Synthesis of Novel N-Phosphonoalkyl Dipeptide Inhibitors of Human Collagenase

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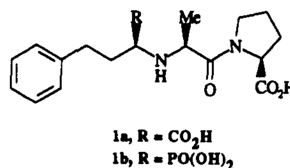
The synthesis of a series of N-phosphonoalkyl dipeptides **6** is described. Syntheses were devised that allowed the preparation of single diastereoisomers and the assignment of stereochemistry. The compounds were evaluated *in vitro* for their ability to inhibit the degradation of radiolabeled collagen by purified human lung fibroblast collagenase. Several of the compounds were potent collagenase inhibitors and were at least 10-fold more potent than their corresponding N-carboxyalkyl analogues. Activity was lost when the phosphonic acid group $P(O)(OH)_2$ was replaced by the phosphinic acid groups P(O)(H)(OH) and P(O)(Me)(OH). At the P_1 position, (R)- or (S)-alkyl groups, especially ethyl and methyl (e.g., **12a,b**, **52a,b**, and **53a,b**), or an (R)-phenethyl moiety (**55a**) conferred high potency (IC_{50} values in the range 0.23-0.47 μM). (S)-Stereochemistry was preferred for the P_1' isobutyl side chain. Structure-activity relationships were also investigated at the P_2' site, and interestingly, compounds with basic side chains, such as the guanidine **57a**, were equipotent with more lipophilic compounds, such as **52a**. As with other series of collagenase inhibitors, potency was enhanced by introducing bicyclic aromatic P_2' substituents. The most potent phosphonic acid of the series was the bicyclic aromatic P_2' tryptophan analogue **59a** (IC_{50} 0.05 μM).

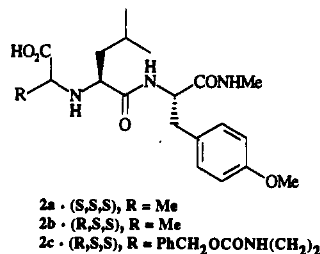
Introduction

The matrix metalloproteinases (MMPs) are a family of zinc-containing enzymes that are involved in tissue remodeling and are normally produced together with a range of selective, proteinaceous tissue inhibitors of metalloproteinases (TIMPs) to control their proteolytic activities.[1-3] Synthetic inhibitors of matrix metalloproteinases, especially of collagenase (MMP-1)[4] and stromelysin/proteoglycanase (MMP-3),[5] are important targets for drug discovery,[6] since an imbalance between the matrix metalloproteinase synthesis and activation, on the one hand, and the synthesis of the endogenous inhibitors, on the other, is believed to be responsible for the excessive cartilage and bone destruction that occurs in diseases such as rheumatoid arthritis and osteoarthritis. Moreover, low molecular weight (MW) inhibitors are more effective in penetrating cartilage to the sites of connective tissue proteolysis than are high MW inhibitors, such as TIMP, which are excluded because of their size.[7] There are currently no marketed antiarthritic drugs that effectively prevent joint destruction. MMP inhibitors could also be useful in other diseases in which connective tissue degradation is a causative or contributory factor, such as tumor metastasis, corneal ulceration, and periodontal disease.[8]

Mammalian collagenase cleaves all three α-chains of native interstitial collagen at a unique cleavage site (either a Gly-Leu or Gly-Ile bond) to give characteristic one-quarter and three-quarter products.[9] The rational design of low MW collagenase inhibitors, based on the structure of the substrate cleavage site, has recently been reviewed,[6,8] and several potent collagenase inhibitors, with IC_{50} values in the nanomolar range, have been described. These compounds contain hydroxamic acid[8,10] or β-mercaptocarbonyl[11] ligands that bind, probably in a bidentate manner, to the active site zinc ion in the enzyme. In contrast, substituted N-carboxymethyl ligands, which were first used in potent inhibitors of angiotensin-converting enzyme (ACE)[12,13] such as enalaprilat (**1a**), when used in compounds such as **2** produce less potent collagenase inhibitors (IC_{50} values in the micromolar range).[8,14,15]



1a, R = CO_2H
1b, R = $PO(OH)_2$



2a - (S,S,S), R = Me
2b - (R,S,S), R = Me
2c - (R,S,S), R = $PhCH_2OCONH(CH_2)_2$

Collagenase inhibitors with phosphorus-containing zinc ligands have also been described. Phosphoramidates such as **3**[16] have K_i values in the micromolar range against human skin fibroblast collagenase in a synthetic thio peptolide spectrophotometric assay, but inhibitors of this type are unlikely to be useful drugs because the phosphoramidate moiety has extremely poor *in vivo* stability. Phosphinic acids such as **4a**[17] are relatively weak collagenase inhibitors *in vitro* (IC_{50} 37 μM), but, for reasons that are unclear, potency is enhanced in compounds such as **4b** when phthalimido or naphthalimido groups are incorporated at the P_1 position.[17,18] Positioning a phosphonic acid ligand one methylene spacer unit away from the P_1' isobutyl side chain leads to inhibitors such as **5**[8a] with micromolar potency. In this paper, we describe the synthesis of a series of N-phosphonoalkyl dipeptides **6**, which were evaluated *in vitro* for their ability to inhibit the degradation of radiolabeled collagen by purified human lung fibroblast collagenase.

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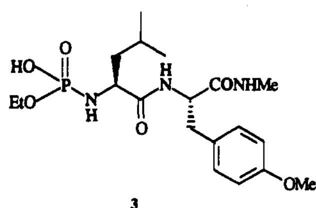
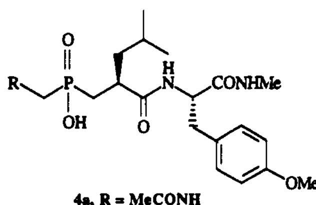
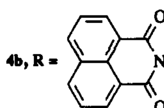
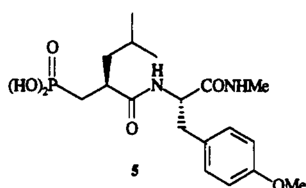
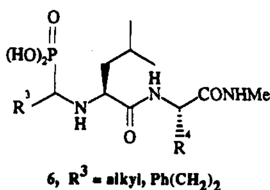
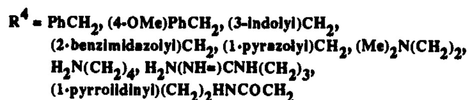












Chemistry

The target molecules in Tables 2 and 3 were prepared according to Schemes 1–6.

The initial synthetic approach to the esters **9a–d** (Scheme 1) involved reductive amination of the α-keto ester **8** with the amino phosphonic esters **7a** or **7b**[19] and subsequent separation of diastereoisomers to give the single isomers **9a–d**. Hydrolysis and coupling with Tyr(Me)-NHMe gave the intermediate phosphonic esters **11a–d**, which on treatment with bromotrimethylsilane gave the phosphonic acids **12a–d**. Reaction of **7b** with the (*R*)-triflate **13** provided an alternative approach to **9b**, and subsequently to **10b**, and allowed the assignment of the stereochemistry of **9b** (*S*,*S*) and **9d** (*S*,*R*). The stereochemistry of the corresponding enantiomers **9c** (*R*,*R*) and **9a** (*R*,*S*) could then be assigned by NMR analysis. This work allowed the assignment of stereochemistry to the amino phosphonic acids **12a–d**.

Scheme 2 shows a different approach: displacement of the triflate group from the dibenzyl phosphonate **15a** with L-leucine methyl ester (**16a**) gave a mixture of the esters **17a** and **17b** in modest yield. Separation of the diastereoisomer **17a** and subsequent hydrolysis, coupling with the appropriate P_2' amino component,[20] and hydrogenolysis gave the phosphonic acids **12a**, **26a**, and **27a**. This preparation of **12a** (previously shown to have (*R*,*S*,*S*)-stereochemistry) allowed the stereochemistry of **17a** and **17b** to be assigned as (*R*,*S*) and (*S*,*S*), respectively. A more direct approach, involving displacement with the dipeptide **19**, gave, after partial separation by chromatography, the dibenzyl ester **20a** and the dibenzyl esters **23–25** (inseparable mixtures of two diastereoisomers). Debenzylation provided the amino phosphonic acids **12a** and **28–30**.

The above routes did not allow the ready variation of P_1 substituents and the preparation of single diastereoisomers. An alternative strategy, involving the thermal addition of a trivalent phosphorus ester to an imine,[21] was therefore investigated. The addition of dimethyl phosphite to the imine prepared from isobutyraldehyde (**31**) and L-leucine methyl ester (**16a**) (Scheme 3) gave the ester **32**, which was elaborated to the amino phosphonic acid **35**. This was shown by NMR to be a mixture of four diastereoisomers; presumably, racemization occurs due to the forcing conditions of the phosphite addition reaction. In contrast, the addition of highly reactive dibenzyl trimethylsilyl phosphite,[22] generated *in situ*, to imines at 0 °C (Scheme 4) provided a mild and high-yielding route to single diastereoisomers of the esters **17a–d**, **37a,b**, **38a,b**, and **39a**. Subsequent hydrolysis, coupling with the appropriate amino component,[23,24] and hydrogenolysis gave single diastereoisomers of the desired amino phosphonic acids **12a**, **52a–d**, **53a,b**, **54a**, **55a,b**, **56a,b**, and **57a–60a**. A comparison of the NMR data for the acids **18a,b** of known stereochemistry, and related compounds with different P_1 substituents, allowed the assignment of the stereochemistry and the confirmation of stereochemical purity. The proton α to the carboxylate group (H_a) (see Table 1) appears downfield in the NMR spectrum of the (*S*,*S*)-isomers, relative to the (*R*,*S*)-isomers. Further confirmation of the stereochemical assignments was provided by an X-ray crystal structure analysis of **50a**, which was shown to be the (*R*,*S*,*S*)-diastereoisomer.[25]

Addition of ethyl (diethoxymethyl)phosphinate (**61**)[26] to the imine **62** (Scheme 5) gave the ethyl ester **63**, which on reductive amination with the α-keto ester **8** gave the phosphinic ester **66**. Similarly, reductive amination of **8** with the phosphinic ester **65**, prepared from the acid **64**,[27] gave the ester **67**. Treatment of **70** with concentrated hydrochloric acid and **71** with bromotrimethylsilane provided the amino phosphinic acids **72** and **73** as mixtures of four diastereoisomers.

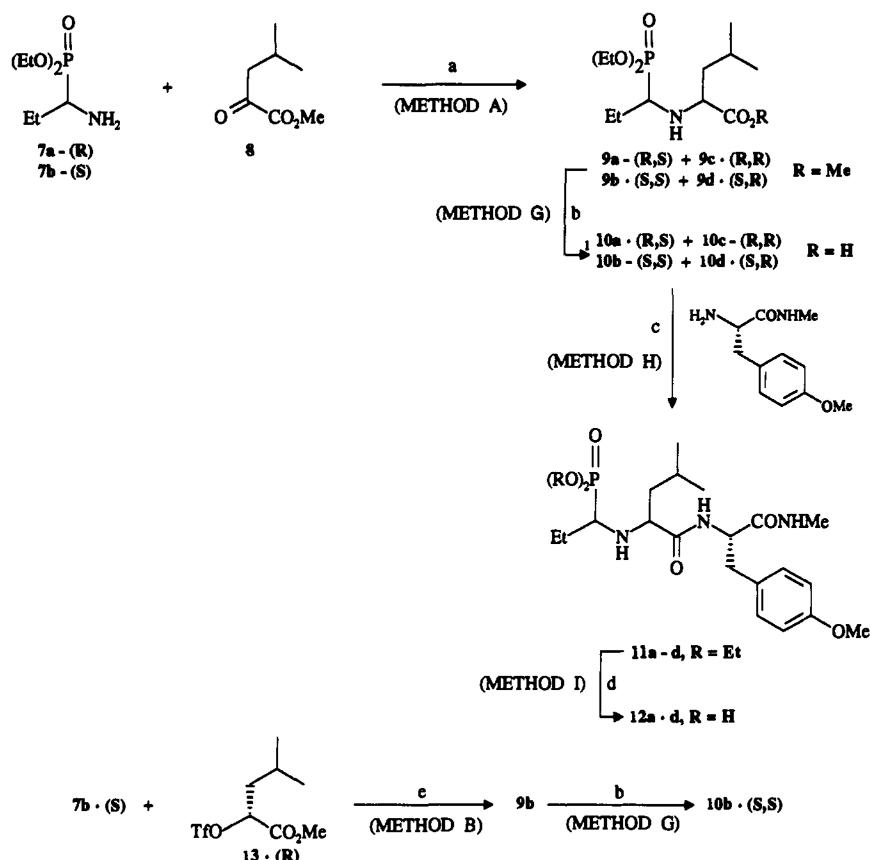
The amino carboxylic acids **2a** and **2b** were prepared, as single diastereoisomers, from the known acids **74a** and **74b**[14a] (Scheme 6).

Results and Discussion

Structure–Activity Relationship (SAR) *in Vitro*. Compounds were evaluated for their ability to inhibit the degradation of radiolabeled rat skin type I collagen by semipurified human lung fibroblast collagenase. The inhibitory activities (IC_{50} values) for the test compounds are shown in Table 3.

(1) Stereochemical SAR of P_1 and P_1' Substituents. (*S*)-Tyr(Me)NHMe and (*S*)-PheNHMe P_2' residues are known to confer high potency in other series of collagenase inhibitors.[14] Therefore, the initial *N*-phosphonoalkyl dipeptides contained one or the other of these P_2' moieties

Scheme 1[a]



[a] (a) MeOH, 10% Pd/C, H_2; (b) NaOH, MeOH, H_2O; (c) EDC, HOBT, CH_2Cl_2; (d) Me_3SiBr, CH_2Cl_2; (e) 1,8-bis(dimethylamino)naphthalene, CH_2Cl_2.

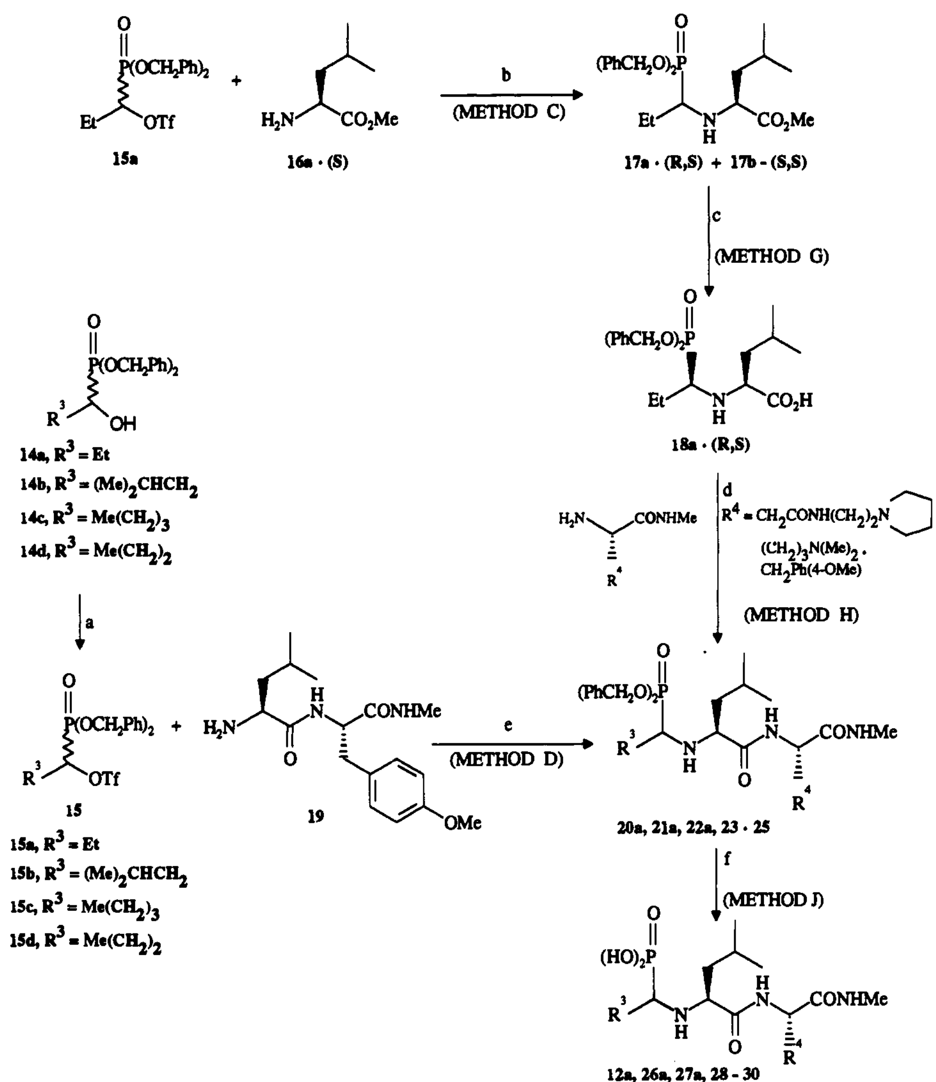
together with an isobutyl substituent at the P_1' position, and the effect of varying the P_1 substituent was investigated. The preferred stereochemistry at the P_1 and P_1' centers was unknown, and so, compounds **12a–d** and **52a–d**, containing an ethyl P_1 moiety and differing in stereochemistry at these centers, were evaluated. Compounds **12a** (*R,S,S*), **12b** (*S,S,S*) [Tyr(Me)NHMe P_2' substituent] and **52a** (*R,S,S*), **52b** (*S,S,S*) [PheNHMe P_2' substituent] were equipotent, allowing for experimental error (IC_{50} values in the range 0.23–0.47 μM); diastereoisomers **12c**, **12d**, **52c**, and **52d** ((*R*)-stereochemistry at the P_1' position) were greater than 30-fold less potent. Thus, (*S*)-stereochemistry was preferred at the P_1' center, but the configuration of the P_1 substituent did not markedly influence inhibitory potency.

(2) SAR of P_1 Substituents. The effect of varying the size of the P_1 alkyl substituent was also investigated. Compounds **53a** and **53b**, with methyl P_1 substituents, were equipotent with **12a** and **12b** (ethyl P_1 substituent), but compounds **28**, **29**, **30**, and **35**, with bulkier isobutyl, *n*-butyl, *n*-propyl, and isopropyl substituents, were less potent (IC_{50} values 2.9, 41.2, 15.7, and 2.9 μM, respectively). Similarly, compound **54a** (isobutyl P_1 substituent) was less potent than its ethyl-substituted analogue **52a**. For the alkyl substituents investigated, the inhibitory potency declined in the order: ethyl = methyl > isobutyl = isopropyl > *n*-propyl > *n*-butyl; thus, branched alkyl chains were preferred over their straight-chain congeners, but ethyl or methyl moieties were preferred overall.

The effect of introducing a phenethyl substituent was also investigated (compounds **55a** and **55b**), and for the first time, a clear difference in potency between P_1 diastereoisomers was observed. Compound **55a** ((*R,S,S*)-diastereoisomer; IC_{50} 0.4 μM) was approximately equipotent with the original lead compound **52a**, but its (*S,S,S*)-diastereoisomer **55b** was (4–5)-fold less potent (IC_{50} 1.82 μM). It is likely that the relatively poor binding of the (*S,S,S*)-diastereoisomer **55b** is a consequence of an unfavorable interaction between the bulky phenethyl side chain and certain residues at the enzyme's active site, and this interaction is absent for the diastereoisomer **55a**. This unfavorable interaction is probably not observed with compounds **52b** and **53b** because of their smaller P_1 substituents. It is unclear why the preferred diastereoisomer **55a** (*R,S,S*) has the opposite absolute stereochemistry to the preferred diastereoisomer (*R,S,S*) of the carboxylic acid **2c** (CI-1).[14]

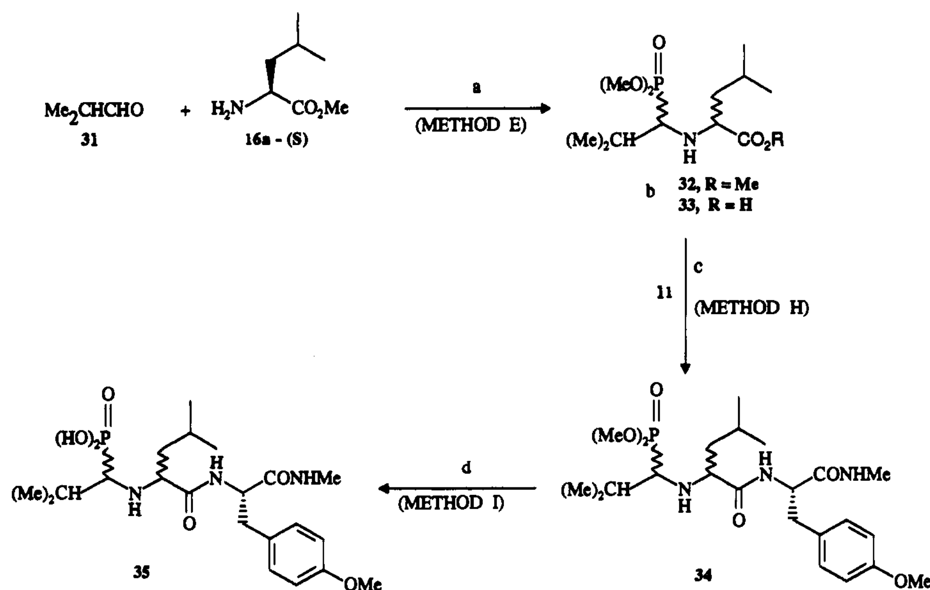
(3) Comparison of Collagenase SAR with ACE SAR. It was disappointing, but not surprising, that inhibitory potency could not be enhanced by introducing a P_1 phenethyl group (cf. ACE inhibitors[12,13]), and in this respect, the phosphonic acids of the present series mirror the activity profile of the corresponding carboxylic acids **2**.[14] One reason for the relatively low potency of compounds **55** is that, unlike ACE, the collagenase enzyme does not appear to possess a S_1 subsite pocket to interact with the P_1 inhibitor side chains; in the natural collagen substrate, the P_1 residue (glycine) lacks an α-side chain. Indeed, it has been shown that a wide variety of substituents is allowed at the P_1 position of collagenase substrates.[9] It is also noteworthy that the preferred stereochemistry (*R*) of the substituted *N*-carboxymethyl ligand in collagenase inhibitors is opposite to that required by ACE.[8,14]

Scheme 2[a]



[a] (a) 2,6-Lutidine, $(CF_3SO_2)_2O$, CH_2Cl_2; (b) K_2CO_3, MeOH; (c) NaOH, MeOH, H_2O; (d) EDC, HOBT, CH_2Cl_2; (e) 1,8-bis(dimethylamino)naphthalene, CH_2Cl_2; (f) EtOH, 10% Pd/C, H_2.

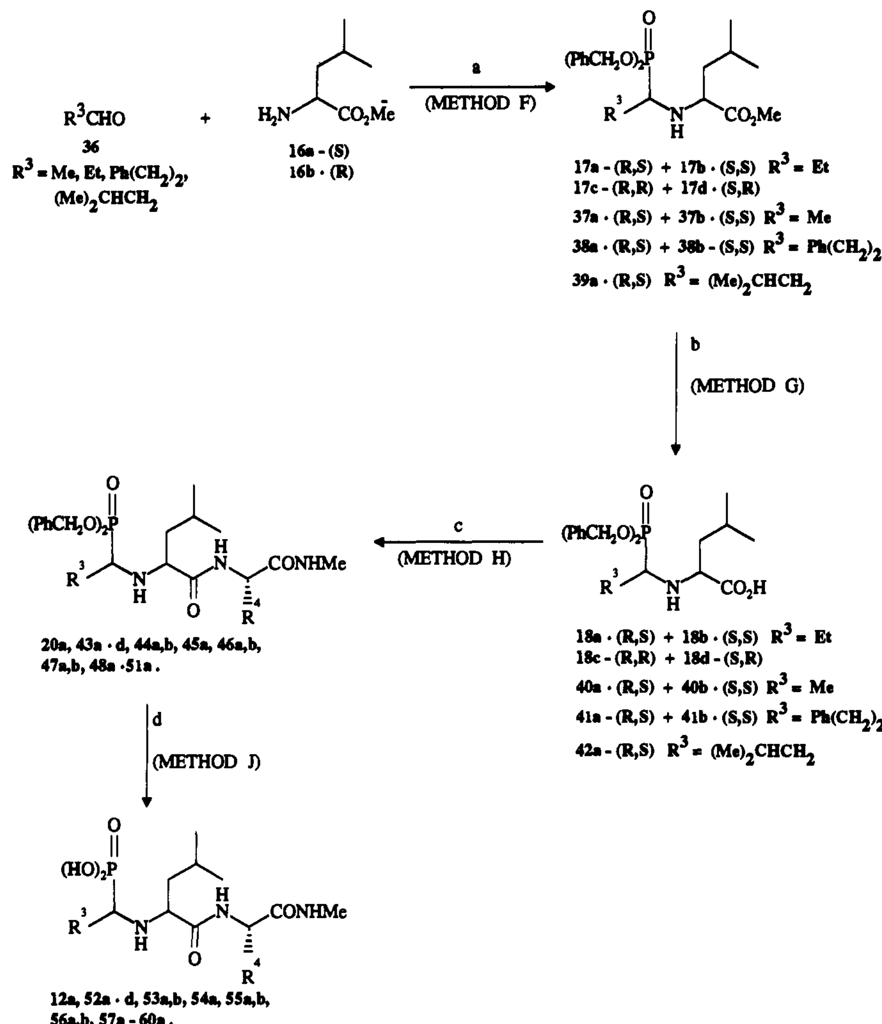
Scheme 3[a]



[a] (a) Dimethyl phosphite, Δ, toluene; (b) NaOH, MeOH, H_2O; (c) Tyr(Me)NHMe, EDC, HOBT, CH_2Cl_2; (d) Me_3SiBr, CH_2Cl_2.

(4) SAR of P_2' Substituents. Additional phosphonic acids, **26a**, **27a**, and **56a–60a**, were prepared to investigate structure–activity relationships at the P_2' site. It has been reported previously that binding at the P_2' position involves

Scheme 4[a]



[a] (a) Dibenzyl trimethylsilyl phosphite, CH_2Cl_2, 0 °C; (b) NaOH, MeOH, H_2O; (c) $H_2NCH(R^4)CONHMe$, EDC, HOBT, CH_2Cl_2; (d) EtOH, 10% Pd/C, H_2.

Table 1. Proton Chemical Shifts

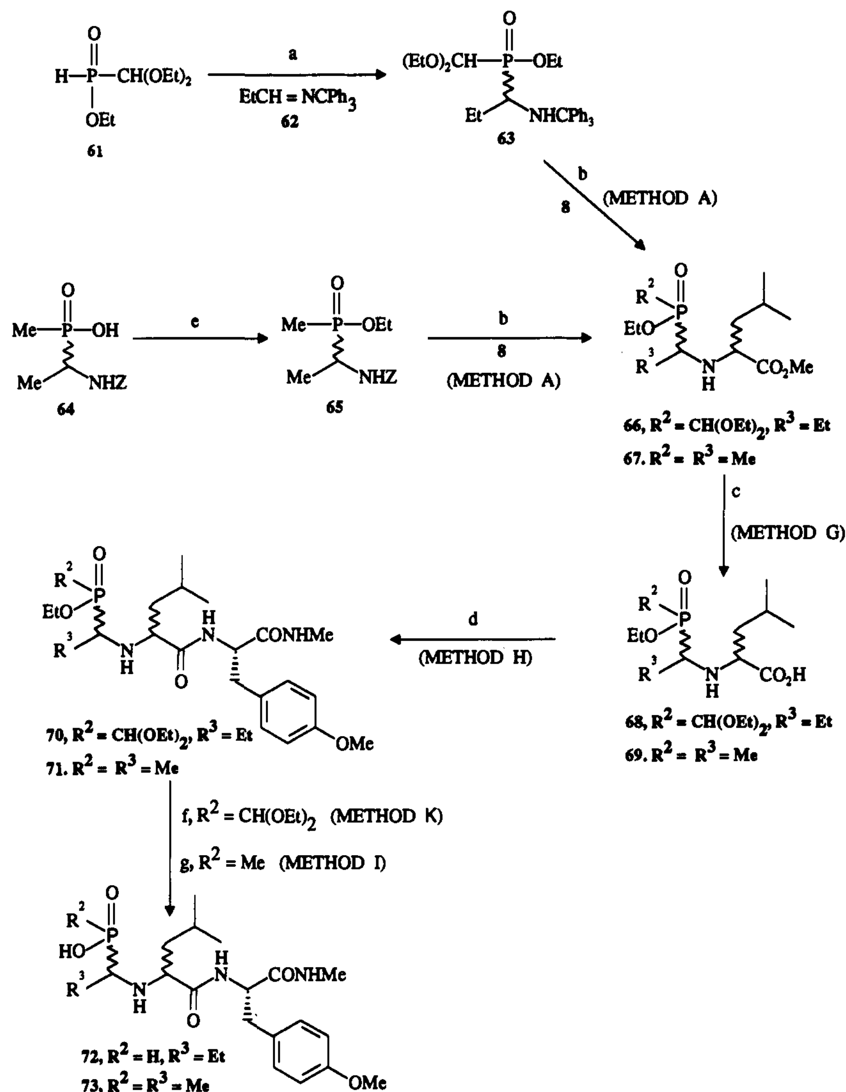
compd	R^1	R^2	R^3	chirality	H_a shift, δ ($CDCl_3$)
10a	EtO	EtO	Et	*R,S*	3.72
10b	EtO	EtO	Et	*S,S*	3.42
18a	$PhCH_2O$	$PhCH_2O$	Et	*R,S*	3.75
18b	$PhCH_2O$	$PhCH_2O$	Et	*S,S*	3.40
40a	$PhCH_2O$	$PhCH_2O$	Me	*R,S*	3.65
40b	$PhCH_2O$	$PhCH_2O$	Me	*S,S*	3.40
41a	$PhCH_2O$	$PhCH_2O$	$Ph(CH_2)_2$	*R,S*	3.75
41b	$PhCH_2O$	$PhCH_2O$	$Ph(CH_2)_2$	*S,S*	3.37
42a	$PhCH_2O$	$PhCH_2O$	$(Me)_2CHCH_2$	*R,S*	3.81

an enzyme interaction up to the C^γ position of the inhibitor side chain and that no upper size limitation exists.[8a] The effect of introducing basic groups at the P_2' position has not previously been reported in any series of collagenase inhibitors. Compounds **26a**, **56a,b**, and **57a** containing the basic P_2' side chains $Me_2N(CH_2)_3$, $H_2N(CH_2)_4$, and $H_2N(NH{=})CNH(CH_2)_3$, derived from ornithine, lysine, and arginine, respectively, were investigated. Interestingly, the highly basic guanidine **57a** ((*R,S,S*)-stereochemistry) had an IC_{50} value of 0.29 μM and was equipotent with the corresponding P_2' phenylalanine analogue **52a**. Compounds **26a** (*R,S,S*) and **56b** (*S,S,S*) were only slightly less potent, and **56a** (*R,S,S*) was the least potent with an IC_{50} value of 4.3 μM. It is not known why diastereoisomers **56a** and **56b** (lysine P_2' substituent) showed a 6-fold variation in potency when this was not found for compounds **12a,b** and **52a,b** with lipophilic P_2' side chains. Compound **27a**, with the bulky extended P_2' side chain (1-pyrrolidinyl)$(CH_2)_2NHCOCH_2$, had a still respectable IC_{50} value of 1.36 μM, confirming the report of no upper size limitation for the P_2' substituent.[8a]

It is known that aromatic residues, such as tryptophan or (2-naphthyl)alanine, at the P_2' position increase inhibitory potency.[16,28] In the present series, compounds **58a**, **59a**, and **60a**, with (1-pyrazolyl)CH_2, (3-indolyl)CH_2, and (2-benzimidazolyl)CH_2 P_2' substituents, were compared with the corresponding phenylalanine analogue **52a** (all (*R,S,S*)-stereochemistry). The order of potency was **59a** > **60a** ≥ **52a** > **58a**; thus, the compound with an indole ring in the P_2' side chain exhibited increased potency over the phenylalanine analogue **52a**, confirming the enhancement of potency with bicyclic aromatic P_2' substituents reported for other collagenase inhibitor series.[16,28] The P_2' tryptophan analogue **59a** (IC_{50} 0.05 μM) is the most potent phosphonic acid of the present series.

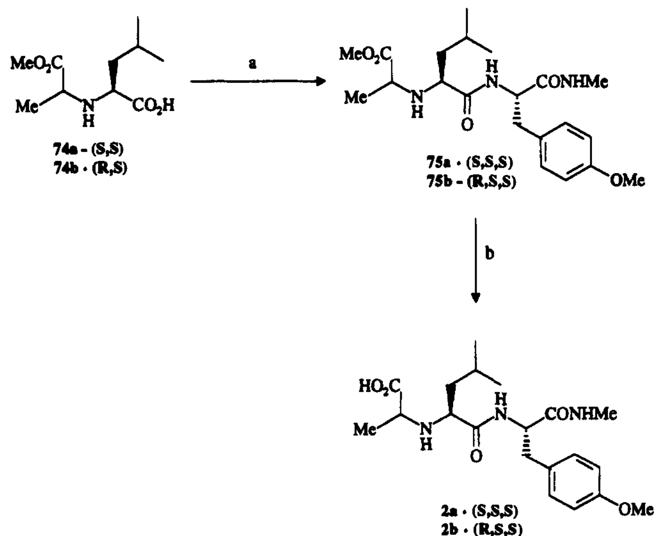
(5) Comparison of Phosphonic, Phosphinic, and Carboxylic Acid Ligands. It is reported that, for the ACE inhibitor enalaprilat (**1a**), replacement of the car-

Scheme 5[a]



[a] (a) Δ, toluene; (b) MeOH, 10% Pd/C, H_2; (c) NaOH, MeOH, H_2O; (d) Tyr(Me)NHMe, EDC, HOBT, CH_2Cl_2; (e) EtOH, DCC, DMAP, THF; (f) concentrated HCl, Δ; (g) Me_3SiBr, CH_2Cl_2.

Scheme 6[a]

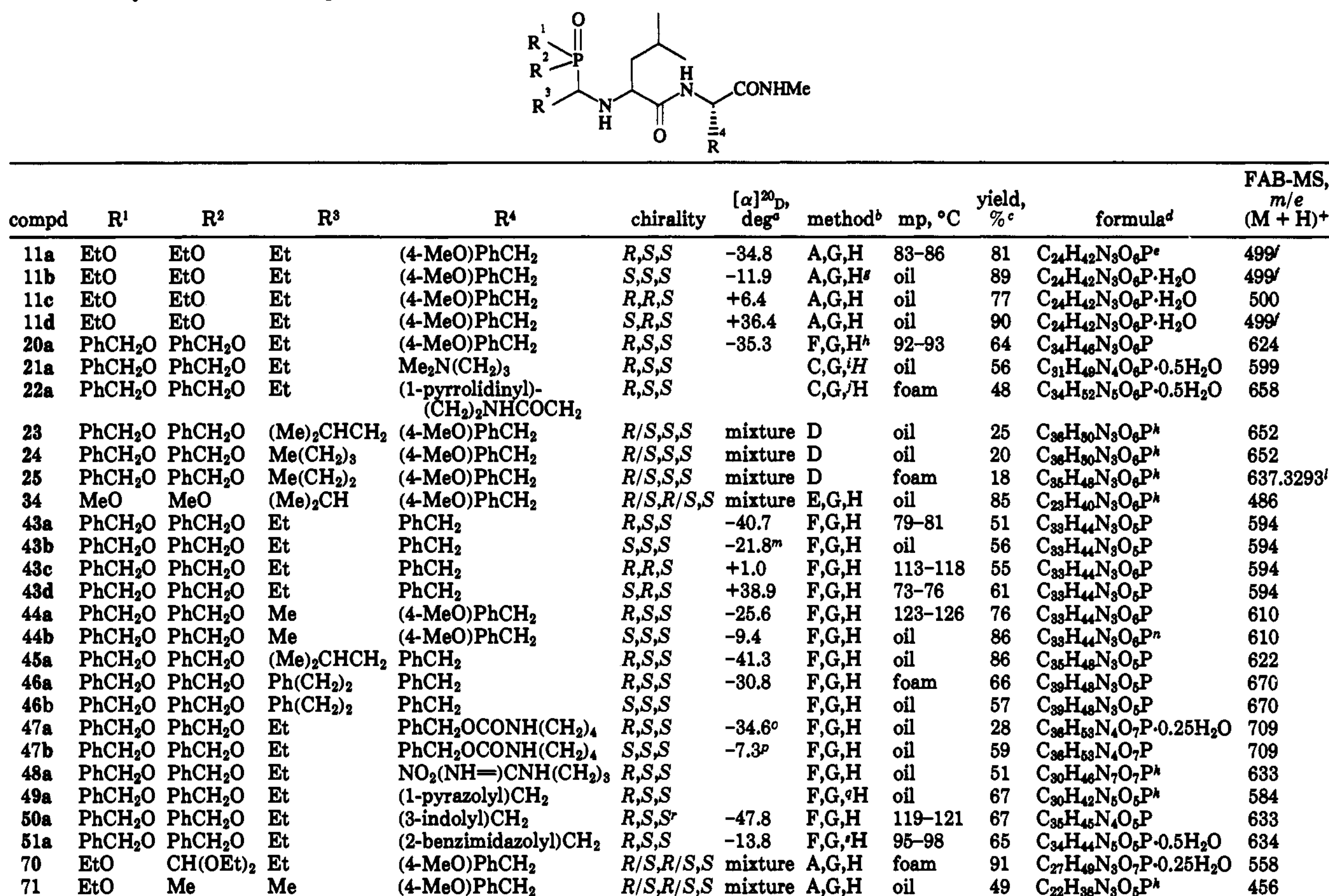


[a] (a) Tyr(Me)NHMe, EDC, HOBT, CH_2Cl_2; (b) NaOH, MeOH, H_2O.

boxylic acid ligand by a phosphonic acid residue (**1b**) leads to a significant loss of binding affinity.[29] The previously described carboxylic acids **2a** (*S,S,S*) and **2b** (*R,S,S*),[14a] with methyl P_1 substituents, were also evaluated in our enzyme assay. The diastereoisomer **2b** was more potent than **2a** (IC_{50} values 3.46 and >10 μM, respectively), confirming the published patent data.[14a] The corresponding IC_{50} values for the analogous phosphonic acids **53a** and **54b** were 0.52 and 0.26 μM, respectively. Thus, in the present inhibitors, a phosphonic acid moiety, as the zinc ligand, generates a more potent collagenase inhibitor than does a carboxylic acid moiety by at least 10-fold. By contrast, compounds **72** and **73**, with the phosphonic acid group $P(O)(OH)_2$ replaced by the phosphinic acid groups P(O)(H)(OH) and P(O)(Me)(OH), were devoid of activity at 100 μM. The inactivity of the phosphinic acids **72** and **73** was surprising, as phosphinic acids have been employed previously as zinc ligands in inhibitors of collagenase,[17,18] ACE,[30] and thermolysin.[31] The fact that phosphonic acids are doubly ionized at physiological pH may be an important factor in determining their high potency.[32]

In conclusion, we have described a series of *N*-phosphonoalkyl dipeptide collagenase inhibitors with potent activity *in vitro* against human lung fibroblast collagenase. Several compounds are at least 10-fold more potent than their corresponding *N*-carboxyalkyl analogues. We are presently studying the phosphonic acid collagenase inhibitors *in vivo*, and preliminary studies have indicated

Table 2. Physical Data for Phosphonic Esters



compd	R[1]	R[2]	R[3]	R[4]	chirality	$[\alpha]^{20}_D$, deg[a]	method[b]	mp, °C	yield, %[c]	formula[d]	FAB-MS, *m/e* $(M + H)^+$
11a	EtO	EtO	Et	(4-MeO)PhCH$_2$	*R,S,S*	−34.8	A,G,H	83–86	81	$C_{24}H_{42}N_3O_6P$[e]	499[f]
11b	EtO	EtO	Et	(4-MeO)PhCH$_2$	*S,S,S*	−11.9	A,G,H[g]	oil	89	$C_{24}H_{42}N_3O_6P \cdot H_2O$	499[f]
11c	EtO	EtO	Et	(4-MeO)PhCH$_2$	*R,R,S*	+6.4	A,G,H	oil	77	$C_{24}H_{42}N_3O_6P \cdot H_2O$	500
11d	EtO	EtO	Et	(4-MeO)PhCH$_2$	*S,R,S*	+36.4	A,G,H	oil	90	$C_{24}H_{42}N_3O_6P \cdot H_2O$	499[f]
20a	PhCH$_2$O	PhCH$_2$O	Et	(4-MeO)PhCH$_2$	*R,S,S*	−35.3	F,G,H[h]	92–93	64	$C_{34}H_{46}N_3O_6P$	624
21a	PhCH$_2$O	PhCH$_2$O	Et	Me$_2$N(CH$_2$)$_3$	*R,S,S*		C,G,[i]H	oil	56	$C_{31}H_{49}N_4O_6P \cdot 0.5H_2O$	599
22a	PhCH$_2$O	PhCH$_2$O	Et	(1-pyrrolidinyl)-(CH$_2$)$_2$NHCOCH$_2$	*R,S,S*		C,G,[j]H	foam	48	$C_{34}H_{52}N_5O_6P \cdot 0.5H_2O$	658
23	PhCH$_2$O	PhCH$_2$O	(Me)$_2$CHCH$_2$	(4-MeO)PhCH$_2$	*R/S,S,S*	mixture	D	oil	25	$C_{36}H_{50}N_3O_6P$[k]	652
24	PhCH$_2$O	PhCH$_2$O	Me(CH$_2$)$_3$	(4-MeO)PhCH$_2$	*R/S,S,S*	mixture	D	oil	20	$C_{36}H_{50}N_3O_6P$[k]	652
25	PhCH$_2$O	PhCH$_2$O	Me(CH$_2$)$_2$	(4-MeO)PhCH$_2$	*R/S,S,S*	mixture	D	foam	18	$C_{35}H_{48}N_3O_6P$[k]	637.3293[l]
34	MeO	MeO	(Me)$_2$CH	(4-MeO)PhCH$_2$	*R/S,R/S,S*	mixture	E,G,H	oil	85	$C_{23}H_{40}N_3O_6P$[k]	486
43a	PhCH$_2$O	PhCH$_2$O	Et	PhCH$_2$	*R,S,S*	−40.7	F,G,H	79–81	51	$C_{33}H_{44}N_3O_5P$	594
43b	PhCH$_2$O	PhCH$_2$O	Et	PhCH$_2$	*S,S,S*	−21.8[m]	F,G,H	oil	56	$C_{33}H_{44}N_3O_5P$	594
43c	PhCH$_2$O	PhCH$_2$O	Et	PhCH$_2$	*R,R,S*	+1.0	F,G,H	113–118	55	$C_{33}H_{44}N_3O_6P$	594
43d	PhCH$_2$O	PhCH$_2$O	Et	PhCH$_2$	*S,R,S*	+38.9	F,G,H	73–76	61	$C_{33}H_{44}N_3O_5P$	594
44a	PhCH$_2$O	PhCH$_2$O	Me	(4-MeO)PhCH$_2$	*R,S,S*	−25.6	F,G,H	123–126	76	$C_{33}H_{44}N_3O_6P$	610
44b	PhCH$_2$O	PhCH$_2$O	Me	(4-MeO)PhCH$_2$	*S,S,S*	−9.4	F,G,H	oil	86	$C_{33}H_{44}N_3O_6P$[n]	610
45a	PhCH$_2$O	PhCH$_2$O	(Me)$_2$CHCH$_2$	PhCH$_2$	*R,S,S*	−41.3	F,G,H	oil	86	$C_{35}H_{48}N_3O_5P$	622
46a	PhCH$_2$O	PhCH$_2$O	Ph(CH$_2$)$_2$	PhCH$_2$	*R,S,S*	−30.8	F,G,H	foam	66	$C_{39}H_{48}N_3O_5P$	670
46b	PhCH$_2$O	PhCH$_2$O	Ph(CH$_2$)$_2$	PhCH$_2$	*S,S,S*		F,G,H	oil	57	$C_{39}H_{48}N_3O_5P$	670
47a	PhCH$_2$O	PhCH$_2$O	Et	PhCH$_2$OCONH(CH$_2$)$_4$	*R,S,S*	−34.6[o]	F,G,H	oil	28	$C_{38}H_{53}N_4O_7P \cdot 0.25H_2O$	709
47b	PhCH$_2$O	PhCH$_2$O	Et	PhCH$_2$OCONH(CH$_2$)$_4$	*S,S,S*	−7.3[p]	F,G,H	oil	59	$C_{38}H_{53}N_4O_7P$	709
48a	PhCH$_2$O	PhCH$_2$O	Et	NO$_2$(NH═)CNH(CH$_2$)$_3$	*R,S,S*		F,G,H	oil	51	$C_{30}H_{46}N_7O_7P$[k]	633
49a	PhCH$_2$O	PhCH$_2$O	Et	(1-pyrazolyl)CH$_2$	*R,S,S*		F,G,[q]H	oil	67	$C_{30}H_{42}N_5O_5P$[k]	584
50a	PhCH$_2$O	PhCH$_2$O	Et	(3-indolyl)CH$_2$	*R,S,S*[r]	−47.8	F,G,H	119–121	67	$C_{35}H_{45}N_4O_5P$	633
51a	PhCH$_2$O	PhCH$_2$O	Et	(2-benzimidazolyl)CH$_2$	*R,S,S*	−13.8	F,G,[s]H	95–98	65	$C_{34}H_{44}N_5O_5P \cdot 0.5H_2O$	634
70	EtO	CH(OEt)$_2$	Et	(4-MeO)PhCH$_2$	*R/S,R/S,S*	mixture	A,G,H	foam	91	$C_{27}H_{49}N_3O_7P \cdot 0.25H_2O$	558
71	EtO	Me	Me	(4-MeO)PhCH$_2$	*R/S,R/S,S*	mixture	A,G,H	oil	49	$C_{22}H_{38}N_3O_5P$[k]	456

[a] (*c* 1, MeOH) except where indicated. [b] See the Experimental Section for a description of general methods. [c] Percent yield for method D or G. [d] Analyses for C, H, and N within ±0.4% except where characterized by high-resolution mass spectra or as otherwise indicated. [e] N: calcd, 8.41; found, 7.62. [f] EI-MS *m/e* M$^+$. [g] Also prepared by methods B, G, and H. [h] Also prepared by methods C, G, and H and method D. [i] Amino component prepared by the procedure described in ref 20. [j] Amino component prepared from BocAspNHMe and 1-(2-aminoethyl)pyrrolidine by EDC coupling. [k] Accurate C, H, and N were not obtained. [l] EI-MS calcd for $C_{35}H_{48}N_3O_6P$ (M$^+$) 637.3286. [m] (*c* 0.2, MeOH). [n] N: calcd, 6.89; found, 7.30. [o] (*c* 0.4, MeOH). [p] (*c* 0.5, MeOH). [q] Amino component prepared by the procedure described in ref 23. [r] Structure confirmed by X-ray analysis. [s] Amino component prepared by the procedure described in ref 24.

that compounds from this series are bioavailable in rats following oral administration.[33] Oral absorption of the amino phosphonic acids is likely to be aided by the compounds' good aqueous solubility and relatively low MW.

Experimental Section

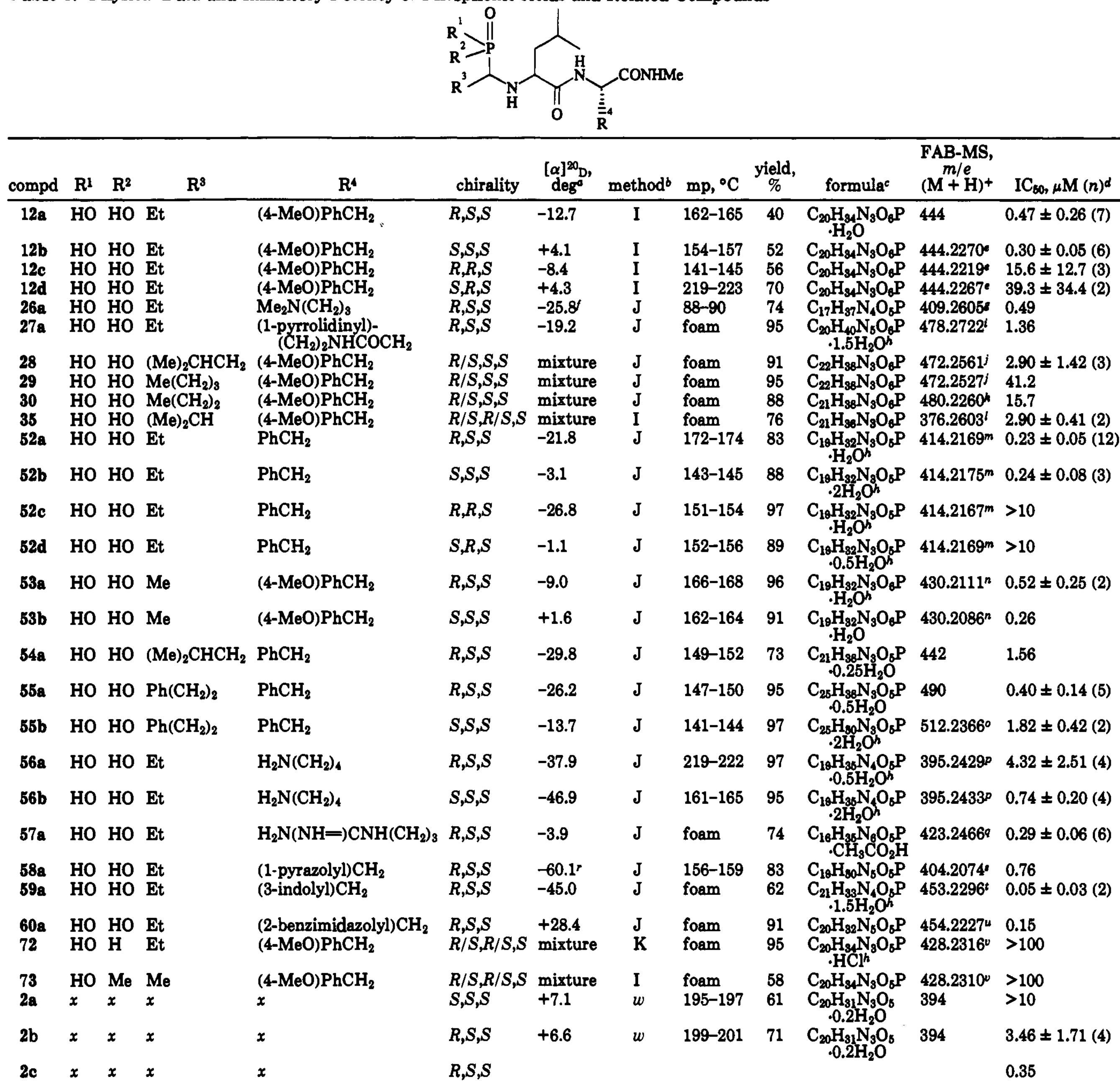
Melting points were determined on a Buchi 510 machine and are uncorrected. Proton magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker AM400, a Bruker AC250, a JEOL GX270, or a Varian EM360A spectrometer using Me$_4$Si as an internal standard. Mass spectra (MS) data were obtained on a JEOL DX303 spectrometer using electrical or chemical (NH$_3$) ionization procedures or fast atom bombardment (FAB) using glycerol as the matrix. Elemental analyses were within 0.4% of the theoretical values unless otherwise stated. All evaporations of solvents were caried out under reduced pressure. Unless otherwise stated, organic solutions were dried over Na$_2$SO$_4$ and for column chromatography, the silica gel used was Merck Kieselgel 60. Brine refers to saturated sodium chloride solution.

Collagenase Inhibitor Assay. The test is essentially as described by Cawston and Barrett.[34] The test compounds were dissolved in MeOH by sonication and then were serially diluted as necessary. Trypsin-activated, semipurified human collagenase was obtained from culture supernatants of the WI-38 human lung fibroblast cell line and was added together with diluent/buffers. Assay tubes were cooled to 4 °C, and either ^{3}H- or ^{14}C-acetylated rat skin type I collagen (100 μg/tube) was added. The choice of radiolabel did not alter the ability of collagenase to degrade the collagen substrate. Following incubation of the assay tubes at 37 °C for 1000 min, the tubes were centrifuged at 12 000 rpm for 15 min at 4 °C. Undigested radiolabeled collagen was pelleted, while digested radiolabeled collagen fibrils were found as soluble peptides in the supernatant. Aliquots of the supernatant were taken for liquid scintillation counting. A collagenase standard curve demonstrated a linear relationship between enzyme concentration and collagen degradation up to 70% of the total collagen degraded. For inhibitor assays, an amount of enzyme was added such that 70% of the total collagen would be degraded during the course of the assay. Different preparations of collagenase and collagen were tested to ensure assay comparability. The activity of the test compounds (IC$_{50}$) is expressed as that concentration of compound that inhibited a known concentration of enzyme by 50%.

Method A. *N*-[(*R*)-1-(Diethoxyphosphinyl)propyl]-(*S*)-leucine, Methyl Ester (9a). A solution of **7a**[19] (5.63 g, 29 mmol) and methyl 4-methyl-2-oxopentanoate (**8**) (12.47 g, 87 mmol) in EtOH (200 mL) was hydrogenated at room temperature and atmospheric pressure over 10% Pd/C. After 72 h, the catalyst was filtered off and the solvent evaporated. The residue was dissolved in CH$_2$Cl$_2$, washed successively with saturated NaHCO$_3$, 5% citric acid, and brine, and then dried, and the solvent was evaporated. The residue was purified by column chromatography on silica gel, eluting with ether to give **9a** (1.72 g, 18%) as a colorless oil: $[\alpha]^{22}_D$ −32.4° (*c* 0.2, MeOH); ^{1}H NMR (CDCl$_3$) δ 0.94 (6 H, t, *J* = 6 Hz), 1.06 (3 H, t, *J* = 5 Hz), 1.32 (3 H, t, *J* = 5 Hz), 1.34 (3 H, t, *J* = 5 Hz), 1.40–2.00 (6 H, m), 2.68 (1 H, m), 3.70 (3 H, s), 3.78 (1 H, t, *J* = 5 Hz), 4.13 (4 H, m); MS *m/e* 323 (M)$^+$.

Further elution gave **9c** (1.26 g, 13%) as a colorless oil: $[\alpha]^{22}_D$ +6.4° (*c* 0.4, MeOH); ^{1}H NMR (CDCl$_3$) δ 0.90 (6 H, dd, *J* = 3,

Table 3. Physical Data and Inhibitory Potency of Phosphonic Acids and Related Compounds



compd	R[1]	R[2]	R[3]	R[4]	chirality	$[\alpha]^{20}_D$, deg[a]	method[b]	mp, °C	yield, %	formula[c]	FAB-MS, *m/e* (M + H)+	IC_{50}, μM (*n*)[d]
12a	HO	HO	Et	(4-MeO)PhCH$_2$	*R,S,S*	−12.7	I	162–165	40	$C_{20}H_{34}N_3O_6P\cdot H_2O$	444	0.47 ± 0.26 (7)
12b	HO	HO	Et	(4-MeO)PhCH$_2$	*S,S,S*	+4.1	I	154–157	52	$C_{20}H_{34}N_3O_6P$	444.2270[e]	0.30 ± 0.05 (6)
12c	HO	HO	Et	(4-MeO)PhCH$_2$	*R,R,S*	−8.4	I	141–145	56	$C_{20}H_{34}N_3O_6P$	444.2219[e]	15.6 ± 12.7 (3)
12d	HO	HO	Et	(4-MeO)PhCH$_2$	*S,R,S*	+4.3	I	219–223	70	$C_{20}H_{34}N_3O_6P$	444.2267[e]	39.3 ± 34.4 (2)
26a	HO	HO	Et	Me$_2$N(CH$_2$)$_3$	*R,S,S*	−25.8[f]	J	88–90	74	$C_{17}H_{37}N_4O_5P$	409.2605[g]	0.49
27a	HO	HO	Et	(1-pyrrolidinyl)-(CH$_2$)$_2$NHCOCH$_2$	*R,S,S*	−19.2	J	foam	95	$C_{20}H_{40}N_5O_6P\cdot 1.5H_2O$[h]	478.2722[i]	1.36
28	HO	HO	(Me)$_2$CHCH$_2$	(4-MeO)PhCH$_2$	*R/S,S,S*	mixture	J	foam	91	$C_{22}H_{38}N_3O_6P$	472.2561[j]	2.90 ± 1.42 (3)
29	HO	HO	Me(CH$_2$)$_3$	(4-MeO)PhCH$_2$	*R/S,S,S*	mixture	J	foam	95	$C_{22}H_{38}N_3O_6P$	472.2527[j]	41.2
30	HO	HO	Me(CH$_2$)$_2$	(4-MeO)PhCH$_2$	*R/S,S,S*	mixture	J	foam	88	$C_{21}H_{36}N_3O_6P$	480.2260[k]	15.7
35	HO	HO	(Me)$_2$CH	(4-MeO)PhCH$_2$	*R/S,R/S,S*	mixture	I	foam	76	$C_{21}H_{36}N_3O_6P$	376.2603[l]	2.90 ± 0.41 (2)
52a	HO	HO	Et	PhCH$_2$	*R,S,S*	−21.8	J	172–174	83	$C_{18}H_{32}N_3O_5P\cdot H_2O$[h]	414.2169[m]	0.23 ± 0.05 (12)
52b	HO	HO	Et	PhCH$_2$	*S,S,S*	−3.1	J	143–145	88	$C_{18}H_{32}N_3O_5P\cdot 2H_2O$[h]	414.2175[m]	0.24 ± 0.08 (3)
52c	HO	HO	Et	PhCH$_2$	*R,R,S*	−26.8	J	151–154	97	$C_{18}H_{32}N_3O_5P\cdot H_2O$[h]	414.2167[m]	>10
52d	HO	HO	Et	PhCH$_2$	*S,R,S*	−1.1	J	152–156	89	$C_{18}H_{32}N_3O_5P\cdot 0.5H_2O$[h]	414.2169[m]	>10
53a	HO	HO	Me	(4-MeO)PhCH$_2$	*R,S,S*	−9.0	J	166–168	96	$C_{19}H_{32}N_3O_6P\cdot H_2O$[h]	430.2111[n]	0.52 ± 0.25 (2)
53b	HO	HO	Me	(4-MeO)PhCH$_2$	*S,S,S*	+1.6	J	162–164	91	$C_{19}H_{32}N_3O_6P\cdot H_2O$	430.2086[n]	0.26
54a	HO	HO	(Me)$_2$CHCH$_2$	PhCH$_2$	*R,S,S*	−29.8	J	149–152	73	$C_{21}H_{36}N_3O_5P\cdot 0.25H_2O$	442	1.56
55a	HO	HO	Ph(CH$_2$)$_2$	PhCH$_2$	*R,S,S*	−26.2	J	147–150	95	$C_{25}H_{38}N_3O_5P\cdot 0.5H_2O$	490	0.40 ± 0.14 (5)
55b	HO	HO	Ph(CH$_2$)$_2$	PhCH$_2$	*S,S,S*	−13.7	J	141–144	97	$C_{25}H_{30}N_3O_5P\cdot 2H_2O$[h]	512.2366[o]	1.82 ± 0.42 (2)
56a	HO	HO	Et	H$_2$N(CH$_2$)$_4$	*R,S,S*	−37.9	J	219–222	97	$C_{18}H_{35}N_4O_5P\cdot 0.5H_2O$[h]	395.2429[p]	4.32 ± 2.51 (4)
56b	HO	HO	Et	H$_2$N(CH$_2$)$_4$	*S,S,S*	−46.9	J	161–165	95	$C_{18}H_{35}N_4O_5P\cdot 2H_2O$[h]	395.2433[p]	0.74 ± 0.20 (4)
57a	HO	HO	Et	H$_2$N(NH═)CNH(CH$_2$)$_3$	*R,S,S*	−3.9	J	foam	74	$C_{16}H_{35}N_6O_5P\cdot CH_3CO_2H$	423.2466[q]	0.29 ± 0.06 (6)
58a	HO	HO	Et	(1-pyrazolyl)CH$_2$	*R,S,S*	−60.1[r]	J	156–159	83	$C_{16}H_{30}N_5O_5P$	404.2074[s]	0.76
59a	HO	HO	Et	(3-indolyl)CH$_2$	*R,S,S*	−45.0	J	foam	62	$C_{21}H_{33}N_4O_5P\cdot 1.5H_2O$[h]	453.2296[t]	0.05 ± 0.03 (2)
60a	HO	HO	Et	(2-benzimidazolyl)CH$_2$	*R,S,S*	+28.4	J	foam	91	$C_{20}H_{32}N_5O_5P$	454.2227[u]	0.15
72	HO	H	Et	(4-MeO)PhCH$_2$	*R/S,R/S,S*	mixture	K	foam	95	$C_{20}H_{34}N_3O_5P\cdot HCl$[h]	428.2316[v]	>100
73	HO	Me	Me	(4-MeO)PhCH$_2$	*R/S,R/S,S*	mixture	I	foam	58	$C_{20}H_{34}N_3O_5P$	428.2310[v]	>100
2a	*x*	*x*	*x*	*x*	*S,S,S*	+7.1	*w*	195–197	61	$C_{20}H_{31}N_3O_5\cdot 0.2H_2O$	394	>10
2b	*x*	*x*	*x*	*x*	*R,S,S*	+6.6	*w*	199–201	71	$C_{20}H_{31}N_3O_5\cdot 0.2H_2O$	394	3.46 ± 1.71 (4)
2c	*x*	*x*	*x*	*x*	*R,S,S*							0.35

[a] (*c* 1, MeOH) except where indicated. [b] See the Experimental Section for a description of general methods. [c] Analyses for C, H, and N within ±0.4% except where characterized by high-resolution FAB-MS. [d] Values are mean ± SEM of the number of experiments indicated in parentheses. [e] Calcd for $C_{20}H_{35}N_3O_6P$ $(M + H)^+$ 444.2263. [f] (*c* 0.4, MeOH). [g] Calcd for $C_{17}H_{38}N_4O_5P$ $(M + H)^+$ 409.2580. [h] Characterized by elemental analysis as well as by high-resolution FAB-MS. [i] Calcd for $C_{20}H_{41}N_5O_5P$ $(M + H)^+$ 478.2794. [j] Calcd for $C_{22}H_{39}N_3O_6P$ $(M + H)^+$ 472.2576. [k] Calcd for $C_{21}H_{36}N_3O_6PNa$ $(M + Na)^+$ 480.2239. [l] Calcd for $C_{21}H_{37}N_3O_6P$ $(M + H - H_2PO_3)^+$ 376.2600. [m] Calcd for $C_{19}H_{33}N_3O_5P$ $(M + H)^+$ 414.2157. [n] Calcd for $C_{19}H_{33}N_3O_6P$ $(M + H)^+$ 430.2107. [o] Calcd for $C_{25}H_{36}N_3O_5PNa$ $(M + Na)^+$ 512.2290. [p] Calcd for $C_{16}H_{36}N_4O_5P$ $(M + H)^+$ 395.2423. [q] Calcd for $C_{16}H_{36}N_6O_5P$ $(M + H)^+$ 423.2485. [r] (*c* 0.3, MeOH). [s] Calcd for $C_{16}H_{31}N_5O_5P$ $(M + H)^+$ 404.2063. [t] Calcd for $C_{21}H_{34}N_4O_5P$ $(M + H)^+$ 453.2267. [u] Calcd for $C_{20}H_{33}N_5O_5P$ $(M + H)^+$ 454.2220. [v] Calcd for $C_{20}H_{35}N_3O_5P$ $(M + H)^+$ 428.2314. [w] See the Experimental Section. [x] For the carboxylic acids, see text and Scheme 4 for structures.

5 Hz), 1.05 (3 H, t, *J* = 5 Hz), 1.32 (3 H, t, *J* = 5 Hz), 1.34 (3 H, t, *J* = 5 Hz), 1.40–1.95 (6 H, m), 2.76 (1 H, m), 3.48 (1 H, t, *J* = 5 Hz), 3.72 (3 H, s), 4.12 (4 H, m); MS *m/e* 323 $(M)^+$.

Compounds **9b** and **9d** were prepared from **7b**[19] by the same procedure. Column chromatography, as above, gave **9d**: $[\alpha]^{22}_D$ +27.3° (*c* 1, MeOH); ^{1}H NMR and MS data were identical to **9a**. Further elution gave **9b**: $[\alpha]^{22}_D$ +1.0° (*c* 1, MeOH); ^{1}H NMR and MS data were identical to **9c**.

Compound **66** was obtained by method A from **63**[26] as a mixture of four stereoisomers after column chromatography with EtOAc as eluent: ^{1}H NMR (CDCl$_3$) δ 0.92 (12 H, m), 1.03 (6 H, m), 1.20–1.37 (18 H, m), 1.40–2.00 (12 H, m), 2.85 (2 H, m), 3.50–3.97 (10 H, m), 3.78 (6 H, s), 4.21 (4 H, m), 4.96 (2 H, dd, *J* = 7, 15 Hz); MS *m/e* 382 $(M + H)^+$.

Similarly, **67** was prepared from **65** as a mixture of four stereoisomers after column chromatography with EtOAc/MeOH (20:1) as eluent: ^{1}H NMR (CDCl$_3$) δ 0.91 (12 H, m), 1.17–1.40 (22 H, m), 1.75 (4 H, m), 2.93 (2 H, m), 3.46 (2 H, m), 3.72 (6 H, m), 4.10 (4 H, m); FAB-MS *m/e* 280 $(M + H)^+$.

Method B. *N*-[(*S*)-1-(Diethoxyphosphinyl)propyl]-(*S*)-leucine, Methyl Ester (9b). The triflate **13** (1.33 g, 4.77 mmol) was prepared by the addition of trifluoromethanesulfonic anhydride (0.92 mL, 5.47 mmol) to methyl L-2-hydroxy-4-methylpentanoate (0.69 g, 4.77 mmol) and 2,6-lutidine (0.68 mL) in CH$_2$Cl$_2$ (10 mL) at −60 °C. After the temperature had risen to 0 °C, a solution of **7b**[19] (0.93 g, 4.77 mmol) in CHCl$_3$ (10 mL) was added followed by 1,8-bis(dimethylamino)naphthalene (1.02 g, 4.77 mmol). The mixture was stirred at room temperature for

4 days, filtered, washed with 10% citric acid and water, and then dried with $MgSO_4$. The solvent was evaporated and the residue purified by column chromatography, eluting with a gradient of 0–2% MeOH/EtOAc, to give **9b** (0.69 g, 47%) as a pale yellow oil: $[\alpha]^{22}_D$ +0.3° (*c* 1.1, MeOH); ^1H NMR and MS data were identical to **9b** prepared by method A.

1-[Bis(benzyloxy)phosphinyl]propanol (14a). Dibenzyl phosphite (36.9 g, 141 mmol) and propionaldehyde (8.2 g, 141 mmol) were stirred together at room temperature, and alumina (70 g) was added in one portion, following a literature procedure.[35] After 24 h, $CHCl_3$ was added, the mixture was filtered, and the solvent was evaporated. The residue was purified by column chromatography, eluting with a gradient of 0–5% MeOH/Et_2O, to give **14a** (27.8 g, 64%) as white needles: mp 81–82 °C (Et_2O/pentane); ^1H NMR ($CDCl_3$) δ 1.04 (3 H, t, *J* = 7 Hz), 1.60–1.95 (2 H, m), 3.81 (1 H, m), 5.07 (4 H, m), 7.35 (10 H, s). Anal. ($C_{17}H_{21}O_4P$) C, H.

Compounds **14b–d** were prepared by the same procedure from dibenzyl phosphite and the appropriate aldehyde.

Compound 14b: mp 71–73 °C (Et_2O/pentane); ^1H NMR ($CDCl_3$) δ 0.85 (3 H, d, *J* = 6 Hz), 0.92 (3 H, d, *J* = 6 Hz), 1.47 (1 H, m), 1.60–1.78 (2 H, m), 1.90 (1 H, br s), 3.97 (1 H, m), 5.08 (4 H, m), 7.35 (10 H, s). Anal. ($C_{19}H_{24}O_4P$) C, H.

Compound 14c: colorless oil; ^1H NMR ($CDCl_3$) δ 0.86 (3 H, t, *J* = 6 Hz), 1.20–1.80 (6 H, m), 2.60 (1 H, br s), 3.87 (2 H, m), 5.06 (4 H, m), 7.35 (10 H, s).

Compound 14d: mp 61–65 °C (Et_2O/pentane); ^1H NMR ($CDCl_3$) δ 0.90 (3 H, d, *J* = 7 Hz), 1.25–1.80 (4 H, m), 2.40 (1 H, br s), 3.90 (1 H, m), 5.08 (4 H, m), 7.35 (10 H, s). Anal. ($C_{19}H_{23}O_4P$) C, H.

Method C. *N*-[(*R*)-1-(Bis(benzyloxy)phosphinyl)propyl]-(*S*)-leucine, Methyl Ester (17a). The triflate **15a** (1.35 g, 3 mmol), prepared by a literature procedure[36] from the alcohol **14a**, in MeOH (2 mL) was added to **16a** (0.43 g, 3 mmol) and K_2CO_3 (1 g) in MeOH (3 mL), and the reaction mixture was heated at 50 °C for 4 h. After the mixture was stirred at room temperature for 18 h, the solvent was evaporated, $CHCl_3$ was added, and the mixture was filtered. The solvent was evaporated and the residue purified by column chromatography, eluting with Et_2O/pentane (1:1), to give **17a** (0.15 g, 11%) as a colorless oil: $[\alpha]^{22}_D$ −32.1° (c 0.9, MeOH); ^1H NMR ($CDCl_3$) δ 0.86 (3 H, d, *J* = 6 Hz), 0.91 (3 H, d, *J* = 6 Hz), 1.02 (3 H, t, *J* = 7 Hz), 1.42 (2 H, m), 1.50–1.95 (4 H, m), 2.74 (1 H, m), 3.70 (3 H, s), 3.78 (1 H, t, *J* = 7 Hz), 5.03 (4 H, m), 7.37 (10 H, s); MS *m/e* 448 (M + H)$^+$. Anal. ($C_{24}H_{34}NO_5P$) C, H, N.

Further elution gave **17b** (0.14 g, 10%) as a colorless oil: $[\alpha]^{22}_D$ −1.1° (*c* 1, MeOH); ^1H NMR ($CDCl_3$) δ 0.88 (3 H, d, *J* = 3 Hz), 0.90 (3 H, d, *J* = 3 Hz), 1.00 (3 H, t, *J* = 7 Hz), 1.44 (2 H, t, *J* = 6 Hz), 1.50–1.95 (4 H, m), 2.80 (1 H, m), 3.49 (1 H, t, *J* = 7 Hz), 3.66 (3 H, s), 5.03 (4 H, m), 7.35 (10 H, s); MS *m/e* 448 (M + H)$^+$. Anal. ($C_{24}H_{34}NO_5P$) C, H, N.

Method D. *N*-[*N*-((*R*)-1-(Bis(benzyloxy)phosphinyl)propyl)-(*S*)-leucyl]-*O*-methyl-(*S*)-tyrosine *N*-Methyl Amide (20a). The triflate **15a**[36] (0.42 g, 0.93 mmol), 1,8-bis(dimethylamino)naphthalene (0.20 g, 0.93 mmol), and **19** (0.3 g, 0.93 mmol) in MeOH (1 mL) were stirred at room temperature for 10 days, with the exclusion of light. The solvent was evaporated, and the residue was dissolved in $CHCl_3$, washed with 10% citric acid and water, and then dried. The solvent was evaporated and the residue partially purified by column chromatography, eluting with a gradient of 0–5% MeOH/$CHCl_3$. Further chromatography, eluting with a gradient of 0–5% MeOH/EtOAc, gave a mixture of **20a** and the corresponding (*S*,*S*,*S*)-diastereoisomer (0.23 g, 41%).

Further elution gave pure **20a** (0.02 g, 4%) as a white crystalline solid: mp 92–93 °C (EtOAc); $[\alpha]^{22}_D$ −35.3° (*c* 1, MeOH); ^1H NMR ($CDCl_3$) δ 0.80 (3 H, d, *J* = 3 Hz), 0.83 (3 H, d, *J* = 3 Hz), 0.96 (3 H, t, *J* = 6 Hz), 1.13–1.32 (2 H, m), 1.40–1.60 (2 H, m), 1.60–1.86 (2 H, m), 2.58 (1 H, m), 2.72 (3 H, d, *J* = 5 Hz), 2.99 (2 H, m), 3.60 (1 H, m), 3.74 (3 H, s), 4.50 (1 H, m), 4.97 (4 H, m), 6.08 (1 H, br s), 6.79 (2 H, d, *J* = 7 Hz), 7.10 (2 H, d, *J* = 7 Hz), 7.33 (11 H, s); MS *m/e* 624 (M + H)$^+$. Anal. ($C_{34}H_{46}N_3O_6P$) C, H, N.

Compounds **23–25** were prepared, as mixtures of two diastereoisomers, from **19** and the corresponding alcohol by the same procedure.

Ethyl [1-((Benzyloxycarbonyl)amino)ethyl]methylphosphinate (65). *N*,*N*-Dicyclohexylcarbodiimide (1.08 g, 5.2 mmol) was added to a stirred solution of the phosphinic acid **64**[27] (1.06 g, 4.1 mmol) in dry THF (25 mL). 4-(Dimethylamino)pyridine (0.06 g, 0.5 mmol) and ethanol (0.26 g, 5.7 mmol) were added, and the mixture was stirred for 18 h. The filtered solution was washed with saturated $NaHCO_3$ and dried and the solvent evaporated to give a colorless oil which was purified by column chromatography, eluting with EtOAc, to give **65** (0.8 g, 68%): ^1H NMR ($CDCl_3$) δ 1.25–1.50 (9 H, m), 4.05 (3 H, m), 5.12 (2 H, s), 5.35 (1 H, br d), 7.33 (5 H, s); MS *m/e* 285 (M)$^+$.

Method E. *N*-[(*R*,*S*)-1-(Dimethoxyphosphinyl)-2-methylpropyl]-(*R*,*S*)-leucine, Methyl Ester (32). A solution of **31** (1.08 g, 15 mmol) and **16a** (2.17 g, 15 mmol) in toluene (100 mL) was heated at reflux for 2 h with azeotropic removal of water. Dimethyl phosphite (1.65 g, 15 mmol) was added and the solution refluxed for a further 18 h. The solution was allowed to cool to room temperature, the solvent was evaporated, and the residue was purified by column chromatography, eluting with EtOAc, to give **32** (2.9 g, 63%) as a yellow oil (mixture of four stereoisomers): ^1H NMR ($CDCl_3$) δ 0.92 (12 H, m), 1.06 (12 H, m), 1.60 (4 H, m), 1.76 (4 H, m), 2.10 (2 H, m), 2.77 (2 H, m), 3.37 (1 H, t, *J* = 7 Hz), 3.75 (19 H, m); MS *m/e* 309 (M)$^+$.

Method F. *N*-[(*R*)-1-(Bis(benzyloxy)phosphinyl)propyl]-(*S*)-leucine, Methyl Ester (17a). Dibenzyl trimethylsilyl phosphite (7.25 g, 22 mmol) was prepared from dibenzyl phosphite (5.75 g, 22 mmol), triethylamine (4.7 g, 22 mmol), and chlorotrimethylsilane (3.6 g, 22 mmol) by a literature procedure.[22]

Propionaldehyde (1.2 g, 20 mmol) was added to **16a** (2.9 g, 20 mmol) at 0 °C. Magnesium sulfate (10 g) was added and the mixture stirred at room temperature for 1 h. After addition of CH_2Cl_2 (20 mL), the solution was filtered and added to dibenzyl trimethylsilyl phosphite (7.35 g, 22 mmol) under N_2 at 0 °C. The solution was allowed to warm to room temperature and stirred for 18 h, washed with water, 10% citric acid, and saturated $NaHCO_3$, and then dried. The solvent was evaporated to give a yellow oil which was purified by column chromatography, eluting with Et_2O/pentane (1:1), to give **17a** (2.7 g, 30%) as a colorless oil: $[\alpha]^{22}_D$ −32.1° (*c* 0.9, MeOH); ^1H NMR and MS data were identical to **17a** prepared by method C. Anal. ($C_{24}H_{34}NO_5P$) C, H, N.

Futher elution gave **17b** (2.2 g, 25%) as a colorless oil: $[\alpha]^{22}_D$ −1.1° (*c* 1, MeOH); ^1H NMR and MS data were identical to **17b** prepared by method C. Anal. ($C_{24}H_{34}NO_5P$) C, H, N.

Compounds **17c** and **17d** were prepared from propionaldehyde and **16b** by the same procedure.

Compound 17c: ^1H NMR and MS data were identical to **17b**.

Compound 17d: ^1H NMR and MS data were identical to **17a**.

The following compounds were prepared from **16a** and the appropriate aldehyde by the same procedure.

Compound 37a: ^1H NMR ($CDCl_3$) δ 0.85 (3 H, d, *J* = 6 Hz), 0.90 (3 H, d, *J* = 6 Hz), 1.16–1.46 (5 H, m), 1.53–1.80 (2 H, m), 2.90 (1 H, m), 3.65 (1 H, t, *J* = 6 Hz), 3.70 (3 H, s), 5.03 (4 H, m), 7.31 (10 H, s); MS *m/e* 434 (M + H)$^+$.

Compound 37b: ^1H NMR ($CDCl_3$) δ 0.90 (6 H, t, *J* = 6 Hz), 1.19–1.48 (5 H, m), 1.73 (1 H, m), 1.93 (1 H, m), 3.09 (1 H, m), 3.48 (1 H, t, *J* = 6 Hz), 3.69 (3 H, s), 5.03 (4 H, m), 7.31 (10 H, s); MS *m/e* 434 (M + H)$^+$.

Compound 38a: $[\alpha]^{22}_D$ −13.7° (*c* 1, MeOH); ^1H NMR ($CDCl_3$) δ 0.89 (3 H, d, *J* = 6 Hz), 0.90 (3 H, d, *J* = 6 Hz), 1.40 (2 H, m), 1.61–1.90 (3 H, m), 2.10 (1 H, m), 2.65 (1 H, m), 2.83 (2 H, m), 3.63 (3 H, s), 3.75 (1 H, t, *J* = 7 Hz), 4.97 (4 H, m), 7.25 (15 H, m); MS *m/e* (M + H)$^+$. Anal. ($C_{24}H_{34}NO_5P$) H, N. C: calcd, 68.82; found, 69.72.

Compound 38b: $[\alpha]^{22}_D$ −5.3° (*c* 1, MeOH); ^1H NMR ($CDCl_3$) δ 0.87 (3 H, d, *J* = 3 Hz), 0.90 (3 H, d, *J* = 3 Hz), 1.40 (2 H, m), 1.75 (2 H, m), 2.05 (1 H, m), 2.65 (1 H, m), 2.83 (3 H, br m), 3.42 (1 H, t, *J* = 7 Hz), 3.59 (3 H, s), 4.94 (4 H, m), 7.25 (15 H, m); MS *m/e* 524 (M + H)$^+$. Anal. ($C_{24}H_{34}NO_5P$) C, H, N.

Compound 39a: ^1H NMR ($CDCl_3$) δ 0.79 (3 H, d, *J* = 6 Hz), 0.83 (3 H, d, *J* = 6 Hz), 0.88 (3 H, d, *J* = 6 Hz), 1.32–1.74 (5 H, m), 1.84 (1 H, br s), 2.10 (1 H, m), 2.87 (1 H, m), 3.63 (3 H, s), 3.80 (1 H, t, *J* = 7 Hz), 4.99 (4 H, m), 7.31 (10 H, m); MS *m/e* 476 (M + H)$^+$.

Method G. *N*-[(*S*)-1-(Diethoxyphosphinyl)propyl]-(*S*)-leucine (10b). A solution of **9b** (1.08 g, 5.2 mmol) and sodium

hydroxide (0.17 g, 4.2 mmol) in EtOH (30 mL) and water (20 mL) was stirred for 24 h at room temperature. The EtOH was evaporated, and the aqueous solution was acidified with 5 N HCl, extracted with CH_2Cl_2, dried, and evaporated to give **10b** (1.05 g, 89%) as a white crystalline solid: mp 59–60 °C (pentane); $[\alpha]^{22}_D$ +4.1° (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.95 (6 H, d, *J* = 6 Hz), 1.05 (3 H, t, *J* = 6 Hz), 1.35 (6 H, t, *J* = 6 Hz), 1.43–1.98 (5 H, m), 2.78 (1 H, m), 3.42 (1 H, dd, *J* = 3, 5 Hz), 4.16 (4 H, m), 5.70 (1 H, br s); MS *m/e* 309 $(M)^+$. Anal. ($C_{13}H_{28}NO_5P$) C, H, N.

The same procedure was used to prepare the following compounds.

Compound 10a: mp 90–92 °C ($CHCl_3$); $[\alpha]^{22}_D$ −26.5° (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.94 (3 H, d, *J* = 3 Hz), 0.98 (3 H, d, *J* = 3 Hz), 1.08 (3 H, t, *J* = 6 Hz), 1.35 (6 H, t, *J* = 6 Hz), 1.40–1.96 (5 H, m), 2.73 (1 H, m), 3.72 (1 H, dd, *J* = 7, 10 Hz), 4.16 (4 H, m), 5.40 (1 H, br s); FAB-MS *m/e* 310 $(M + H)^+$.

Compound 10c: $[\alpha]^{22}_D$ −4.3° (*c* 1, MeOH); ^{1}H NMR and MS data were identical to **10b**.

Compound 10d: $[\alpha]^{22}_D$ +23.7° (*c* 1, MeOH); ^{1}H NMR and MS data were identical to **10a**.

Compound 18a: mp 112–114 °C (Et_2O); $[\alpha]^{22}_D$ −12.6° (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.88 (6 H, t, *J* = 5 Hz), 1.03 (3 H, t, *J* = 6 Hz), 1.35–1.97 (6 H, m), 2.72 (1 H, m), 3.75 (1 H, t, *J* = 7 Hz), 5.02 (4 H, m), 7.31 (10 H, s); MS *m/e* 434 $(M + H)^+$. Anal. ($C_{23}H_{32}NO_5P\cdot 1.5H_2O$) C, H, N.

Compound 18b: mp 71–73 °C (Et_2O); $[\alpha]^{22}_D$ +0.5° (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.90 (3 H, t, *J* = 6 Hz), 0.92 (3 H, d, *J* = 6 Hz), 1.33–1.90 (6 H, m), 2.75 (1 H, m), 3.40 (1 H, dd, *J* = 5, 7 Hz), 5.01 (4 H, m), 7.33 (10 H, s); MS *m/e* 434 $(M + H)^+$. Anal. ($C_{23}H_{32}NO_5P$) C, H, N.

Compound 18c: $[\alpha]^{22}_D$ +0.2° (*c* 0.9, MeOH); ^{1}H NMR and MS data were identical to **18b**. Anal. ($C_{23}H_{32}NO_5P$) C, H, N.

Compound 18d: $[\alpha]^{22}_D$ +12.4° (*c* 0.9, MeOH); ^{1}H NMR and MS data were identical to **18a**. Anal. ($C_{23}H_{32}NO_5P$) C, H, N.

Compound 33: mixture of four stereoisomers; ^{1}H NMR δ 0.90 (12 H, m), 1.03 (12 H, m), 1.59 (4 H, m), 1.76 (4 H, m), 2.10 (2 H, m), 2.75 (2 H, m), 3.40 (1 H, t, *J* = 7 Hz), 3.73 (13 H, m); MS *m/e* 296 $(M + H)^+$.

Compound 40a: $[\alpha]^{22}_D$ −13.6° (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.96 (3 H, d, *J* = 3 Hz), 0.99 (3 H, d, *J* = 3 Hz), 1.35 (3 H, dd, *J* = 6, 16 Hz), 1.40–1.60 (2 H, m), 1.75 (1 H, m), 3.08 (1 H, m), 3.65 (1 H, dd, *J* = 5, 7 Hz), 5.04 (4 H, m), 7.34 (10 H, s); MS *m/e* 420 $(M + H)^+$. Anal. ($C_{22}H_{30}NO_5P\cdot 0.5H_2O$) C, H, N.

Compound 40b: $[\alpha]^{22}_D$ −7.0° (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.90 (6 H, t, *J* = 5 Hz), 1.31 (3 H, dd, *J* = 6, 16 Hz), 1.43 (2 H, m), 1.62 (2 H, m), 2.97 (1 H, m), 3.40 (1 H, dd, *J* = 5, 7 Hz), 5.04 (4 H, m), 7.33 (10 H, s); MS *m/e* 420 $(M + H)^+$. Anal. ($C_{22}H_{30}NO_5P\cdot 0.5H_2O$) C, H, N.

Compound 41a: $[\alpha]^{22}_D$ −12.1° (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.87 (3 H, d, *J* = 3 Hz), 0.90 (3 H, d, *J* = 3 Hz), 1.47 (2 H, m), 1.76 (2 H, m), 2.12 (1 H, m), 2.63 (1 H, m), 2.87 (2 H, m), 3.75 (1 H, t, *J* = 7 Hz), 5.02 (4 H, m), 7.08 (2 H, d, *J* = 7 Hz), 7.20 (3 H, m), 7.33 (10 H, m); MS *m/e* 510 $(M + H)^+$. Anal. ($C_{29}H_{36}NO_5P\cdot 0.5H_2O$) C, H, N.

Compound 41b: ^{1}H NMR ($CDCl_3$) δ 0.88 (6 H, t, *J* = 5 Hz), 1.39 (1 H, m), 1.62 (2 H, m), 1.85 (1 H, m), 2.10 (1 H, m), 2.70 (1 H, m), 2.82 (2 H, m), 3.37 (1 H, dd, *J* = 5, 7 Hz), 5.03 (4 H, m), 7.06 (2 H, d, *J* = 7 Hz), 7.22 (3 H, m), 7.33 (10 H, m); MS *m/e* 510 $(M + H)^+$.

Compound 42a: $[\alpha]^{22}_D$ −28.3° (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.79 (3 H, d, *J* = 6 Hz), 0.89 (6 H, t, *J* = 7 Hz), 0.90 (3 H, d, *J* = 6 Hz), 1.32–1.60 (4 H, m), 1.73 (1 H, m), 1.83 (1 H, m), 2.92 (1 H, m), 3.81 (1 H, t, *J* = 7 Hz), 5.03 (4 H, m), 7.34 (10 H, d), 7.20 (3 H, m); MS *m/e* 461 $(M)^+$. Anal. ($C_{25}H_{36}NO_5P\cdot 0.25H_2O$) C, H, N.

Compound 68: mixture of four stereoisomers; ^{1}H NMR ($CDCl_3$) δ 0.96 (12 H, m), 1.08 (6 H, t, *J* = 6 Hz), 1.22–1.40 (18 H, m), 1.40–2.00 (12 H, m), 2.85–3.04 (2 H, m), 3.43 (1 H, m), 3.58 (1 H, t, *J* = 6 Hz), 3.70 (5 H, m), 3.88 (4 H, m), 4.24 (4 H, m), 4.87 (2 H, dd, *J* = 7, 15 Hz), 5.70 (2 H, br s); MS *m/e* 368 $(M + H)^+$.

Compound 69: mixture of four stereoisomers; ^{1}H NMR ($CDCl_3$) δ 0.89 (12 H, m), 1.23 (12 H, m), 1.41 (12 H, m), 1.75 (2 H, m), 2.94 (2 H, m), 3.40 (4 H, br s), 3.99 (4 H, m); FAB-MS *m/e* 266 $(M + H)^+$.

Method H. *N*-[*N*-((*S*)-1-(Diethoxyphosphinyl)propyl)-(*S*)-leucyl]-*O*-methyl-(*S*)-tyrosine *N*-Methyl Amide (11b). A solution of the diethyl ester **10b** (0.25 g, 0.81 mmol) and 1-hydroxybenzotriazole monohydrate (0.12 g, 0.9 mmol) in CH_2Cl_2 (25 mL) at 0 °C, under N_2, was treated with 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (0.17 g, 0.9 mmol). After 1 h at 0 °C, a solution of *O*-methyl-L-tyrosine *N*-methyl amide (0.2 g, 0.9 mmol) in CH_2Cl_2 (10 mL) was added. The reaction was stirred at 0 °C for 1 h and then at room temperature for 18 h. The solution was washed with water, saturated $NaHCO_3$, 5% citric acid, and brine and then dried. The solvent was evaporated and the residue purified by column chromatography, eluting with Et_2O/MeOH (20:1), to give the single diastereoisomer **11b** (0.36 g, 89%) as a colorless oil: $[\alpha]^{22}_D$ −11.9° (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.84 (3 H, d, *J* = 5 Hz), 0.88 (3 H, d, *J* = 5 Hz), 1.01 (3 H, t, *J* = 7 Hz), 1.16 (1 H, m), 1.34 (3 H, t, *J* = 6 Hz), 1.35 (3 H, t, *J* = 6 Hz), 1.40–1.90 (5 H, m), 2.65 (1 H, m), 2.77 (3 H, d, *J* = 5 Hz), 2.91 (1 H, dd, *J* = 10, 14 Hz), 3.23 (2 H, m), 3.77 (3 H, s), 4.10 (4 H, m), 4.77 (1 H, m), 6.80 (2 H, d, *J* = 8 Hz), 7.11 (2 H, d, *J* = 8 Hz), 7.68 (1 H, br s), 7.72 (1 H, br s); MS *m/e* 499 $(M)^+$. Anal. ($C_{24}H_{42}N_3O_6P\cdot H_2O$) C, H, N.

Compounds **11a,c,d** were prepared from the corresponding diethyl esters **10a,c,d** by the same procedure.

Compound 11a: mp 83–86 °C (EtOAc); $[\alpha]^{22}_D$ −34.8° (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.89 (6 H, d, *J* = 6 Hz), 1.00 (3 H, t, *J* = 7 Hz), 1.25 (1 H, m), 1.33 (6 H, t, *J* = 6 Hz), 1.46–1.90 (5 H, m), 2.57 (1 H, m), 2.73 (3 H, d, *J* = 5 Hz), 3.02 (2 H, m), 3.60 (1 H, br s), 3.77 (3 H, s), 4.12 (4 H, m), 4.52 (1 H, m), 6.12 (1 H, br s), 6.82 (2 H, d, *J* = 8 Hz), 7.13 (2 H, d, *J* = 8 Hz), 7.45 (1 H, d, *J* = 8 Hz); MS *m/e* 499 $(M)^+$. Anal. ($C_{24}H_{42}N_3O_6P$) C, H. N: calcd, 8.41; found, 7.62.

Compound 11c: $[\alpha]^{22}_D$ +6.4° (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.87 (3 H, d, *J* = 2 Hz), 0.89 (3 H, d, *J* = 2 Hz), 1.00 (3 H, t, *J* = 7 Hz), 1.25–1.85 (6 H, m), 1.34 (3 H, t, *J* = 6 Hz), 1.36 (3 H, t, *J* = 6 Hz), 2.53 (1 H, m), 2.73 (3 H, d, *J* = 5 Hz), 3.00 (1 H, dd, *J* = 8, 14 Hz), 3.15 (1 H, m), 3.22 (1 H, dd, *J* = 8, 14 Hz), 3.78 (3 H, s), 4.13 (4 H, m), 4.62 (1 H, m), 6.80 (2 H, d, *J* = 8 Hz), 6.88 (1 H, br s), 7.07 (1 H, d, *J* = 8 Hz), 7.13 (2 H, d, *J* = 8 Hz); FAB-MS *m/e* 500 $(M + H)^+$. Anal. ($C_{24}H_{42}N_3O_6P\cdot H_2O$) C, H, N.

Compound 11d: $[\alpha]^{22}_D$ +36.4° (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.87 (3 H, d, *J* = 3 Hz), 0.90 (3 H, d, *J* = 3 Hz), 1.02 (3 H, t, *J* = 6 Hz), 1.25–1.80 (6 H, m), 1.34 (3 H, t, *J* = 7 Hz), 1.36 (3 H, t, *J* = 7 Hz), 2.60 (1 H, m), 2.71 (3 H, d, *J* = 5 Hz), 2.97 (1 H, dd, *J* = 6, 14 Hz), 3.10 (1 H, dd, *J* = 6, 14 Hz), 3.58 (1 H, t, *J* = 6 Hz), 3.79 (3 H, s), 4.12 (4 H, m), 4.60 (1 H, m), 6.24 (1 H, br s), 6.83 (2 H, d, *J* = 8 Hz), 7.13 (3 H, d, *J* = 8 Hz); MS *m/e* 499 $(M)^+$. Anal. ($C_{24}H_{42}N_3O_6P\cdot H_2O$) C, H, N.

The same procedure was also used to prepare compounds **34**, **70**, and **71** from the esters **33**, **68**, and **69**, respectively.

***N*-[*N*-((*R*)-1-(Bis(benzyloxy)phosphinyl)propyl)-(*S*)-leucyl]-(*S*)-phenylalanine *N*-Methyl Amide (43a).** The dibenzyl ester **18a** (2.0 g, 4.61 mmol) and L-phenylalanine *N*-methyl amide (0.92 g, 5.16 mmol) were coupled by the procedure described above, to give, after column chromatography with EtOAc as eluent, **43a** (2.6 g, 95%) as a single diastereoisomer: mp 79–81 °C (EtOAc); $[\alpha]^{22}_D$ −40.7° (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.80 (3 H, d, *J* = 3 Hz), 0.82 (3 H, d, *J* = 3 Hz), 0.95 (3 H, t, *J* = 7 Hz), 1.20 (2 H, m), 1.51 (2 H, m), 1.80 (2 H, m), 2.56 (1 H, m), 2.71 (3 H, d, *J* = 5 Hz), 2.97 (1 H, dd, *J* = 6, 14 Hz), 3.12 (1 H, dd, *J* = 6, 14 Hz), 3.61 (1 H, m), 4.60 (1 H, m), 4.97 (4 H, m), 6.15 (1 H, br s), 7.18 (5 H, m), 7.34 (11 H, s); FAB-MS *m/e* 594 $(M + H)^+$. Anal. ($C_{33}H_{44}N_3O_5P$) C, H, N.

Compounds **43b–d** were prepared from the corresponding dibenzyl esters **18b–d** and L-phenylalanine *N*-methyl amide by the same procedure.

Compound 43b: $[\alpha]^{22}_D$ −21.8° (*c* 0.2, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.79 (6 H, d, *J* = 5 Hz), 0.94 (3 H, t, *J* = 7 Hz), 1.02–1.87 (6 H, m), 2.61 (1 H, m), 2.75 (3 H, d, *J* = 5 Hz), 2.90 (1 H, dd, *J* = 6, 14 Hz), 3.15 (1 H, m), 3.34 (1 H, dd, *J* = 6, 14 Hz), 4.82 (1 H, m), 5.00 (4 H, m), 7.20 (5 H, m), 7.33 (10 H, s), 7.77 (1 H, d, *J* = 7 Hz), 7.82 (1 H, br s); FAB-MS *m/e* 594 $(M + H)^+$. Anal. ($C_{33}H_{44}N_3O_5P$) C, H, N.

Compound 43c: mp 113–118 °C (EtOAc); $[\alpha]^{22}_D$ +1.0° (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.83 (3 H, d, *J* = 3 Hz), 0.86 (3 H,

d, $J = 3$ Hz), 0.94 (3 H, t, $J = 6$ Hz), 1.22 (2 H, t, $J = 6$ Hz), 1.37 (1 H, br s), 1.50 (2 H, m), 1.65–1.85 (2 H, m), 2.52 (1 H, m), 2.73 (3 H, d, $J = 5$ Hz), 2.99 (1 H, dd, $J = 8, 14$ Hz), 3.04 (1 H, t, $J = 7$ Hz), 3.27 (1 H, dd, $J = 6, 14$ Hz), 4.65 (1 H, m), 4.88 (1 H, dd, $J = 6, 13$ Hz), 5.00 (3 H, m), 6.90 (1 H, br s), 7.10 (1 H, d, $J = 8$ Hz), 7.19 (5 H, m), 7.32 (5 H, s), 7.34 (5 H, s); FAB-MS *m/e* 594 (M + H)+. Anal. ($C_{33}H_{44}N_3O_5P$) C, H, N.

Compound 43d: mp 73–76 °C (EtOAc); $[\alpha]^{22}_D$ +38.9° (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.80 (6 H, d, $J = 3$ Hz), 0.97 (3 H, t, $J = 6$ Hz), 1.27 (2 H, m), 1.40–1.80 (4 H, m), 2.61 (1 H, m), 2.70 (3 H, d, $J = 5$ Hz), 2.99 (1 H, dd, $J = 6, 14$ Hz), 3.15 (1 H, dd, $J = 6, 14$ Hz), 3.15 (1 H, dd, $J = 6, 14$ Hz), 3.55 (1 H, t, $J = 7$ Hz), 4.64 (1 H, m), 4.97 (4 H, m), 6.29 (1 H, br s), 7.09 (1 H, d, $J = 8$ Hz), 7.20 (5 H, m), 7.34 (10 H, s); FAB-MS *m/e* 594 (M + H)+. Anal. ($C_{33}H_{44}N_3O_5P$) C, H, N.

Compounds **20a** (also prepared by method D), **21a**, **22a**, **23–25**, **44a,b**, **45a**, **46a,b**, **47a,b**, and **48a–51a** were prepared by the same procedure from the corresponding dibenzyl ester and the appropriate amino component.

Method I. *N*-[*N*-((*S*)-1-Phosphonopropyl)-(*S*)-leucyl]-*O*-methyl-(*S*)-tyrosine *N*-Methyl Amide (12b). Bromotrimethylsilane (1.32 g, 8.6 mmol) was added to a solution of **11b** (0.54 g, 1.08 mmol) in CH_2Cl_2 (50 mL). After the mixture was stirred at room temperature for 24 h, the solvent was evaporated and the residue was dissolved in MeOH (100 mL) and stirred for 1 h at room temperature. The solvent was evaporated, and the residue was purified by column chromatography on reverse-phase silica, eluting with a gradient of 5–30% MeOH in water, to give **12b** (0.25 g, 52%) as a single diastereoisomer: mp 154–157 °C (MeOH/Et_2O); $[\alpha]^{22}_D$ +4.1° (*c* 1, MeOH); ^{1}H NMR (CD_3OD) δ 0.78 (3 H, d, $J = 6$ Hz), 0.82 (3 H, d, $J = 6$ Hz), 0.90 (3 H, t, $J = 7$ Hz), 1.32 (2 H, m), 1.50 (2 H, m), 1.72 (1 H, m), 2.53 (1 H, m), 2.60 (3 H, s), 2.77 (1 H, dd, $J = 10, 14$ Hz), 3.00 (1 H, dd, $J = 6, 14$ Hz), 3.61 (1 H, m), 3.65 (3 H, s), 4.49 (1 H, m), 6.73 (2 H, d, $J = 8$ Hz), 7.08 (2 H, d, $J = 8$ Hz); HR FAB-MS calcd for $C_{20}H_{35}N_3O_6P$ (M + H)+ 444.2263, found 444.2270.

Compounds **12a,c,d** were prepared from the corresponding diethyl esters **11a,c,d** by the same procedure.

Compound 12a: mp 162–165 °C (MeOH/Et_2O); $[\alpha]^{22}_D$ −12.7° (*c* 1, MeOH); ^{1}H NMR (CD_3OD) δ 1.02 (9 H, m), 1.50–2.00 (5 H, m), 2.48 (1 H, m), 2.80 (3 H, s), 2.96 (1 H, dd, $J = 10, 14$ Hz), 3.15 (1 H, dd, $J = 6, 14$ Hz), 3.87 (3 H, s), 4.15 (1 H, t, $J = 7$ Hz), 4.66 (1 H, m), 6.96 (2 H, d, $J = 8$ Hz), 7.29 (2 H, d, $J = 8$ Hz); FAB-MS *m/e* 444 (M + H)+. Anal. ($C_{20}H_{34}N_3O_6P \cdot H_2O$) C, H, N.

Compound 12c: mp 141–145 °C (MeOH/Et_2O); $[\alpha]^{22}_D$ −8.4° (*c* 1, MeOH); ^{1}H NMR (CD_3OD) δ 0.65 (3 H, d, $J = 6$ Hz), 0.69 (3 H, d, $J = 6$ Hz), 0.89 (1 H, m), 0.99 (3 H, t, $J = 7$ Hz), 1.15–1.90 (4 H, m), 2.65 (3 H, s), 2.74 (2 H, m), 3.07 (1 H, dd, $J = 5, 14$ Hz), 3.66 (3 H, s), 3.85 (1 H, t, $J = 7$ Hz), 4.52 (1 H, m), 6.75 (2 H, d, $J = 8$ Hz), 7.03 (2 H, d, $J = 8$ Hz); HR FAB-MS calcd for $C_{20}H_{35}N_3O_6P$ (M + H)+ 444.2263, found 444.2219.

Compound 12d: mp 219–223 °C (MeOH/Et_2O); $[\alpha]^{22}_D$ +4.3° (*c* 1, MeOH); ^{1}H NMR (CD_3OD) δ 0.72 (3 H, d, $J = 6$ Hz), 0.80 (3 H, d, $J = 6$ Hz), 1.12 (3 H, t, $J = 7$ Hz), 1.20–2.10 (5 H, m), 2.70 (1 H, m), 2.75 (3 H, s), 2.90 (1 H, m), 3.27 (1 H, dd, $J = 5, 14$ Hz), 3.77 (3 H, s), 4.31 (1 H, m), 4.60 (1 H, m), 6.86 (2 H, d, $J = 8$ Hz), 7.17 (2 H, d, $J = 8$ Hz); HR FAB-MS calcd for $C_{20}H_{35}N_3O_6P$ (M + H)+ 444.2263, found 444.2267.

Compounds **35** and **73** were prepared from **34** and **71**, respectively, by the above procedure.

Method J. *N*-[*N*-((*R*)-1-Phosphonopropyl)-(*S*)-leucyl]-(*S*)-phenylalanine *N*-Methyl Amide (52a). A solution of the dibenzyl ester **43a** (2.8 g, 4.7 mmol) in EtOH (100 mL) was hydrogenated at room temperature and atmospheric pressure over 10% Pd/C. After 8 h, the catalyst was filtered off and the solvent evaporated to give **52a** (1.6 g, 83%) as a single diastereoisomer: mp 172–174 °C (MeOH/Et_2O); $[\alpha]^{22}_D$ −21.8° (*c* 1, MeOH); ^{1}H NMR (CD_3OD) δ 0.88 (3 H, t, $J = 6$ Hz), 0.95 (3 H, d, $J = 5$ Hz), 1.00 (3 H, d, $J = 5$ Hz), 1.68 (4 H, m), 1.84 (1 H, m), 2.40 (1 H, m), 2.70 (3 H, s), 2.95 (1 H, dd, $J = 8, 14$ Hz), 3.10 (1 H, dd, $J = 5, 14$ Hz), 4.44 (1 H, t, $J = 6$ Hz), 4.67 (1 H, m), 7.31 (5 H, s); HR FAB-MS calcd for $C_{19}H_{33}N_3O_5P$ (M + H)+ 414.2157, found 414.2169. Anal. ($C_{19}H_{32}N_3O_5P \cdot H_2O$) C, H, N.

Compounds **52b–d** were prepared from the corresponding dibenzyl esters **43b–d** by the same procedure.

Compound 52b: mp 143–145 °C (MeOH/Et_2O); $[\alpha]^{22}_D$ −3.1° (*c* 1, MeOH); ^{1}H NMR (CD_3OD) δ 0.91 (3 H, t, $J = 5$ Hz), 1.00 (6 H, m), 1.50–1.90 (5 H, m), 2.69 (3 H, s), 2.80 (1 H, m), 3.00 (1 H, dd, $J = 8, 14$ Hz), 3.12 (1 H, dd, $J = 6, 14$ Hz), 4.04 (1 H, m), 4.70 (1 H, m), 7.30 (5 H, s); HR FAB-MS calcd for $C_{19}H_{33}N_3O_5P$ (M + H)+ 414.2157, found 414.2175. Anal. ($C_{19}H_{32}N_3O_5P \cdot 2H_2O$) C, N. H: calcd, 8.07; found, 6.95.

Compound 52c: mp 151–154 °C (MeOH/Et_2O); $[\alpha]^{22}_D$ −26.8° (*c* 1, MeOH); ^{1}H NMR (CD_3OD) δ 0.60 (3 H, d, $J = 5$ Hz), 0.64 (3 H, d, $J = 5$ Hz), 0.78 (1 H, m), 1.02 (3 H, t, $J = 6$ Hz), 1.38 (2 H, t, $J = 6$ Hz), 1.60–1.90 (2 H, m), 2.67 (3 H, s), 2.76 (1 H, dd, $J = 10, 14$ Hz), 2.88 (1 H, m), 3.16 (1 H, dd, $J = 5, 14$ Hz), 4.00 (1 H, t, $J = 6$ Hz), 4.60 (1 H, m), 7.20 (5 H, s); HR FAB-MS calcd for $C_{19}H_{33}N_3O_5P$ (M + H)+ 414.2157, found 414.2167. Anal. ($C_{19}H_{32}N_3O_5P \cdot H_2O$) C, H, N.

Compound 52d: mp 152–156 °C (MeOH/Et_2O); $[\alpha]^{22}_D$ −1.1° (*c* 1, MeOH); ^{1}H NMR (CD_3OD) δ 0.70 (3 H, d, $J = 5$ Hz), 0.80 (3 H, d, $J = 5$ Hz), 0.94 (1 H, m), 1.10 (3 H, t, $J = 6$ Hz), 1.45 (2 H, t, $J = 6$ Hz), 1.73 (1 H, m), 2.01 (1 H, m), 2.77 (3 H, s), 2.86 (2 H, m), 3.35 (1 H, dd, $J = 5, 14$ Hz), 4.34 (1 H, t, $J = 6$ Hz), 4.65 (1 H, m), 7.30 (5 H, s); HR FAB-MS calcd for $C_{19}H_{33}N_3O_5P$ (M + H)+ 414.2157, found 414.2169. Anal. ($C_{19}H_{32}N_3O_5P \cdot 0.5H_2O$) C, H, N.

The same procedure was used to prepare compounds **12a** (also prepared by method I from **11a**), **26a**, **27a**, **28–30**, **53a,b**, **54a**, **55a,b**, **56a,b**, and **57a–60a** from the corresponding dibenzyl esters.

Method K. *N*-[*N*-((*R,S*)-1-Phosphinopropyl)-(*R,S*)-leucyl]-*O*-methyl-(*S*)-tyrosine *N*-Methyl Amide (73). A solution of **70** (0.4 g, 0.72 mmol) in 36% HCl (10 mL) was refluxed under N_2 for 4 h. The solution was allowed to cool and evaporated to give **73** (0.29 g, 95%), after recrystallization from MeOH/Et_2O, as the hydrochloride salt (mixture of four diastereoisomers): ^{1}H NMR (CD_3OD) δ 0.88 (12 H, m), 1.09 (24 H, m), 1.15–1.30 (12 H, m), 1.47–2.20 (12 H), 2.65 (12 H, br s), 2.80–3.05 (8 H, m), 3.38 (4 H, m), 3.85 (12 H, br s), 4.05 (2 H, m), 4.25–4.50 (2 H, m), 4.77–4.98 (4 H, m), 6.97 (8 H, m), 7.28 (8 H, m); HR FAB-MS calcd for $C_{20}H_{35}N_3O_5P$ (M + H)+ 428.2314, found 428.2316.

***N*-[*N*-((*S*)-1-(Methoxycarbonyl)ethyl)-(*S*)-leucyl]-*O*-methyl-(*S*)-tyrosine *N*-Methyl Amide (75a).** **75a** was prepared from the acid **74a**[14a] (4.14 g, 19 mmol) and *O*-methyl-L-tyrosine *N*-methyl amide (4.22 g, 19 mmol) by the coupling procedure described in method H. Column chromatography, eluting with EtOAc/pentane (1:1), gave **75a** (2.4 g, 31%) as a white crystalline solid: mp 108–109 °C (EtOAc/Et_2O); $[\alpha]^{22}_D$ −40.4° (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.90 (6 H, t, $J = 6$ Hz), 1.27 (3 H, d, $J = 6$ Hz), 1.33 (1 H, m), 1.67 (1 H, m), 1.82 (2 H, br s), 2.75 (3 H, d, $J = 5$ Hz), 3.00 (3 H, m), 3.13 (1 H, q, $J = 6$ Hz), 3.71 (3 H, s), 3.79 (3 H, s), 4.50 (1 H, q, $J = 6$ Hz), 5.93 (1 H, br s), 6.82 (2 H, d, $J = 8$ Hz), 7.12 (2 H, d, $J = 8$ Hz), 7.72 (1 H, d, $J = 8$ Hz); FAB-MS *m/e* 408 (M + H)+. Anal. ($C_{21}H_{33}N_3O_5$) C, H, N.

***N*-[*N*-((*R*)-1-(Methoxycarbonyl)ethyl)-(*S*)-leucyl]-*O*-methyl-(*S*)-tyrosine *N*-Methyl Amide (75b).** **75b** was prepared from the acid **74b**[14a] in the same way as described for **75a**. Column chromatography, eluting with EtOAc/pentane (1:1), gave **75b** (2.2 g, 28%): mp 98–100 °C (EtOAc/Et_2O); $[\alpha]^{22}_D$ −9.3° (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.88 (3 H, d, $J = 2$ Hz), 0.90 (3 H, d, $J = 2$ Hz), 1.10 (1 H, m), 1.31 (3 H, d, $J = 6$ Hz), 1.35–1.62 (3 H, m), 1.76 (1 H, br s), 2.77 (3 H, d, $J = 5$ Hz), 3.01 (2 H, m), 3.18 (1 H, dd, $J = 6, 14$ Hz), 3.38 (1 H, q, $J = 6$ Hz), 3.70 (3 H, s), 3.79 (3 H, s), 4.63 (1 H, m), 6.75 (1 H, br s), 6.81 (2 H, d, $J = 8$ Hz), 7.11 (2 H, d, $J = 8$ Hz), 7.71 (1 H, d, $J = 8$ Hz); FAB-MS *m/e* 408 (M + H)+. Anal. ($C_{21}H_{33}N_3O_5$), C, H, N.

***N*-[*N*-((*S*)-1-Carboxyethyl)-(*S*)-leucyl]-*O*-methyl-(*S*)-tyrosine *N*-Methyl Amide (2a).** A solution of **75a** (0.51 g, 1.25 mmol) and KOH (0.21 g, 3.75 mmol) in MeOH (3 mL) and water (1.5 mL) was stirred at room temperature. After 3 h, excess acetic acid was added and the solution evaporated. The residue was purified by column chromatography on reverse-phase silica, eluting with a gradient of 0–10% MeOH/H_2O, to give **2a** (0.3 g, 61%): mp 195–197 °C (H_2O); $[\alpha]^{22}_D$ +7.1° (*c* 0.9, MeOH); ^{1}H NMR (DMSO-d_6) δ 0.79 (3 H, d, $J = 5$ Hz), 0.83 (3 H, d, $J = 5$ Hz), 1.11 (3 H, d, $J = 6$ Hz), 1.18 (2 H, m), 1.58 (1 H, m), 2.61 (3 H, d, $J = 4$ Hz), 2.74 (1 H, dd, $J = 6, 10$ Hz), 2.91 (2 H, m), 2.98 (1 H, t, $J = 5$ Hz), 3.71 (3 H, s), 4.47 (1 H, m), 6.80 (2 H, d, $J = 6$ Hz), 7.07 (2 H, d, $J = 6$ Hz), 7.88 (1 H, d, $J = 6$ Hz), 7.98

(1 H, d, J = 3 Hz); FAB-MS m/e 394 (M + H)$^+$. Anal. ($C_{20}H_{31}N_3O_5$·0.2H_2O) C, H, N.

***N*-[*N*-((*R*)-1-Carboxyethyl)-(*S*)-leucyl]-*O*-methyl-(*S*)-tyrosine *N*-Methyl Amide (2b).** **2b** was prepared from **75b** (0.51 g, 1.25 mmol) by the method described for **2a**. The residue was recrystallized from MeOH/H_2O to give **2b** (0.35 g, 71%): mp 199–201 °C (H_2O); $[\alpha]^{22}_D$ +6.6° (c 1, MeOH); ^{1}H NMR (DMSO-d_6) δ 0.78 (3 H, d, J = 5 Hz), 0.83 (3 H, d, J = 5 Hz), 1.08 (3 H, d, J = 5 Hz), 1.20 (2 H, t, J = 5 Hz), 1.55 (1 H, m), 2.58 (3 H, d, J = 3 Hz), 2.69 (1 H, dd, J = 8, 11 Hz), 2.76 (1 H, m), 2.90 (1 H, dd, J = 4, 10 Hz), 3.14 (1 H, t, J = 5 Hz), 3.70 (3 H, s), 4.46 (1 H, m), 6.79 (2 H, d , J = 6 Hz), 7.11 (2 H, d, J = 6 Hz), 7.88 (1 H, d, J = 4 Hz), 8.20 (1 H, d, J = 6 Hz); FAB-MS m/e 394 (M + H)$^+$. Anal. ($C_{20}H_{31}N_3O_5$·0.2H_2O) C, H, N.

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