyl (*R*)-[1-[(Benzyloxycarbonyl)amino]-2-phenylethyl]phosphonic Acid ((*R*)-3b). The (+)-α-methylbenzylamine salt of (±)-[1-[(benzyloxycarbonyl)amino]-2-phenylethyl]-phosphonous acid was obtained and recrystallized according to ref 17 to give the salt of one of the two enantiomers: mp 187–190 °C; $[\alpha]^{20}_D$ −49 (*c* 1, EtOH) (lit.[17] mp 190–193 °C; $[\alpha]^{24}_D$ −47.6 (*c* 1, EtOH)).

1. Absolute Configuration. This pure salt was treated with HBr in AcOH according to ref 17 to furnish (*R*)-(1-amino-2-phenylethyl)phosphonous acid: mp 224–226 °C; $[\alpha]^{20}_D$ −64 (*c* 1, EtOH) (lit.[17] mp 224 °C; $[\alpha]^{25}_D$ −62.2 (*c* 1, EtOH)). To this compound (100 mg, 0.5 mmol) in dioxane (1 mL) was added $NaIO_4$ (129 mg, 0.6 mmol). After stirring at room temperature for 12 h, the mixture was filtered, acidified with 1 N HCl, and evaporated under reduced pressure. The residue was dissolved in EtOH (1 mL), and propylene oxide was added until complete precipitation of the zwitterionic compound (1*R*)-(1-amino-2-phenylethyl)phosphonic acid. This solid was filtered (80 mg, 75%): $[\alpha]^{20}_D$ −41 (*c* 1, 1 N NaOH) (lit.[44] $[\alpha]^{20}_D$ −38.9 (*c* 2, 2 N NaOH)).

2. Synthesis of (*R*)-3b. (*R*)-[1-[(Benzyloxycarbonyl)amino]-2-phenylethyl]phosphonous acid was obtained from its (+)-α-methylbenzylamine salt by adding 1 N HCl. This compound was esterified with DCC/DMAP/MeOH using the same method as above in the case of the synthesis of **3a**. From 2.8 g (8.77 mmol) was obtained 2.7 g (93%). The crude product was used for the next step. From 2.5 g (7.5 mmol), oxidized as for **3a**, was obtained 2.3 g (87%) of (*R*)-**3b**: mp 163 °C; $[\alpha]^{20}_D$ −50 (*c* 0.5, EtOH); HPLC (condition 2) t_R 6.1 min; ^1H NMR (DMSO-d_6) δ 7.57 (d, J = 9.6 Hz, 1H), 7.24 (m, 10H), 4.96 and 4.88 (AB, J = 13 Hz, 2H), 3.98 (m, 1H), 3.59 (d, J = 10.5 Hz, 3H), 3.03 (dt, J = 15.0 Hz, J = 3.7 Hz, 1H), 2.75 (td, J = 13.3 Hz, J = 6.5 Hz, 1H); ^{31}P NMR (DMSO-d_6) δ 28.7; MS (FAB+, NBA) m/z (relative intensity) 699 (2M + H^+, 1), 372 (M + Na^+, 15), 350 (M + H^+, 18). Anal. Calcd for $C_{17}H_{20}NO_5P$: C, 58.45; H, 5.77; N, 4.01. Found: C, 58.62; H, 5.82; N, 4.40.

Methyl (±)-[1-[(Benzyloxycarbonyl)amino]-2-methylpropyl]phosphonic Acid (3c). To a solution of (±)-[1-[(benzyloxycarbonyl)amino]-2-methylpropyl]phosphonous acid[17] (2.7 g, 10 mmol) and DMAP (0.12 g, 1 mmol) in THF (10 mL) was added dropwise, at room temperature, under stirring a solution of EDC (2.3 g, 12 mmol) and MeOH (6 mL, 150 mmol) in THF. After reaction for 4 h, the solvents were evaporated. The oily residue was dissolved with ethyl acetate, washed with 5% $NaHCO_3$ and brine, and dried (Na_2SO_4), and the solvent was evaporated under reduced pressure to furnish an oil (2.66 g): HPLC (condition 3) t_R 7.0 min. This crude product, used without purification, was oxidized as for **3a** to give a white solid (2.1 g, 73%): mp 103 °C; HPLC (condition 1) t_R 7.0 min; ^1H NMR (DMSO-d_6) δ 7.35 (m, 5H), 7.28 (d, J = 10.3 Hz, 1H), 5.06 (AB, 2H), 3.69 (ddd, J = 5.4 Hz, J = 10.1 Hz, J = 16.2 Hz, 1H), 3.53 (d, J = 10.4 Hz, 3H), 2.0 (m, 1H), 0.93 (d, J = 6.5 Hz, 6H); ^{31}P NMR (DMSO-d_6) δ 28.1 (27.2, rotamer, 8%); MS (FAB+, NBA) m/z (relative intensity) 603 (2M + H^+, 1), 324 (M + Na^+, 16), 302 (M + H^+, 15). Anal. Calcd for $C_{13}H_{20}NO_5P$: C, 51.83; H, 6.69; N, 4.65. Found: C, 52.14; H, 6.56; N, 4.73.

Synthesis of Mixed Phosphonates 4–13 and 16–19: General Procedure. To a solution of monophosphonate (1 equiv), alcohol (1.5 equiv), and BOP or PyBOP (1.5 equiv) in DMF (2 mL/mmol) was added at room temperature, under stirring, DIEA (4 equiv). After a reaction time t, DMF was

(42) (a) Horner, L.; Gehring, R. *Phosphorus Sulfur* **1981**, *11*, 157–176. (b) Horner, L.; Gehring, R. *Phosphorus Sulfur* **1982**, *12*, 295–304. (c) Weidert, P. J.; Geyer, E.; Horner, L. *Phosphorus, Sulfur Silicon* **1989**, *44*, 255–259. (d) Horner, L. *J. Prakt. Chem.* **1992**, *334*, 645–655.

(43) (a) Losse, G.; Bachmann, G. *Chem. Ber.* **1964**, *97*, 2671–2680. (b) Losse, G.; Klengel, H. *Tetrahedron* **1971**, *27*, 1423–1434.

(44) Dhawan, B.; Redmore, D. *Phosphorus Sulfur* **1987**, *32*, 119–144.

evaporated under reduced pressure, and the residue was dissolved in ethyl acetate. The crude product obtained after usual workup was purified by chromatography.

Dibenzyl (±)-[1-[(Benzyloxycarbonyl)amino]-2-phenylethyl]phosphonate (4). The reaction was carried out according to the general procedure on **3a** (500 mg, 1.18 mmol), benzyl alcohol, and BOP; t = 30 min: column chromatography eluent 30:70 ethyl acetate/pentane; R_f 0.21; solid; yield 87%; mp 87 °C; HPLC (conditions 1) t_R 13.0 min; ^{1}H NMR (DMSO-d_6) δ 7.88 (d, J = 9.5 Hz, 1H), 7.40−7.10 (m, 20H), 5.05 (m, 4H), 4.94, 4.89 (AB, J = 12.9 Hz, 2H), 4.23 (m, 1H), 3.03 (dt, J = 14.5 Hz, J = 3.5 Hz, 1H), 2.83 (td, J = 13.1 Hz, J = 7.6 Hz, 1H), rotamer (7%) at δ 7.46 (d, J = 9.5 Hz), 4.74 and 4.87 (AB, J = 13.0 Hz); ^{31}P NMR (DMSO-d_6) δ 25.9, rotamer (8%) at δ 25.5; MS (FAB+, GT) m/z (relative intensity) 516 (M + H$^+$, 60). Anal. Calcd for $C_{30}H_{30}NO_5P$: C, 69.90; H, 5.82; N, 2.72. Found: C, 69.72; H, 5.95; N, 2.68.

Isopropyl Benzyl [(*R,S*)-1-[(Benzyloxycarbonyl)amino]-2-phenylethyl]phosphonate (5). The reaction was carried out according to the general procedure on **3a** (500 mg, 1.18 mmol), isopropyl alcohol, and BOP; t = 90 min: column chromatography eluent 40:60 ethyl acetate/hexane; oil (0.48 g, 87%); R_f 0.24 (40:60 ethyl acetate/hexane); HPLC (conditions 1) t_R 13.6 min; ^{1}H NMR (DMSO-d_6) δ 7.79 (d, J = 9.6 Hz, 0.5H), 7.77 (d, J = 9.6 Hz, 0.5H), 7.1−7.5 (m, 15H), 5.05 (m, 2H), 4.95 (m, 2H), 4.62 (m, 1H), 4.10 (m, 1H), 3.05 (m, 1H), 2.82 (m, 1H), 1.20 (m, 6H); ^{31}P NMR (DMSO-d_6) δ 24.6 and 24.3 (50:50); MS (FAB+, NBA) m/z (relative intensity) 468 (M + H$^+$, 38). Anal. Calcd for $C_{26}H_{30}NO_5P$: C, 66.80; H, 6.47; N, 3.00. Found: C, 66.55; H, 6.53; N, 3.44.

Methyl [[(Benzyloxy)[(*R,S*)-1-[(benzyloxycarbonyl)amino]-2-phenylethyl]phosphoryl]oxy]acetate (6). The reaction was carried out according to the general procedure on **3a** (500 mg, 1.18 mmol), methyl glycolate, and BOP; t = 30 min: column chromatography eluent 30:70 ethyl acetate/hexane; R_f 0.25; oil (498 mg, 85%); HPLC (condition 2) t_R 10.3 min; ^{1}H NMR (DMSO-d_6) δ 7.85 (d, J = 9.7 Hz, 0.7H), 7.83 (d, J = 10.7 Hz, 0.3H), 7.1−7.5 (m, 15H), 5.15 (m, 2H), 4.90 (m, 2H), 4.64 (m, 2H), 4.26 (m, 1H), 3.7 (s, 3H), 3.11 (m, 1H), 2.83 (m, 1H); ^{31}P NMR (DMSO-d_6) δ 26.4, 26.3 (70:30); MS (FAB+, GT) m/z (relative intensity) 520 (M + Na$^+$, 7), 498 (M + H$^+$, 65). Anal. Calcd for $C_{26}H_{28}NO_7P$: C, 62.78; H, 5.63; N, 2.82. Found: C, 62.63; H, 5.71; N, 2.95.

Benzyl [[(Benzyloxy)[(*R,S*)-1-[(benzyloxycarbonyl)amino]-2-phenylethyl]phosphoryl]oxy]acetate (7). The reaction was carried out according to the general procedure on **3a** (2.5 g, 5.9 mmol), benzyl glycolate, and BOP; t = 30 min: column chromatography eluent 30:70 ethyl acetate/hexane; R_f 0.17; oil (2.9 g, 85%); HPLC (condition 3) t_R 14.1 min; ^{1}H NMR (DMSO-d_6) δ 7.88, 7.85 (2d, J = 9.7 Hz, 0.6H and 0.4H), 7.1−7.5 (m, 20H), 5.2 (m, 2H), 5.11 (m, 2H), 4.91 (m, 2H), 4.69 (m, 2H), 4.24 (m, 1H), 3.09 (m, 1H), 2.83 (m, 1H); ^{31}P NMR (DMSO-d_6) δ 26.5, 26.3 (62:38), 26.1 and 25.9 (rotamers, 8%). Anal. Calcd for $C_{32}H_{32}NO_7P$: C, 67.01; H, 5.62; N, 2.44. Found: C, 67.07; H, 5.83; N, 2.76.

Methyl (*S*)-2-[[(Benzyloxy)[(*R,S*)-1-[(benzyloxycarbonyl)amino]-2-phenylethyl]phosphoryl]oxy]propionate (8). The reaction was carried out according to the general procedure on **3a** (500 mg, 1.18 mmol), methyl (*S*)-lactate, and BOP or PyBOP; t = 2 h: column chromatography eluent 40:60 ethyl acetate/hexane; R_f 0.34; oil (0.49 g, 82%; yield was the same by using BOP or PyBOP); HPLC (condition 1) t_R large pic at 12.5 min; ^{1}H NMR (DMSO-d_6) δ 7.87, 7.86, 7.80 and 7.77 (4d, J = 9.6 Hz, 1H), 7.1−7.4 (m, 15H), 5.1 (m, 2H), 4.9 (m, 3H), 4.22 (m, 1H), 3.684, 3.678, 3.672 (3s (1:2:1), 3H), 3.1 (m, 1H), 2.8 (m, 1H), 1.35 (m, 3H); ^{31}P NMR (DMSO-d_6) δ 25.75, 25.54, 25.47 (15:57:28); MS (FAB+, NBA) m/z (relative intensity) 534 (M + Na$^+$, 5), 512 (M + H$^+$, 50). Anal. Calcd for $C_{27}H_{30}NO_7P$: C, 63.40; H, 5.91; N, 2.74. Found: C, 63.60; H, 6.01; N, 2.89.

Benzyl (*R*)-2-[[(Benzyloxy)[(*R,S*)-1-[(benzyloxycarbonyl)amino]-2-phenylethyl]phosphoryl]oxy]-3-methylbutanoate (9). The reaction was carried out according to the general procedure on **3a** (500 mg, 1.18 mmol), (*R*)-2-hydroxy-3-methylbutyric acid benzyl ester, and PyBOP; t = 3 h: column chromatography eluent 30:70 ethyl acetate/hexane; R_f 0.31; oil (0.59 g, 81%); HPLC (condition 1) t_R 15.85, 16.03, 16.35, 16.43 min (20:16:36:28); ^{1}H NMR (DMSO-d_6) δ 7.86, 7.85, 7.78, 7.74 (4d (36:28:20:16), J = 9.7 Hz, 1H), 7.1−7.4 (m, 20H), 5.15 (m, 2H), 5.05 (m, 2H), 4.93 (m, 2H), 4.70 (m, 1H), 4.18 and 4.24 (2m, 1H), 3.06 (m, 1H), 2.80 (m, 1H), 2.1 (m, 1H), 0.85 (m, 6H); ^{31}P NMR (DMSO-d_6) δ 26.1, 26.0, 25.9, 25.8 (36:20:16:28); MS (FAB+, NBA) m/z (relative intensity) 616 (M + H$^+$, 44), 480 (2), 390 (4), 300 (19), 210 (43), 120 (36), 91 (100). Anal. Calcd for $C_{35}H_{38}NO_7P$: C, 68.28; H, 6.22; N, 2.28. Found: C, 68.38; H, 6.38; N, 2.52.

Benzyl (*S*)-2-[[Methoxy[(*R*)-1-[(benzyloxycarbonyl)amino]-2-phenylethyl]phosphoryl]oxy]-3-methylbutanoate (10). The reaction was carried out according to the general procedure on (*R*)-**3b** (500 mg, 1.66 mmol), (*S*)-2-hydroxy-3-methylbutyric acid benzyl ester, and BOP; t = 2 h: column chromatography eluent 30:70 ethyl acetate/hexane; R_f 0.42; oil (0.65 g, 85%); HPLC (condition 3) t_R 13.8, 14.1 min; ^{1}H NMR (DMSO-d_6) δ 7.81, 7.72 (2d, J = 9.7 Hz, 0.7H and 0.3H), 7.1−7.4 (m, 15H), 5.2 (m, 2H), 4.95, 4.85 (AB, J = 12.0 Hz, 2H), 4.77 (dd, J = 7.7 Hz, J = 4.2 Hz, 0.3H), 4.65 (dd, J = 6.8 Hz, J = 4.4 Hz, 0.7H), 4.18 (m, 1H), 3.64 (d, J = 10.5 Hz, 3H), 3.09 and 3.00 (2m, 1H), 2.81 (m, 1H), 2.05, 2.13 (2m, 0.3H and 0.7H), 0.96 (m, 6H); ^{31}P NMR (DMSO-d_6) δ 26.8, 26.6 (7:3), rotamers (7%) at δ 26.2 and 25.9 (7:3). Anal. Calcd for $C_{29}H_{34}NO_7P$: C, 64.56; H, 6.35; N, 2.60. Found: C, 64.36; H, 6.15; N, 2.96.

Benzyl (2*S*,3*S*)-2-[[Methoxy[(*R*)-1-[(benzyloxycarbonyl)amino]-2-phenylethyl]phosphoryl]oxy]-3-methylpentanoate (11). The reaction was carried out according to the general procedure on (*R*)-**3b** (350 mg, 1.16 mmol), (*S*)-2-hydroxy-3-methylpentanoic acid benzyl ester, and PyBOP; t = 2 h: column chromatography eluent 30:70 ethyl acetate/cyclohexane; R_f 0.35; oil (0.48 g, 81%); HPLC (conditions 3) t_R 12.4, 12.7 min; ^{1}H NMR (DMSO-d_6) δ 7.83 (d, J = 10.4 Hz, 0.75H), 7.72 (d, J = 9.4 Hz, 0.25H), 7.10−7.45 (m, 15H), 5.21 (m, 2H), 4.82−4.98 (m, 2H), 4.80 (dd, J = 8.3 Hz, J = 4.3 Hz, 0.25H), 4.71 (dd, J = 7.6 Hz, J = 5.4 Hz, 0.75H), 4.15 (m, 1H), 3.65 (d, J = 9.3 Hz, 3H), 3.10, 3.02 (2m, 1H), 2.79 (m, 1H), 1.92 and 1.84 (2m, 0.25H and 0.75H), 1.35 (m, 1H), 1.16 (m, 1H), 0.92 (d, J = 6.9 Hz, 0.75H), 0.85 (d, J = 6.9 Hz, 2.25H), 0.82 (partly masked, 0.75H), 0.78 (t, J = 7.5 Hz, 2.25H); ^{31}P NMR (DMSO-d_6) δ 26.8, 26.5 (72:28), rotamer (5%) at δ 26.2; MS (FAB+, GT) m/z (relative intensity) 554 (M + H$^+$, 10). Anal. Calcd for $C_{30}H_{36}NO_7P$: C, 65.10; H, 6.55; N, 2.53. Found: C, 64.84; H, 6.39; N, 2.82.

Methyl [[Methoxy[(*R,S*)-1-[(benzyloxycarbonyl)amino]-2-methylpropyl]phosphoryl]oxy]acetate (12). The reaction was carried out according to the general procedure on **3c** (400 mg, 1.33 mmol), methyl glycolate, and PyBOP; t = 1 h: column chromatography eluent 99:1 DCM/MeOH; R_f 0.40; oil (0.37 g, 75%); HPLC (condition 1) t_R 10.6 min; ^{1}H NMR (DMSO-d_6) δ 7.62, 7.61 (2d, J = 10.1 Hz, 0.4H and 0.6H), 7.4 (m, 5H), 5.07, 5.10 (AB, J = 12.0 Hz, 2H), 4.58 (m, 2H), 3.84 (m, 1H), 3.68 (m, 6H), 2.07 (m, 1H), 0.94 (m, 6H); ^{31}P NMR (DMSO-d_6) δ 27.5, 27.3 (35:65); MS (FAB+, GT) m/z (relative intensity) 374 (M + H$^+$, 33), 360 (8), 330 (27), 258 (91), 242 (100), 162 (18), 91 (97), 72 (78). Anal. Calcd for $C_{16}H_{24}NO_7P$: C, 51.47; H, 6.48; N, 3.75. Found: C, 51.35; H, 6.59; N, 4.13.

Benzyl (2*S*,3*S*)-2-[[Methoxy[(*R,S*)-1-[(benzyloxycarbonyl)amino]-2-methylpropyl]phosphoryl]oxy]-3-methylpentanoate (13). The reaction was carried out according to the general procedure on **3c** (400 mg, 1.33 mmol), (*S*)-2-hydroxy-3-methylpentanoic acid benzyl ester, and PyBOP; t = 2 h: column chromatography eluent 30:70 ethyl acetate/cyclohexane; R_f 0.44; oil (0.435 g, 65%); HPLC (condition 1) t_R 13.88, 14.13, 14.46 min (28:55:17); ^{1}H NMR (DMSO-d_6) δ 7.65, 7.58 and 7.47 (3d, J = 10.1 Hz, 1H), 7.36 (m, 10H), 5.16 (m, 2H), 5.08 (m, 2H), 4.66 (m, 1H), 3.85 (m, 1H), 3.61 (m, 3H), 2.05 (m, 1H), 1.85 (m, 1H), 1.33 (m, 1H), 1.12 (m, 1H), 0.72−0.92 (m, 12H); ^{31}P NMR (DMSO-d_6) δ 27.16, 27.12, 26.66, 26.51 (27:39:16:18); MS (FAB+, GT) m/z (relative intensity) 506 (M + H$^+$, 20). Anal. Calcd for $C_{26}H_{36}NO_7P$: C, 61.77; H, 7.18; N, 2.77. Found: C, 61.75; H, 7.34; N, 3.09.

Benzyl (*S*)-2-[[[(*R*)-1-[(Benzyloxycarbonyl)amino]-2-phenylethyl]hydroxyphosphoryl]oxy]-3-methylbutanoate ((*R,S*)-14). According to Campbell,[15a] to **10** (300

mg, 0.55 mmol) in DCM (5 mL) was added Me_3SiBr (0.238 mL, 1.8 mmol). After stirring for 3 h at room temperature, to the mixture were added ethyl acetate (50 mL) and 1 N HCl (20 mL). The organic phase was washed with 1 N HCl and brine and dried (Na_2SO_4) and the solvent evaporated under reduced pressure to furnish an oil (0.150 g, 52%): HPLC (condition 3) t_R 11.2 min; ^1H NMR (DMSO-d_6) δ 7.1–7.4 (m, 15H), 6.27 (d, J = 8.7 Hz, 1H), 5.08 (s, 2H), 4.92, 4.76 (AB, J = 13.0 Hz, 2H), 4.44 (dd, J = 8.1 Hz, J = 4.9 Hz, 1H), 3.64 (m, 1H), 3.10 (m, 1H), 2.65 (m, 1H), 1.92 (m, 1H), 0.83, 0.79 (2d, J = 6.7 Hz, 6H), rotamer (15%) at δ 5.70 (br s), 4.68 and 4.56 (AB, J = 13.0 Hz). To the crude product (100 mg, 0.19 mmol) in ethyl ether (5 mL) was added 1-adamantylamine (28 mg, 0.19 mmol). The solid obtained was washed with ether to furnish 0.035 g of the adamantylamine salt of (*R,S*)-**14**: mp 216–220 °C; $[\alpha]^{20}_D$ −38 (*c* 0.5, EtOH); ^{31}P NMR (DMSO-d_6) δ 15.5, rotamer (10%) at δ 15.2; MS (FAB−, GT) *m/z* (relative intensity) 524 (M^-, 75); HRMS calcd for $C_{28}H_{31}NO_7P$ 524.1838, found 524.1794.

Benzyl (*R*)-2-[[[(*R*)-1-[(Benzyloxycarbonyl)amino]-2-phenylethyl]hydroxyphosphoryl]oxy]-3-methylbutanoate ((*R,R*)-14). 1. Synthesis of Benzyl (*R*)-2-[[Methoxy[(*R*)-1-[(benzyloxycarbonyl)amino]-2-phenylethyl]phosphoryl]oxy]-3-methylbutanoate. The reaction was carried out according to the general procedure on (*R*)-**3b** (500 mg, 1.43 mmol), (*R*)-2-hydroxy-3-methylbutyric acid benzyl ester, and BOP; t = 2 h: column chromatography eluent 30:70 ethyl acetate/hexane; R_f 0.27; oil (0.68 g, 88%); HPLC (condition 3) t_R 13.6, 13.9 min; ^1H NMR (DMSO-d_6) δ 7.78, 7.67 (2d (50:50), J = 9.7 Hz, 1H), 7.1–7.4 (m, 15H), 5.20 (m, 2H), 4.90 (m, 2H), 4.74 (dd, J = 7.8 Hz, J = 4.1 Hz, 0.5H), 4.68 (dd, J = 6.7 Hz, J = 4.5 Hz, 0.5H), 4.24, 4.12 (2m, 1H), 3.64 and 3.68 (2d, J = 10.7 Hz, 2 × 1.5H), 3.11, 3.06 (2m, 1H), 2.81, 2.78 (2m, 1H), 2.15 (m, 1H), (0.95 (d, J = 6.9 Hz), 0.92 (d, J = 6.9 Hz), 0.86 (d, J = 6.8 Hz), 0.85 (d, J = 6.7 Hz), relative intensities 1:1:1:1, total 6H); ^{31}P NMR (DMSO-d_6) δ 26.5, 26.2 (50:50); MS (FAB+, NBA) *m/z* (relative intensity) 540 ($M + H^+$, 10). Anal. Calcd for $C_{29}H_{34}NO_7P$: C, 64.56; H, 6.35; N, 2.60. Found: C, 64.81; H, 6.19; N, 3.06.

2. According to Campbell,[15a] to the preceding product (200 mg, 0.37 mmol) in DCM (5 mL) was added Me_3SiBr (0.330 mL, 2.5 mmol). After reaction and treatment in the same conditions as for (*R,S*)-**14** synthesis, crude (*R,R*)-**14** was obtained as an oil (0.160 g, 82% yield): HPLC (condition 3) t_R 10.9 min; ^1H NMR (DMSO-d_6) δ 7.1–7.4 (m, 15H), 6.50 (br s, 1H), 5.09 (s, 2H), 4.91, 4.77 (AB, J = 12.8 Hz, 2H), 4.46 (m, 1H), 3.71 (m, 1H), 3.11 (br d, J = 13.0 Hz, 1H), 2.61 (m, 1H), 1.94 (m, 1H), 0.81, 0.79 (2d, J = 6.7 Hz, 6H). To the crude (*R,R*)-**14** (0.15 g, 0.28 mmol) in ethyl ether (5 mL) was added 1-adamantylamine (0.043 g, 0.28 mmol). The solid obtained was washed with ether to furnish 0.130 g of the adamantylamine salt of (*R,R*)-**14**: mp 204–206 °C; $[\alpha]^{20}_D$ −24 (*c* 0.5, EtOH); ^{31}P NMR (DMSO-d_6) δ 15.1, rotamer (10%) at δ 14.9; MS (FAB−, GT) *m/z* (relative intensity) 524 (M^-, 95); HRMS calcd for $C_{28}H_{31}NO_7P$ 524.1838, found 524.1678.

3. Synthesis of (*R,R*)-14 using a Mitsunobu reaction according to Campbell.[15a] To a solution of (*R*)-**3b** (100 mg, 0.29 mmol), (*S*)-2-hydroxy-3-methylbutyric acid benzyl ester (94 mg, 0.45 mmol), and triphenylphosphine (118 mg, 0.45 mmol in THF (3 mL), was added DEAD (71 μL, 0.45 mmol). After the mixture was stirred for 6 h at room temperature, despite the presence of starting material (HPLC), Me_3SiBr (132 μL, 1 mmol) was added and the reaction carried out during 2 h. Ethyl ether (20 mL) was added and the solution extracted with 5% $NaHCO_3$ (3×). The aqueous solution was washed with ethyl ether, acidified with 1 N HCl, and extracted with ethyl acetate (3×). The extracts were washed with brine and dried (Na_2SO_4), and the solvent was evaporated. HPLC analysis of the crude product revealed (*R,R*)-**14** ((*R,S*)-**14** was not observed).

Methyl Phenylphosphonic Acid (15). To a solution of phenylphosphonous acid (9 g, 58 mmol) in ethyl acetate (200 mL) was added dropwise, under stirring, at 0 °C, a solution of diazomethane in ether. After stirring overnight, the solution was washed with 5% $NaHCO_3$ (3×) and brine, dried (Na_2SO_4), and evaporated under reduced pressure to give an oil (8.5 g). To a solution of this crude product in dioxane (50 mL) was added a solution of $NaIO_4$ (13.5 g, 63 mmol) in water (50 mL). After stirring for 12 h at room temperature, the mixture was filtered, and the dioxane was evacuated. The residue was dissolved in ethyl acetate, and the solution was washed with 5% $KHSO_4$, 10% $NaHSO_3$, and brine, dried (Na_2SO_4), and evacuated to give an oil (7.5 g, 75%): HPLC (condition 4) t_R 2.68 min; ^1H NMR (DMSO-d_6) δ 11.87 (br s, 1H) 7.5–7.75 (m, 5H), 3.65 (d, J = 11.0 Hz, 3H); ^{31}P NMR (DMSO-d_6) δ 16.8.

Dimethyl Phenylphosphonate (16). The reaction was carried out according to the general procedure on **15** (400 mg, 2.32 mmol), MeOH, and PyBOP; t = 1 h: column chromatography eluent 70:30 to 100:0 ethyl acetate/cyclohexane; R_f 0.40 (ethyl acetate); oil (0.48 g, 90%); HPLC (condition 4) t_R 7.5 min; ^1H NMR (DMSO-d_6) δ 7.75–7.5 (m, 5H), 3.65 (d, J = 11.0 Hz, 6H); ^{31}P NMR (DMSO-d_6) δ 22.2; MS (FAB+, GT) *m/z* (relative intensity) 373 (2M + H^+, 10), 209 (M + Na^+, 28), 187 (M + H^+, 100). Anal. Calcd for $C_8H_{11}O_3P$: C, 51.61; H, 5.91. Found: C, 51.37; H, 6.25.

Methyl (*S*)-2-[(Phenylmethoxyphosphoryl)oxy]propionate (17). The procedure was as it was for **16**, but with (*S*)-lactic acid methyl ester (415 μL, 3.48 mmol) instead of MeOH; t = 2 h: column chromatography eluent 60:40 ethyl acetate/cyclohexane; R_f 0.33; oil (610 mg, 82%); HPLC (condition 4) t_R 8.9 min; ^1H NMR (DMSO-d_6) δ 7.5–7.8 (m, 5H), 4.95 (m, 1H), 3.55–3.8 (m, 6H), 1.48, 1.40 (2d (65:35), J = 6.8 Hz, 3H); ^{31}P NMR (DMSO-d_6) δ 15.5, 15.4; MS (FAB+, GT) *m/z* (relative intensity) 259 (M + H^+, 17). Anal. Calcd for $C_{11}H_{15}O_5P$: C, 51.16; H, 5.81. Found: C, 51.23; H, 5.85.

Methyl (−)-Bornyl Phenylphosphonate (18). The procedure was as it was for **16**, but with (−)-borneol (670 mg, 4.3 mmol) instead of MeOH; t = 2 h: column chromatography eluent 30:70 ethyl acetate/cyclohexane; R_f 0.28; oil (670 mg, 75%); HPLC (condition 4) t_R 16.7 min; ^1H NMR (DMSO-d_6) δ 7.8–7.5 (m, 5H), 4.53 (m, 1H), 3.63 (d, J = 11.2 Hz, 2.2H), 3.62 (d, J = 11.2 Hz, 0.8H), 2.24 (m, 0.27H), 2.11 (m, 0.73H), 1.95–1.8 (m, 1H), 1.76–1.63 (m, 1H), 1.32–1.2 (m, 3.2H), 1.02 (dd, J = 13.6 Hz, J = 3.3 Hz, 0.8H), 0.85, 0.84, 0.807 (3s, 3 × 2.2H), 0.82, 0.81, 0.68 (3s, 3 × 0.8H); ^{31}P NMR (DMSO-d_6) δ 19.7, 19.4 (27:73); MS (FAB+, NBA) *m/z* (relative intensity) 617 (2M + H^+, 3), 331 (M + Na^+, 1), 309 (M + H^+, 3). Anal. Calcd for $C_{17}H_{25}O_3P$: C, 66.23; H, 8.12. Found: C, 66.31; H, 8.25.

Methyl (−)-Menthyl Phenylphosphonate (19). The procedure was as it was for **16**, but with (−)-menthol (680 mg, 4.3 mmol) instead of MeOH; t = 2.5 h: column chromatography eluent 30:70 ethyl acetate/cyclohexane; R_f 0.46; oil (730 mg, 81%); HPLC (condition 1) t_R 16.7 min; ^1H NMR (DMSO-d_6) δ 7.75–7.45 (m, 5H), 4.25–4.09 (m, 1H) (3.62 (d, J = 11.2 Hz), 3.61 (d, J = 11.2 Hz), 3H), 2.2–2.1 (m, 1H), 1.91 (br d, J = 11.9 Hz, 0.4H), 1.80 (ttd, J = 7.0 Hz, J = 7.0 Hz, J = 2.6 Hz, 0.6H), 1.65–1.53 (m, 2H), 1.5–0.8 (m, 5H) (0.90 (d, J = 6.6 Hz), 0.89 (d, J = 7.1 Hz), 0.80 (d, J = 6.6 Hz), 0.77 (d, J = 6.9 Hz), 0.76 (d, J = 7.1 Hz), total 7.2H), 0.48 (d, J = 6.9 Hz, 1.8H); ^{31}P NMR (DMSO-d_6) δ 19.3, 18.7 (66:34); MS (FAB+, NBA) *m/z* (relative intensity) 644 (2M + Na^+, 3), 621 (2M + H^+, 6). Anal. Calcd for $C_{17}H_{27}O_3P$: C, 65.81; H, 8.71. Found: C, 65.93; H, 9.05.

Comparison between the Different Reagents Used for the Synthesis of 7. Reactions were conducted on **3a** (85 mg, 0.2 mmol), with benzyl glycolate (50 mg, 0.3 mmol) in DMF (0.4 mL), under N_2 (except condition B), with stirring at room temperature. Yields were measured by HPLC (condition 3), in the reaction mixture, using an internal standard (*Z*-Pro-Leu-OEt: 78 mg, 0.2 mmol); retention times (min): *Z*-Pro-Leu-OEt (9.8), **3a** (8.6), **7** (13.2), **23** (15.8, 16.1, large signals). All compounds were dried under vacuum in the presence of P_2O_5; DMF was distilled and stored on 4 Å molecular sieves. Results are reported in Table 4.

Condition A: This condition is the same as described above in the general procedure, with PyBOP (156 mg, 0.3 mmol) and DIEA (0.139 mL, 0.8 mmol).

Condition B: It is as described above in the general procedure, with PyBOP (114 mg, 0.22 mmol) and DIEA (0.139 mL, 0.8 mmol). The reaction was not conducted under N_2.

Table 4. Variation of the Yield of 7 as a Function of the Reaction Time and Reaction Conditions

reaction conditions	yield (%) after reaction time (h)[a]							
	0.25	0.5	1	2	4	7	18	24
A	80	90	95	–	95	92	–	80
B	75	78	80	–	80	80	–	–
C	45	50	55	–	67	70	50	–
D	–	50	–	50	–	50	–	38
E	–	40	45	–	45	45		35
F	–	8	–	–	22	22	–	21
G	–	2,5	–	–	10	15	34	44[b]
H	–	6	–	8	–	10	–	12
I	0	–	–	–	5	8	–	15

[a] In the case of conditions D and H, time 0 corresponds to the time of the addition of benzyl glycolate and DIEA. [b] After reaction for 48 h, the yield was 56%, and it was 57% after 72 h.

Condition C: It is as described above in the general procedure, with HBTU (114 mg, 0.3 mmol) and DIEA (0.139 mL, 0.8 mmol).

Condition D: To **3a** in DMF were added DCC (62 mg, 0.3 mmol) and anhydrous HOBt (40 mg, 0.3 mmol). After the mixture was stirred for 30 min at room temperature, benzyl glycolate and DIEA (0.139 mL, 0.8 mmol) were added. Before the addition of alcohol and DIEA, the pyrophosphonate **23** was observed (relative intensity *vs* internal standard: 1.5); 30 min after this addition, **23** was absent.

Condition E: It is as described above in the general procedure, with BroP (116 mg, 0.3 mmol) and DIEA (0.139 mL, 0.8 mmol). **23** was observed at 30 min (relative intensity *vs* internal standard: 0.6) and 1 h (0.6).

Condition F: To **3a** and benzyl glycolate in DMF were added DCC (62 mg, 0.3 mmol) and anhydrous HOBt (40 mg, 0.3 mmol). The pyrophosphonate **23** was observed at 30 min (relative intensity *vs* internal standard: 1.5), 4 h (0.7), and 7 h (0.3); it was not observed at 24 h.

Condition G: To **3a** and benzyl glycolate in DMF were added DCC (62 mg, 0.3 mmol) and DMAP (5 mg, 0.04 mmol). The pyrophosphonate **23** was observed at 30 min (relative intensity *vs* internal standard: 1.4), 3 h (1.2), 24 h (0.7), and 48 h (traces).

Condition H: To **3a** in DMF was added DCC (62 mg, 0.3 mmol). After the mixture was stirred for 30 min, benzyl glycolate and DIEA (0.139 mL, 0.8 mmol) were added.

Condition I: To **3a** and benzyl glycolate in DMF was added DCC (62 mg, 0.3 mmol). The pyrophosphonate **23** was observed at 15 min (relative intensity *vs* internal standard: 1.1), 4 h (1.6), and 24 h (0.7).

Methyl Phenylpyrophosphonate (22). Synthesis and Reactivity. 1. Synthesis of 22. To **15** (40 mg, 0.23 mmol) in DCM (0.2 mL) was added DCC (24 mg, 0.12 mmol). After stirring at room temperature for 2 h, the reaction mixture was filtered, and the solvent was evaporated under reduced pressure to give a product (40 mg) containing DCU: HPLC (condition 4) t_R 10.1 min; ^{31}P NMR ($CDCl_3$) δ 12.10, 12.06 (1:1); MS (FAB+, NBA) *m/z* (relative intensity) 349 ($M + Na^+$, 9), 327 ($M + H^+$, 27).

2. Reactivity of 22 with HOBt/DIEA. To a solution of **22** (38 mg, 0.116 mmol) in $CDCl_3$ (1 mL), in a NMR tube, were added HOBt (63 mg, 0.465 mmol) and DIEA (0.081 mL, 0.465 mmol). ^{31}P NMR ($CDCl_3$) δ 25.8 (**21**, relative intensity I = 0.2), 12.2 (DIEA salt of **15**, relative intensity I = 1); 12.04 (I = 0.1) and 11.99 I = 0.1) (**22**). Under the same conditions, but without DIEA, only **22** was observed.

3. Reactivity of 22 with MeOH/DIEA. To **15** (40 mg, 0.23 mmol) in DMF (0.5 mL) was added DCC (48 mg, 0.23 mmol). After the mixture was stirred at room temperature for 2 h, HPLC revealed **22**. MeOH (0.019 mL, 0.46 mmol) and DIEA (0.080 mL, 0.46 mmol) were added; after reaction for 2 h, HPLC analysis showed the presence of **16** (yield <10%).

PyBOP-Mediated Activation of 15: ^{31}P NMR Study. 1. In a NMR tube, at −40 °C, were dissolved **15** (40 mg, 0.23 mmol), PyBOP (179 mg, 0.345 mmol), and DIEA (0.060 mL, 0.345 mmol) in $CDCl_3$ (1 mL): ^{31}P NMR spectrum after 10 min δ 31.7 (PyBOP, *I* = 1), 26.4 (**21**, *I* = 0.21), 14.7 (OTP, *I* = 0.13), 13.38 and 12.29 (**22**, *I* = 0.01 and 0.01), 12.3 (br, DIEA salt of **15**, *I* = 0.17), −143.9 (hept, PF_6^-).

2. This was carried out in the same conditions, but at room temperature: ^{31}P NMR spectrum after 15 min δ 31.8 (PyBOP, *I* = 1), 25.8 (**21**, *I* = 0.59), 14.3 ppm (OTP, *I* = 0.27), 12.06 and 12.01 (**22**, *I* = 0.18 and 0.18), 9.9 (DIEA salt of **15**, *I* = 0.1), −143.7 (hept, PF_6^-); ^{31}P NMR spectrum after 45 min δ 31.8 (*I* = 1), 25.8 (*I* = 0.69), 14.2 (*I* = 0.77), 12.07 and 12.01 (*I* = 0.22 and 0.22), 9.8 (*I* = 0.3), −143.7 (hept, PF_6^-).

3. In a NMR tube were dissolved **15** (40 mg, 0.23 mmol), PyBOP (131 mg, 0.25 mmol), and DIEA (0.080 mL, 0.46 mmol) in $CDCl_3$ (1 mL): ^{31}P NMR spectrum after 10 min δ 31.8 (PyBOP, *I* = 1), 25.8 (**21**, *I* = 0.65), 14.4 (OTP, *I* = 0.4), 12.07 and 12.01 (**22**, *I* = 0.26 and 0.26), 10.0 (br, DIEA salt of **15**, *I* = 0.22), −143.7 (hept, PF_6^-). MeOH (0.014 mL, 0.34 mmol) and DIEA (0.080 mL, 0.56 mmol) were then added; a spectrum obtained after an additional 10 min showed δ 31.8 (*I* = 1), 25.8 (*I* = 0.08), 22.0 (*I* = 1.6), 14.6 (*I* = 1.25), 10.2 (*I* = 0.65), and −143.7 (hept, PF_6^-) and after an additional 20 min δ 31.7 (*I* = 1), 22.1 (*I* = 4.4), 14.5 (*I* = 5.5), 10.2 (*I* = 2.1), and −143.7 (hept, PF_6^-).

Benzyl [(*R,S*)-1-[(Benzyloxycarbonyl)amino]-2-phenylethyl]pyrophosphonate (23). To **3a** (100 mg, 0.23 mmol) in DCM (0.5 mL) was added DCC (23.7 mg, 0.115 mmol). After stirring at room temperature for 2 h, the reaction mixture was filtered, and the solvent was evaporated under reduced pressure to give an oil (90 mg) containing DCU: HPLC (condition 3) t_R 15.8, 16.1 min (br signals); ^{31}P NMR (DMSO-d_6) δ 18.6 (br), 17.9 br (17%); MS (FAB+, GT) *m/z* (relative intensity) 855 ($M + Na^+$, 2), 833 ($M + H^+$, 1).

(−)-Menthyl Phenylacetate (24). To a solution of phenylacetic acid (400 mg, 2.9 mmol), (−)-menthol (690 mg, 4.4 mmol), and PyBOP (2.29 g, 4.4 mmol) in DCM (5 mL) was added DIEA (2.1 mL, 12 mmol). After the mixture was stirred for 24 h at room temperature, ethyl acetate was added; after the usual workup and column chromatography (5:95 ethyl acetate/pentane), an oil (520 mg, 65%) was obtained. In the same conditions but using BOP, the yield was 68%: $[\alpha]^{20}_D$ −58 (*c* 0.5, DMF); R_f 0.22 (5:95 ethyl acetate/cyclohexane); HPLC (condition 1) t_R 19.5 min; ^{1}H NMR (DMSO-d_6) δ 7.4−7.2 (m, 5H), 4.55 (td, *J* = 10.9 Hz, *J* = 4.3 Hz, 1H), 3.63 (s, 2H), 1.85 (br d, *J* = 11.5 Hz, 1H), 1.72 (ttd, *J* = 7.0 Hz, *J* = 7.0 Hz, *J* = 2.6 Hz, 1H), 1.60 (m, 2H), 1.42 (m, 1H), 1.32 (m, 1H), 1.2−0.8 (m, 3H), 0.86 (d, *J* = 6.5 Hz, 3H), 0.80 (d, *J* = 7.0 Hz, 3H), 0.64 (d, *J* = 6.9 Hz, 3H); MS (FAB+, GT) *m/z* (relative intensity) 275 ($M + H^+$, 30). Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.83; H, 9.49. Found: C, 78.71; H, 9.31.

Methyl (*S*)-2-[(Benzylcarbonyl)oxy]propionate (25). The procedure was as it was for **24**, but with (*S*)-methyl lactate (545 mg, 4.4 mmol) instead of menthol, and reaction for 4 h. After the usual workup and column chromatography (10:90 ethyl acetate/cyclohexane) an oil (465 mg, 72%) was obtained: $[\alpha]^{20}_D$ −44 (*c* 0.5, DMF); R_f 0.41 (20:80 ethyl acetate/pentane); HPLC (condition 4) t_R 12.4 min; ^{1}H NMR (DMSO-d_6) δ 7.33 (m, 5H), 5.03 (q, *J* = 7.2 Hz, 1H), 3.74 (s, 2H), 3.65 (s, 3H), 1.40 (d, *J* = 7.2 Hz, 3H). Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.86; H, 6.31. Found: C, 64.68; H, 6.53.

Methyl *N*-(Benzylcarbonyl)-L-alaninate (26). To a solution of phenylacetic acid (500 mg, 3.7 mmol), H-Ala-OMe·HCl (603 mg, 4.3 mmol), and BOP (1.9 g, 4.3 mmol) in DCM (5 mL) was added DIEA (1.9 mL, 11.1 mmol). After the mixture was stirred at room temperature for 30 min, ethyl acetate was added. After the usual workup, a white solid (730 mg, 90%) was obtained: mp 69−71 °C; $[\alpha]^{20}_D$ −40 (*c* 0.5, DMF); HPLC (condition 4) t_R 8.23 min; ^{1}H NMR ($CDCl_3$) δ 8.49 (d, *J* = 6.9 Hz, 1H), 7.24 (m, 5H), 4.25 (qd, *J* = 7.2 Hz, *J* = 7.2 Hz, 1H), 3.60 (s, 3H), 3.45 (s, 2H), 1.28 (d, *J* = 7.2 Hz, 3H); MS (FAB+, GT) *m/z* (relative intensity) 244 ($M + Na^+$, 18), 222 ($M + H^+$, 9), 130 (100), 91 (11), 44 (8). Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.16; H, 6.79; N, 6.33. Found: C, 65.08; H, 6.83; N, 6.57.

Methyl *N*-(Phenylmethoxyphosphoryl)-L-alaninate (27). The same reaction as for **26** was conducted on **15** (500 mg, 2.9 mmol), H-Ala-OMe·HCl, (838 mg, 6 mmol), BOP (2.65 g, 6 mmol), and DIEA (2.6 mL, 15 mmol) in DCM (6 mL). After

reaction for 4 h, the usual workup and column chromatography (ethyl acetate), an oil (480 mg, 64%) was obtained: R_f 0.27 (ethyl acetate); HPLC (condition 5) t_R 8.3 min; ^{1}H NMR (DMSO-d_6) δ 7.8–7.4 (m, 5H), 5.58 (dd, J = 10.8 Hz, J = 10.8 Hz, 1H), 3.85 (m, 1H), 3.65–3.45 (m, 6H), 1.26, 1.24 (2 × d, J = 7.1 Hz, J = 7.2 Hz, 2 × 1.5H); ^{31}P NMR (DMSO-d_6) δ 22.6, 22.1 (55:45); MS (FAB+, NBA) m/z (relative intensity) 280 (M + Na$^+$, 30), 258 (M + H$^+$, 15). Anal. Calcd for $C_{11}H_{16}NO_4P$: C, 51.36; H, 6.22; N, 5.45. Found: C, 51.48; H, 6.32; N, 5.71.

Competition Reaction of Alcohols and Amines on PyBOP-Promoted Bt Esters of Carboxylic or Phosphonic Acids. 1. To **15** (40 mg, 0.23 mmol), H-Ala-OMe·HCl (32 mg, 0.23 mmol), methyl lactate (0.022 mL, 0.23 mmol), and PyBOP (0.18 g, 0.34 mmol) in DMF (0.5 mL) was added under stirring at room temperature DIEA (0.174 mL, 1 mmol). HPLC analysis (condition 4) after 2 h showed **27** (t_R 7.5 min) and **17** (t_R 9.0 min) with a **27/17** ratio of 20:80. When the same rection was conducted with PyBOP/DIEA-promoted preactivation (15 min) of **15**, followed by the addition of alcohol and amine, the **27/17** ratio was 16:84 after reaction for 1 h.

2. Phenylacetic acid (50 mg, 0.37 mmol) was allowed to react as above for **15**. HPLC (condition 4) of the one-pot reaction, after 10 min, showed **26** (t_R 7.8 min) and **25** (t_R 12.4 min), with a **26/25** ratio of 95:5; after 4 h, the ratio was 93:7. When the reaction was conducted under preactivation conditions (15 min), the **26/25** ratio was 95:5 after 1 h.

Acknowledgment. We are grateful to SANOFI DIAGNOSTICS-PASTEUR for a grant (J.-M.C.) and to Dr. L. Sahli for the correction of the paper.

JO950297X