New Aza-Dipeptide Analogues as Potent and Orally Absorbed HIV-1 Protease Inhibitors: Candidates for Clinical Development

Guido Bold,* Alexander Fässler, Hans-Georg Capraro, Robert Cozens, Thomas Klimkait, Janis Lazdins, Jürgen Mestan, Bernard Poncioni, Johannes Rösel, David Stover, Marina Tintelnot-Blomley, Figan Acemoglu, Werner Beck, Eugen Boss, Martin Eschbach, Thomas Hürlimann, Elvira Masso, Serge Roussel, Katharina Ucci-Stoll, Dominique Wyss, and Marc Lang

Research Laboratories Cancer and Infectious Diseases, Ciba-Geigy AG, CH-4002 Basel, Switzerland[†]

Received December 31, 1997

On the basis of previously described X-ray studies of an enzyme/aza-dipeptide complex,[8] aza-dipeptide analogues carrying *N*-(bis-aryl-methyl) substituents on the (hydroxethyl)hydrazine moiety have been designed and synthesized as HIV-1 protease inhibitors. By using either equally (**12**) or orthogonally (**13**) protected dipeptide isosteres, symmetrically and asymmetrically acylated aza-dipeptides can be synthesized. This approach led to the discovery of very potent inhibitors with antiviral activities (ED_{50}) in the subnanomolar range. Acylation of the (hydroxethyl)hydrazine dipeptide isostere with the L-*tert*-leucine derivative **29** increased the oral bioavailability significantly when compared to the corresponding L-valine or L-isoleucine derivatives. The bis(L-*tert*-leucine) derivatives CGP 75355, CGP 73547, CGP 75136, and CGP 75176 combine excellent antiviral activity with high blood concentration after oral administration. Furthermore, they show no cross-resistance with saquinavir-resistant strains and maintain activity against indinavir-resistant ones. Consequently they qualify for further profiling as potential clinical candidates.

Introduction

The causative agent for the pathogenesis of the acquired immunodeficiency disease syndrome (AIDS) is the human immunodeficiency virus (HIV). For the maturation of viral particles to a fully infectious virus, it has been proven that a functional viral protease (HIV protease), an enzyme that is responsible for the processing of polyproteins to structural proteins and viral enzymes, is essential.[1] This made the HIV protease a promising target for an effective AIDS therapy. Recent clinical results from studies with HIV protease inhibitors as single therapy or in combination with reverse transcriptase inhibitors showed indeed excellent efficacy in AIDS patients.[2] During the past decade, many different classes of HIV-1 protease inhibitors have been synthesized, showing excellent profiles.[3] Yet it remained a challenge to introduce new potent and orally bioavailable inhibitors that show activity against mutant strains of HIV to overcome cross-resistance in patients.[4] In this paper we describe aza-dipeptides with bis-aryl substituents as ligands for the P_1' pocket, which combine excellent antiviral activity against wild-type and mutant HIV strains with high bioavailability in mice after oral administration. Additionally, the synthesis of these aza-dipeptides follows a series of trivial transformations, which is considered to be a major advantage compared to available drugs for large-scale production.

The particular C_2-symmetry of HIV-1 protease, which functions as a dimer with each subunit contributing an amino acid triad (Asp-Thr-Gly) to the active site,[5] stimulated the design of *pseudo*-symmetric inhibitors of the aza-dipeptide structure type (see Chart 1).[6] Recently we published on a novel series of aza-dipeptide analogues as HIV protease inhibitors with oral bioavailability.[7] As an example to describe their profile best, Chart 1 illustrates compound **1**, an orally well-absorbed aza-dipeptide isostere with only slight antiviral activity (see Table 1), and compound **2**, a highly potent inhibitor of viral replication in cellular assays with poor oral bioavailability. However, since the ultimate goal of

Chart 1. Aza-Dipeptide Isosteres as Pseudosymmetric HIV-1 Protease Inhibitors

aza-dipeptide isostere

1

2

[†] Present address: Research Oncology, NOVARTIS Pharma AG, CH-4002 Basel, Switzerland.

S0022-2623(97)00873-X CCC: $15.00 © 1998 American Chemical Society
Published on Web 08/01/1998

Table 1. Antiviral Activity of the HIV Protease Inhibitors[a]

CGP	Cpd	R_1	R_2	R_3	formula	IC_{50} [nM]	ED_{50} [nM]	ED_{90} [nM]	c_{30} [μM]	c_{90} [μM]
	1				$C_{33}H_{55}N_5O_7$	177	55	1000	6.7	7.8
	2				$C_{29}H_{49}N_5O_7$	16	2.7	30	<0.2	0.4
	22a	A	A	phenyl	$C_{37}H_{49}N_5O_7$	35	1.8	10	<0.1	0.3
	23a	A	B	phenyl	$C_{38}H_{51}N_5O_7$	51	1.5	3	6.3	5.4
	24a	B	A	phenyl	$C_{38}H_{51}N_5O_7$	85	0.7	3	0.6	1.1
75355	**25a**	B	B	phenyl	$C_{39}H_{53}N_5O_7$	58	0.7	3	5.5	4.9
	22b	A	A	2-pyridyl	$C_{36}H_{48}N_6O_7$	29	7.4	30	2.7	2.2
	23b	A	B	2-pyridyl	$C_{37}H_{50}N_6O_7$	20	2	10	13.8	12.7
	24b	B	A	2-pyridyl	$C_{37}H_{50}N_6O_7$	31	2.6	10	15.3	13.3
73547	**25b**	B	B	2-pyridyl	$C_{38}H_{52}N_6O_7$	26	1.4	3	21.8	31.8
	26b	C	A	2-pyridyl	$C_{37}H_{50}N_6O_7$	28	2.8	10	0.4	0.3
	27b	A	D	2-pyridyl	$C_{37}H_{50}N_6O_7$	34	5.4	30	0.5	0.2
	23c	A	B	2-thiazolyl	$C_{35}H_{48}N_6O_7S$	18	2.1	10	17.5	14.9
75136	**25c**	B	B	2-thiazolyl	$C_{36}H_{50}N_6O_7S$	33	0.5	3	9.1	10.2
	22d	A	A	5-thiazolyl	$C_{34}H_{46}N_6O_7S$	32	5.6	30	1.8	0.1
	23d	A	B	5-thiazolyl	$C_{35}H_{48}N_6O_7S$	13	1.4	10	8.5	4.4
	24d	B	A	5-thiazolyl	$C_{35}H_{48}N_6O_7S$	14	1.9	10	8.5	5.7
	25d	B	B	5-thiazolyl	$C_{36}H_{50}N_6O_7S$	41	0.8	3	12.6	9.9
	28d	B	D	5-thiazolyl	$C_{36}H_{50}N_6O_7S$	22	1.2	3	1.4	1.4
75176	**25e**	B	B	2-methyltetrazol-5-yl	$C_{35}H_{51}N_9O_7$	27	0.8	10	20.3	14.7
	25f	B	B	2-tert-butyltetrazol-5-yl	$C_{38}H_{57}N_9O_7$	72	0.8	3	4.2	4.6
	25g	B	B	diethylamino	$C_{37}H_{58}N_6O_7$	41	1.6	10	11.8	7.6
	Ro 31-8959					35	3.4	10	2.4	0.5

[a] Activity was measured as previously described.[7] The enzymatic activity (IC_{50}) was determined with respect to the icosapeptide H-Arg-Arg-Ser-Asn-Gln-Val-Ser-Gln-Asn-Tyr-Pro-Ile-Val-Gln-Asn-Ile-Gln-Gly-Arg-Arg-OH by HPLC method. The antiviral effect of the compounds is determined as percent reduction of the reverse transcriptase (RT) activity in HIV-1/MN-infected MT-2 cells. HIV-1/MN stocks were prepared from cell culture supernatants of the permanently infected cell line H9/HIV-1/MN obtained through the AIDS Research and Reference Reagent Program, Division of AIDS, NIAID, NIH. The ED_{50} indicates the concentration of compound required to inhibit 50% of RT production in this assay; similarly ED_{90} reflects 90% inhibition of RT formation. The pharmacokinetic studies were performed in mice, and drug concentrations in blood samples were analyzed by reversed-phase HPLC 30 min (→ c_{30}) and 90 min (→ c_{90}) after oral application of 120 mg/kg in a standardized formulation: 5% DMSO, 19% hydroxypropyl-β-cyclodextrin in water (for details see the Experimental Section). The data represent averages of at least three determinations.

combining excellent antiviral activity with good oral bioavailability was not achieved, we evaluated the available information from our X-ray structure of an enzyme/aza-dipeptide complex.[8] This structural data suggested that there should be available space for larger P_1' substituents, thus enabling the design of derivatives with higher affinity for the enzyme and hopefully improved physicochemical properties.

Scheme 1. Synthesis of Benzylhydrazine Building Blocks **9a**−**e**,**g** Starting from Aldehydes[a]

[a] Conditions: (a) Mg, THF; (b) 2-bromopyridine, THF, [1,3-bis(diphenylphosphino)propane]nickel(II) chloride, DIBAH; (c) H_3O^+; (d) 2-bromothiazole, THF, [1,3-bis(diphenylphosphino)propane]nickel(II) chloride; (e) thiazole, $Pd(PPh_3)_4$, CH_3CO_2K, DMA, 12h 150 °C; (f) NaN_3, LiCl, methoxyethanol, 6 h, ⇅; (g) CH_3I, K_2CO_3, DMF/dioxane; (h) *tert*-butyloxycarbonylhydrazine, ethanol or 2-propanol, ⇅; (i) H_2, Pd/C, MeOH; (j) $NaCNBH_3$, TsOH, THF, r.t.

Chemistry

The general route to synthesize the aza-dipeptide isosteres is outlined in Scheme 2. Opening of the *N*-Boc-protected epoxide **10**[6b] with the 4-substituted benzylhydrazine building blocks **9a**−**c**,**e** led to symmetrically acylated aza-dipeptide mimetics, whereas the same reaction applied to the *N*-trifluoroacetyl-protected epoxides **11**[7] and **9a**−**d**,**g** opens access to the asymmetrically acylated series.

The synthesis of the 4-substituted benzylhydrazine building blocks **9a**−**e**,**g** is shown in Scheme 1. Nickel(II)-catalyzed coupling of the Grignard reagent prepared from 4-bromobenzaldehyde dimethyl acetal (**3**)[9] to 2-bromopyridine or 2-bromothiazole, followed by acidic hydrolysis, gave the corresponding arylbenzaldehydes **7b**,**c**. Heating of 4-bromobenzaldehyde (**4**) and thiazole in the presence of palladium(0) afforded 4-(thiazol-5-yl)benzaldehyde (**7d**). The structure of **7d** was confirmed by the observation of a ^{1}H NMR signal at 8.22 ppm (s, 1H), which was assigned to the proton on C(4) of the thiazole ring, whereas an isomeric thiazol-4-yl derivative should show a signal at ≈7.7 ppm (H−C(5)). Cycloaddition of azide to the nitrile function of 4-cyanobenzaldehyde (**5**) gave 4-(tetrazol-5-yl)benzaldehyde (**6**) in good yields. Methylation with methyl iodide then led regioselectively to the 2-methyl-2*H*-tetrazole derivative **7e**. By heating the aldehydes **7a**−**e**,**g** with *tert*-butyloxycarbonylhydrazine, the hydrazones **8a**−**e**,**g** were obtained. Hydrogenation (for **8a**,**b**,**g**) or reduction with sodium cyanoborohydride[10] for the more sensitive substrates **8c**−**e**[11] provided the benzyl-hydrazine building blocks **9a**−**e**,**g**.

The required *N*-(*tert*-butyloxycarbonyl)-2(*S*)-amino-1-phenyl-3(*R*)-3,4-epoxybutane (**10**)[6b] as a source for the P_1 substituent and the transition-state hydroxyl group of the dipeptide isostere was prepared according to known procedures:[12] Peterson olefination of *N*-Boc-phenylalaninal,[13] reintroduction of the Boc protecting group, and epoxidation gave an 83:17 mixture of the *threo*- and *erythro*-isomers, which could be separated by crystallization. Nucleophilic attack of **9a**−**c**,**e** on the epoxide **10** gave the symmetrically protected dipeptide isosteres **12a**−**c**,**e**. Both of the Boc protecting groups were simultaneously cleaved off by acidic treatment. The best condition for the deprotection of **12b** is cleavage by HCl in water/THF at 50 °C. The intermediates **14a**−

Scheme 2. Synthesis of Symmetrically Acylated Aza-Dipeptides **22a**,**b** and **25a**–**c**,**e** and Asymmetrically Acylated Analogues **23a**–**d**, **24a**,**b**,**d**, **26b**, **27b**, and **28d**[a]

12a-c,e: R'=Boc
14a-c,e: R'=H

13a-d,g: R'=CF_3CO
15a-d: R'=H

22a,b: R=MeO_2C-Val
25a-c,e: R=MeO_2C-*t*Leu

16a-d: R_1=MeO_2C-Val; R'=Boc
19a-d: R_1=MeO_2C-Val; R'=H
17a,b,d: R_1=MeO_2C-*t*Leu; R'=Boc
20a,b,d: R_1=MeO_2C-*t*Leu; R'=H
18b: R_1=MeO_2C-Ile; R'=Boc
21b: R_1=MeO_2C-Ile; R'=H

23a-d: R_1=MeO_2C-Val; R_2=*t*Leu-CO_2Me
24a,b,d: R_1=MeO_2C-*t*Leu; R_2=Val-CO_2Me
26b: R_1=MeO_2C-Ile; R_2=Val-CO_2Me
27b: R_1=MeO_2C-Val; R_2=Val-CO_2Et
28d: R_1=MeO_2C-*t*Leu; R_2=Val-CO_2Et

[a] Conditions: (a) **9a**–**e**,**g**, 2-propanol, ⇅; (b) formic acid or HCl/dioxane or HCl in THF/H_2O, 50 °C; (c) EDC, HOBT, Et_3N/DMF; or TPTU, NMM/DMF; or TPTU, Hünig's base/DMF; or TPTU, Hünig's base/CH_2Cl_2; (d) K_2CO_3, MeOH/H_2O, 16 h 80 °C. [b] Yield for 2 steps.

c,**e** were coupled with *N*-methoxycarbonyl-L-valine[14] or *N*-methoxycarbonyl-L-*tert*-leucine (**29**), respectively, according to standard peptide synthesis procedures [*N*-ethyl-*N*′-(3-(dimethylamino)propyl)carbodiimide hydrochloride, 1-hydroxybenzotriazole, triethylamine; or *O*-(1,2-dihydro-2-oxo-1-pyridyl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate, *N*-methylmorpholine or Hünig's base] to furnish the target inhibitors **22a**,**b** and **25a**–**c**,**e**. For asymmetrically acylated aza-dipeptide isosteres, the known trifluoroacetyl-protected epoxide **11**[7] was used instead, which was prepared by trifluoroacetylation of 3(*S*)-amino-4-phenyl-1-butene[12] and oxidation using 3-chloroperbenzoic acid, providing **11** as an 87:13 mixture of *threo*- and *erythro*-isomers. Without separation of the isomers, this mixture was carried through the nucleophilic opening step by **9a**–**d**,**g**, leading to the orthogonally protected dipeptide isosteres **13a**–**d**,**g**. Saponification of the trifluoroacetamide (→**15a**–**d**) and amide bond formation with the required carbamoylated amino acid derivatives furnished the N(C-5)-acylated intermediates **16a**–**d**, **17a**,**b**,**d**, and **18b**. Acidic cleavage of the Boc protecting groups (→**19a**–**d**, **20a**,**b**,**d**, and **21b**) and again coupling with carbamoylated amino acid derivatives gave the asymmetrically acylated aza-dipeptides **23a**–**d**, **24a**,**b**,**d**, **26b**, **27b**, and **28d**.

Alternatively, symmetrically acylated aza-dipeptides could also be synthesized via the orthogonally protected dipeptide isosteres **13d**,**g** (Scheme 3): Successive deprotection of the trifluoroacetyl and the Boc protection

Scheme 3. Synthesis of Symmetrically Acylated Aza-Dipeptides **22d** and **25d**,**g**[a]

[a] Conditions: (a) K_2CO_3, $MeOH/H_2O$, 16 h, 80 °C; (b) HCl/dioxane, DMF; (c) EDC, HOBT, Et_3N/DMF; or TPTU, NMM/DMF; or TPTU, Hünig's base/DMF; (d) formic acid. [b] Yield for 2 steps.

group transferred **13g** to the intermediate **14g**, which gave **25g** in good yields via double acylation with *N*-methoxycarbonyl-L-*tert*-leucine (**29**). Coupling of **19d** and **20d** with carbamoylated amino acid derivatives furnished **22d** or **25d**, respectively.

The 4-(2-*tert*-butyl-2*H*-tetrazol-5-yl)benzyl derivative **25f** was synthesized via a different route, outlined in Scheme 4, a sequence that opens access to the symmetrically and asymmetrically acylated aza-dipeptide series: Schotten–Baumann acylation of L-*tert*-leucine (→**29**), followed by a *N*-ethyl-*N'*-(3-(dimethylamino)-propyl)carbodiimide hydrochloride/1-hydroxybenzotriazole-mediated coupling to *tert*-butyloxycarbonylhydrazine gave the L-*tert*-leucinylhydrazine derivative **30** in quantitative yield. Acidic deprotection (→**31**) and condensation with 4-(tetrazol-5-yl)benzaldehyde (**6**) furnished hydrazone **32**. Acid-catalyzed addition of isobutene to the tetrazole functionality then provided **33** regioselectively, which by reduction with sodium cyanoborohydride/*p*-toluenesulfonic acid[10] gave the hydrazine moiety **34**. Nucleophilic attack at the epoxide function of **10** afforded the N(*N*-2)-acylated aza-dipeptide isostere **35**. Selective acidic cleavage of the Boc protecting group by HCl in THF/water (→**36**) and acylation with carbamoylated amino acid derivatives then led to asymmetrically or symmetrically acylated aza-dipeptide isosteres, like **25f**.

Results and Discussion

To minimize the chance of AIDS treatment failure due to induction of HIV strains resistant to a given chemotherapeutic agent, effective blood concentrations of the inhibitor must be maintained.[4a] This prerequisite for a successful treatment calls for drugs that show good pharmacokinetics after oral administration and exert excellent antiviral activity. Therefore, the goal of this optimization program was to find aza-dipeptide isosteres that combine high oral bioavailability and antiviral potency. Some of the previously described leads[7] (e.g., **1** or **2**, see Table 1) showed either good oral pharmacokinetics or good antiviral activity, but none of them were satisfactory in both aspects. CAMM studies based on X-ray data from the enzyme/inhibitor complex of the aza-dipeptide CGP 53820[8] prompted us to examine larger substituents at the P_1' position: Derivatives with 4-substituted benzyl moieties in this position were predicted to have the potential to make additional favorable interactions with Arg8 and/or Phe153, Gly148, and Gly149 of the enzyme. The prevalent opinion[15] that maximizing the number of nonbonded, especially van der Waals, interactions with the enzyme decreases the chances of drug resistance through enzyme mutation led us to suppose that *N*-(bis-aryl-methyl) aza-dipeptide analogues would also be favorable in this respect. Enzymatic inhibition data for the biphenyl derivative **22a** indeed proved that conformationally rigid bulkier residues are well-tolerated. More interestingly, **22a** showed increased potency on the cellular level. Replacement of either one or both of the valine substituents by *tert*-leucine increased the cellular antiviral activity even further, leading to **23a**, **24a**, and **25a** (CGP 75355).

Additionally to the higher potency, these *tert*-leucine derivatives showed very interesting plasma levels after oral administration. These effects of the *tert*-leucine on oral bioavailability motivated us to increase the hydrophilicity of the inhibitors by replacement of the 4-biphenyl unit by 4-heterocyclyl-phenyl substituents in order to enhance the solubility properties in biologically suitable vehicles, hopefully without affecting the favorable pharmacokinetic profile observed so far. In the 4-(pyridin-2-yl)phenyl series, the bis-valinyl derivative **22b** already showed oral bioavailability. Indeed, substitution of either one (→**23b**, **24b**) or, even better, both

Scheme 4. Synthesis of 4-(2-*tert*-Butyl-2*H*-tetrazol-5-yl)phenyl Derivative **25f**[a]

[a] Conditions: (a) methyl chloroformate, NaOH, dioxane/H_2O, 18 h, 60 °C; (b) *tert*-butyloxycarbonylhydrazine, EDC, HOBT, NMM/EtOAc; (c) HCl, dioxane; (d) 4-(tetrazol-5-yl)benzaldehyde (**6**), 2-propanol, 18 h, 90 °C; (e) isobutene, $MeSO_3H$, toluene, 1 h, 110 °C; (f) $NaCNBH_3$, TsOH, THF, r.t.; (g) epoxide **10**, 2-propanol, 16 h, 90 °C; (h) HCl in THF/H_2O, 50 °C; (i) **29**, TPTU, NMM/DMF.

(→**25b**, CGP 73547) of the valine residues by *tert*-leucine increased potency and, more dramatically, oral absorption even further (CGP 73547: c_{90} = 31.8 μM). Efforts to replace *N*-methoxycarbonyl-L-*tert*-leucine by the less expensive isomeric building blocks *N*-methoxycarbonyl-L-isoleucine (→**26b**) or *N*-ethoxycarbonyl-L-valine (→**27b**) failed to lead to derivatives with a comparable pharmacokinetic profile. This tells us once more that oral bioavailability can hardly be controlled by simple modulation of the lipophilicity of the substituents. The bis-*tert*-leucine derivatives displayed the best combination of antiviral potency and oral bioavailability in the thiazol-2-yl (→**25c**, CGP 75136) and thiazol-5-yl (→**25d**) series too.

A rough idea about the size of the pocket in the enzyme is given by the 4-(2-*tert*-butyl-2*H*-tetrazol-5-yl)-phenyl derivative **25f**, which still is a potent enzyme inhibitor (IC_{50} = 72 nM). In respect to cellular antiviral activity, **25f** belongs to the most potent inhibitors of this series (ED_{90} = 3 nM). The enzymatically more potent 4-(2-methyl-2*H*-tetrazol-5-yl)phenyl derivative **25e** (CGP 75176; IC_{50} = 27 nM) is equally potent in respect to its ED_{50} but appears to be slightly weaker if we consider the ED_{90}. However, its blood plasma level after oral administration is again excellent (c_{30} = 20.3 μM). The 4-(diethylamino)phenyl derivative **25g** exerts good antiviral activity too, demonstrating that the 4-arylphenyl substituent directing to the P_1' pocket of the enzyme can be replaced by readily available alkylanilines. However, preliminary pharmacokinetic studies in mice indicated metabolic instability of **25g**: Even though the parent compound appears in high concentration after oral administration, rapid formation of metabolites can be observed. The major metabolite, appearing in concentrations close to those of the parent compound, was identified by LC−MS analysis to be the 4-monoethylaniline derivative. Therefore the 4-diethylaniline derivative **25g** was not pursued further.

As a conclusion of our work, most of the described new compounds have equal or better antiviral activity than the standard HIV protease inhibitor Ro 31-8959 (saquinavir). Their pharmacokinetic profile in mice after oral administration is clearly superior to that of Ro 31-8959. As the pharmacokinetic evaluations were performed in a formulation which is not acceptable for clinical use, we investigated the bioavailability of the mesylate salt of CGP 73547 in mice and dogs: These experiments confirmed the good oral bioavailability of the compound. In mice a dose of 120 mg/kg dissolved in 3% citric acid resulted in plasma concentrations at 30, 60, 90, and 120 min after administration of 11.5, 13.9, 15.6, and 17.0 μM, respectively. In beagle dogs the mesylate salt (given at a dose equivalent to 90 mg of free base/kg in 3% citric acid) resulted in peak plasma levels of 6.1 μM at 2.4 h and an AUC(0−∞) of 38.6 μM. The symmetrically acylated bis(L-*tert*-leucine) derivatives show a biological profile equal to or better than that of the asymmetrically acylated derivatives, and in addition, their synthesis is simpler. Therefore, bis(L-*tert*-leucine) derivatives qualify best for further evaluation. Out of the two symmetrically acylated thiazolyl derivatives CGP 75136 and **25d**, the thiazol-2-yl derivative CGP 75136 was preferred, since the heteroatoms in a thiazol-2-yl fragment are considered to be sterically

Table 2. Antiviral Activity against HIV-1 Protease Inhibitor-Resistant Strains of the HI virus[a]

HI virus	effective dose (μM)				
	wild-type	saquinavir resistant[b]	indinavir resistant[c]	CGP 61755 resistant[d]	CGP 61755 resistant[e]
CGP 75355	0.01	0.01	0.1	0.3	0.9
CGP 73547	0.01	0.004−0.01	0.03−0.1	0.3−0.9	0.3
CGP 75136	0.01	0.004	0.1	0.3	nd[f]
CGP 75176	0.01−0.03	0.01	0.1−0.3	0.9	nd[f]
saquinavir	0.03	0.1−0.3	0.1	0.9	>2.7
indinavir	0.1	0.03−0.1	0.3−0.9	≥0.9	2.7

[a] The indicated effective dose (μM) is the lowest dose at which virus replication (measured as supernatant reverse transcriptase activity) was totally inhibited until day 10 of the experiment (for details see the Experimental Section). The data represent averages of at least three determinations. [b] Mutant: G48V, L90M. [c] Mutant: L10R, M46I, L63P, V82T, I84V. [d] Mutant: K45I, A71Tmix, L76F, I84Vmix. [e] Mutant: V32I, M46I, L63P, I84A. [f] nd, not done.

Chart 2. Bis(L-*tert*-leucine) Derivatives of Aza-Dipeptide Isosteres Selected for Further Profiling

CGP 75355

CGP 73547

CGP 75136

CGP 75176

more hindered and therefore less prone for interactions with cytochrome P_{450} isozymes than in the thiazol-5-yl derivative **25d**. On the basis of its excellent pharmacokinetic properties, CGP 75176 was chosen as a representative of the tetrazolyl derivatives.

Consequently, the four bis(L-*tert*-leucine) derivatives, CGP 75355, CGP 73547, CGP 75136, and CGP 75176, presented in Chart 2 were selected for further profiling against drug-resistant strains of the HI-virus (see Table 2). They all show good antiviral activity against resistant strains raised in the presence of saquinavir and show antiviral activity at submicromolar concentrations against resistant strains selected in vitro in the presence of our Phe-c-Phe hydroxyethylene type HIV protease inhibitor CGP 61755.[16] A description of the resistant strains and further results will be published in due course. Their excellent antiviral potency against a range of HIV strains as well as saquinavir- and indinavir-resistant mutants combined with oral bioavailability qualifies these promising compounds for further characterization toward determining their potential as candidates for clinical evaluation.

Experimental Section

Assay for Antiviral Activity against HIV-1 Protease Inhibitor-Resistant HIV Strains. CEM-SS cells were infected with different HIV-1 protease inhibitor-resistant phenoypes of HIV. The cells were incubated in a small volume of virus-containing supernatant (MOI 0.001−0.005) for 4 h at 37 °C (CO_2). After washing with medium, the cells were dispensed in 96-well tissue culture plates at 20 000 cells/100 μL/well followed by addition of serial 3-fold dilutions of the test compounds (in 100 μL/well) in triplicates (final volume: 200 μL/well). Plates then were incubated at 37 °C (5% CO_2, incubator). On day 4 postinfection, 10-μL supernatant samples were taken from each well, frozen, and stored (−20 °C) for reverse transcriptase (RT) activity determination. Cells were resuspended, and 50 μL/well of the cell suspension was transferred to new 96-well plates containing 150 μL/well fresh medium with test compound. The final test compound concentrations were the same as on day 0. Plates were incubated at 37 °C (5% CO_2, incubator). On day 7, again 10-μL RT samples were taken from each well, frozen, and stored at −20 °C. This time, 150 μL of the culture supernatants was removed and replaced by 150 μL of fresh medium with test compound. Again, the final concentrations of the test compounds were the same as on day 0. Plates were incubated at 37 °C (5% CO_2, incubator). On day 10, 10-μL RT samples were taken from each well, frozen, and stored at −20 °C, and the experiment was terminated. All RT samples from days 4, 7, and 10 were simultaneously assayed for RT activity. As controls, infected but untreated cells as well as noninfected cells were included in each assay.

Bioavailability. The compounds were dissolved in DMSO to a concentration of 240 mg/mL. The stock solution was diluted 1:20 with an aqueous solution of 20% hydroxypropyl-β-cyclodextrin. After brief, low-power sonication a milky, homogeneous suspension was obtained. Then the formulated compounds were given to female Balb/c mice that had free

access to food and water throughout the experiments. The mice received an average dose of 120 mg of compound/kg by gavage. At allotted times four mice were sacrificed, heart blood was collected into heparinized tubes, and plasma was prepared by centrifugation. The plasma was either analyzed immediately or stored frozen at −20 °C. For analysis, the heparinized plasma samples were deproteinated by the addition of an equal volume of acetonitrile. After thorough mixing, the tubes were allowed to stand for 20−30 min at r.t., and the precipitated protein was removed by centrifugation (10 000*g*, 5 min). The supernatant was collected and analyzed by reversed-phase HPLC: 100 μL of the supernatant was injected onto a Nucleosil C18, 5-μm analytical column (125 × 4.6 mm); mobile phase 20% acetonitrile/0.05% trifluoroacetic acid (TFA) in water/0.05% TFA → 100% acetonitrile/0.05% TFA during 20 min + 5 min 100% acetonitrile/0.05% TFA. Compounds were detected by UV absorbance and identified on the chromatograms by retention time and UV spectrum compared to control plasma spiked with compound. Quantitation was by the external standard method using peak heights to quantitate the amounts by reference to a calibration curve. The calibration curve was constructed by the analysis of plasma samples containing known amounts of the compound under evaluation which had been processed as described above. The limit of quantitation was 0.1−0.5 μmol/L (compound-dependent) under these conditions.

Chemistry. All reactions with air- or moisture-sensitive reactants and solvents were carried out under nitrogen atmosphere. In general, reagents and solvents were used as purchased without further purification. THF was freshly distilled from sodium/benzophenone. Analytical thin-layer chromatography was performed on silica F_{254} glass plates (E. Merck). Components were visualized by UV light of 254 nm or by spraying with phosphomolybdic acid. Column flash chromatography was performed on silica gel 60 (230−400 mesh ASTM, E. Merck) under a positive nitrogen pressure of approximately 0.4 atm. Melting points were determined in an open capillary and are not corrected. ^{1}H NMR spectra: Bruker DRX-500 (500 MHz), Bruker AM-360 (360 MHz), Varian Gemini-300 (300 MHz), or Varian Gemini-200 (200 MHz); chemical shifts of signals are expressed in parts per million (ppm) and are referenced to the deuterated solvents used. MS spectra: FAB-ZAB, HF (VG Analytical). HPLC chromatography: stationary phase Nucleosil C18, 5-μm analytical column (125 × 4.6 mm); mobile phase 20% acetonitrile/0.1% TFA in water/0.1% TFA → 100% acetonitrile/0.1% TFA during 20 min + 10 min 100% acetonitrile/0.1% TFA; t_R refers to the retention time. Elemental analyses were performed by the Ciba Analytical Department and are within ±0.4% of the calculated values.

Abbreviations: EDC, *N*-ethyl-*N*′-[3-(dimethylamino)propyl]carbodiimide hydrochloride; HBTU, *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate; HOBT, 1-hydroxybenzotriazole hydrate; NMM, *N*-methylmorpholine; r.t., room temperature; p-TsOH, 4-toluenesulfonic acid monohydrate; TPTU, *O*-(1,2-dihydro-2-oxo-1-pyridyl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluorborate.

4-(Tetrazol-5-yl)benzaldehyde (6). 4-Cyanobenzaldehyde (**5**) (54.3 g, 0.414 mol), lithium chloride (26.3 g, 0.621 mol), and sodium azide (26.9 g, 0.414 mol) in methoxyethanol (0.4 L) were heated for 6 h to reflux temperature. The suspension then was poured into a mixture of ice (1.3 kg) and HCl (37%, 130 mL), stirred, and filtered. Washing with water afforded 66.5 g (92%) of **6**: mp 182−184 °C; ^{1}H NMR (DMSO-d_6) δ 10.11 (s, 1H), 8.29 (d, 2H), 8.15 (d, 2H).

4-(Pyridin-2-yl)benzaldehyde (7b). To magnesium (317 g, 13.0 mol) in THF (3.5 L) was added iodine (11 g) followed by 200 g of 4-bromobenzaldehyde dimethyl acetal[9] (**3**). When the reaction (eventually slightly heating) had started, another 2540 g (total amount: 2740 g, 11.8 mol) of **3** in toluene (3.5 L) was added dropwise (temperature 25−30 °C; 1 h). After stirring for 1 h at 25−30 °C the Grignard reagent was transferred into the dropping funnel of a second apparatus, containing 2-bromopyridine (1750 g, 11.0 mol) in THF (3.3 L), [1,3-bis(diphenylphosphino)propane]nickel(II) chloride (38 g, 70 mmol), and diisobutylaluminum hydride (330 mL, 20% in hexane). The Grignard reagent was added at 15−20 °C during 45 min; the mixture was stirred for 90 min at r.t. and then poured into a mixture of ice (10 kg), HCl (1.5 L, 37%), and citric acid (1.5 kg). After adding Hyflo super cel (1 kg), the mixture was stirred for 1 h and filtered. The solid was washed with water (2 L), 2 × toluene (2 L), and 2 × 1 N HCl (2 L). The first filtrate and the washing water were combined; the aqueous layer was separated and extracted with the two toluene filtrates. The resulting organic layers were washed then with the two HCl filtrates. After toluene (6 L) was added to the combined aqueous layers, NaOH (4.6 L, 30% in water) was added (pH ≈ 8−9). The mixture was filtered through Celite and the aqueous layer separated and extracted twice with toluene (2 L). The organic layers were washed twice with water, dried (Na_2SO_4), and treated with charcoal. Addition of 0.5 kg of silica gel, stirring, filtration, and concentration in vacuo yielded 1820 g (90%) of **7b**: TLC R_f(hexane/ethyl acetate, 2:1) = 0.25; ^{1}H NMR ($CDCl_3$) δ 10.1 (s, HCO), 8.77 (d, 1H), 8.20 (d, 2H), 8.00 (d, 2H), 7.81 (m, 2H), 7.31 (q, 1H); HPLC t_R 6.7 min.

4-(Thiazol-2-yl)benzaldehyde (7c). To magnesium (9.2 g, 378 mmol; activated with iodine) in THF (84 mL) at 60 °C was added a solution of 4-bromobenzaldehyde dimethyl acetal[9] (**3**; 82.6 g, 357 mmol) in THF (677 mL) dropwise. After stirring for 40 min at 65 °C, the Grignard reagent was transferred into the dropping funnel of a second apparatus, containing a red suspension of 2-bromothiazole (31.7 mL, 356 mmol) in THF (1680 mL) and [1,3-bis(diphenylphosphino)propane]nickel(II) chloride. The Grignard reagent was added during 30 min, and the mixture stirred for 12 h at r.t. After the reaction was quenched with water (840 mL), the mixture was partially concentrated in vacuo. Then ethyl acetate (1 L) and 2 N HCl (340 mL) were added, and stirring was continued for 90 min. The aqueous phase was separated and extracted twice with ethyl acetate (0.5 L). The organic layers were washed with 2 N HCl (2 × 250 mL), water, saturated $NaHCO_3$, water, and brine, dried (Na_2SO_4), and concentrated in vacuo. Filtration through silica gel (1 kg; ethyl acetate/hexane, 1:4) and washing with hexane yielded 26.3 g (39%) of **7c**: TLC R_f(hexane/ethyl acetate, 3:1) = 0.21; ^{1}H NMR ($CDCl_3$) δ 10.05 (s, HCO), 8.15 (d, 2H), 7.95 (m, 3H), 7.45 (d, 1H); MS $(M)^+$ = 189. Anal. ($C_{10}H_7NOS$) C, H, N, S.

4-(Thiazol-5-yl)benzaldehyde (7d). 4-Bromobenzaldehyde (**4**) (28.0 g, 150 mmol), thiazole (65.3 g, 767 mmol), potassium acetate (22.3 g, 227 mmol), and tetrakis(triphenylphosphine)palladium(0) (8.7 g, 7.5 mmol) in dimethyl acetamide (376 mL) were heated in a sealed tube for 12 h at 150 °C. The brown suspension was filtered and the filtrate concentrated in vacuo. The resulting residue was redissolved in ethyl acetate/water and the aqueous phase separated and extracted twice with ethyl acetate. The organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. Column chromatography (toluene/acetone, 9:1) and crystallization from diethyl ether/hexane gave 17.3 g (61%) **7d**: TLC R_f(toluene/acetone, 9:1) = 0.28; ^{1}H NMR ($CDCl_3$) δ 10.02 (s, HCO), 8.85 (s, 1H), 8.22 (s, 1H), 7.94 (d, 2H), 7.75 (d, 2H); MS $(M)^+$ = 189.

4-(2-Methyl-2*H*-tetrazol-5-yl)benzaldehyde (7e). A solution of **6** (75.5 g, 0.433 mol) in 550 mL of DMF/dioxane (1:1) was added dropwise to an ice-cooled mixture of potassium carbonate (180 g, 1.3 mol) and DMF/dioxane (1:1) (200 mL). After 30 min of stirring, methyl iodide (40 mL, 0.64 mol) was added, and stirring was continued for 3 h at 0 °C and for 15 h at r.t. The suspension then was poured into ice water (2.8 L), stirred, and filtered. Washing with water afforded 78 g (95%) of **7e**: mp 137−139 °C; ^{1}H NMR ($CD_3OD/CDCl_3$ mixture) δ 10.06 (s, 1H), 8.29 (d, 2H), 8.03 (d, 2H), 4.45 (s, 3H).

***N*-1-(*tert*-Butyloxycarbonyl) *N*-2-(4-Biphenylylmethylidene) Hydrazone (8a).** Preparation from **7a** as described for **8b** yielded 126 g (quantitative) of **8a**: mp 169 °C; ^{1}H NMR (CD_3OD) δ 7.95 (s, 1H), 7.77 (d, 2H), 7.63 (m, 4H), 7.40 (m, 3H), 1.55 (s, 9H).

***N*-1-(*tert*-Butyloxycarbonyl) *N*-2-[4-(Pyridin-2-yl)benzylidene] Hydrazone (8b).** A solution of **7b** (1770 g, 9.67 mol) and *tert*-butyl carbazate (1220 g, 9.2 mol) in ethanol (12.5 L) was heated to reflux temperature during 4 h. The solution was cooled to 40 °C, and then ice (6 kg) was added. Filtration, washing with water (6 L), and drying (50 °C; in vacuo) afforded 2554 g (93%) of **8b**: TLC R_f(hexane/ethyl acetate, 1:2) = 0.38; ^{1}H NMR ($CDCl_3$) δ 8.70 (d, 1H), 8.02 (m, 3H), 7.87 (s, 1H), 7.81 (s, 1H), 7.76 (m, 3H), 7.25 (m, 1H), 1.55 (s, 9H).

***N*-1-(*tert*-Butyloxycarbonyl) *N*-2-[4-(Thiazol-2-yl)benzylidene] Hydrazone (8c).** Preparation from **7c** as described for **8b** yielded 30 g (73%) of **8c**: ^{1}H NMR ($CDCl_3$) δ 8.06 (s, HN), 7.97 (d, 2H), 7.87 (m, 2H), 7.75 (d, 2H), 7.36 (d, 1H), 1.55 (s, 9H).

***N*-1-(*tert*-Butyloxycarbonyl) *N*-2-[4-(Thiazol-5-yl)benzylidene] Hydrazone (8d).** Preparation from **7d** as described for **8b** yielded 25.4 g (92%) of **8d**: ^{1}H NMR (CD_3OD) δ 8.98 (s, 1H), 8.23 (s, 1H), 7.93 (s, 1H), 7.73 (m, 4H), 1.54 (s, 9H).

***N*-1-(*tert*-Butyloxycarbonyl) *N*-2-[4-(2-Methyl-2*H*-tetrazol-5-yl)benzylidene] Hydrazone (8e).** Preparation from **7e** as described for **8b** yielded 61 g (51%) of **8e**: ^{1}H NMR (DMSO-d_6) δ 11.05 (s, 1H), 8.10 (m, 3H), 7.80 (d, 2H), 4.45 (s, 3H), 1.49 (s, 9H). Anal. ($C_{14}H_{18}N_6O_2$) C, H, N.

***N*-1-(*tert*-Butyloxycarbonyl) *N*-2-[4-(Diethylamino)benzylidene] Hydrazone (8 g).** Preparation from **7g** as described for **8b** yielded 149.5 g (91%) of **8g**: ^{1}H NMR ($CDCl_3$) δ 7.68 (s, 1H), 7.65 (s, 1H), 7.53 (d, 2H), 6.62 (d, 2H), 3.38 (q, 4H), 1.53 (s, 9H), 1.18 (t, 6H).

***N*-1-(*tert*-Butyloxycarbonyl)-*N*-2-(4-biphenylylmethyl)hydrazine (9a).** Preparation from **8a** as described for **9b** yielded 58.7 g (62%) of **9a**: mp 84–85 °C; ^{1}H NMR (CD_3OD) δ 7.6 (m, 4H), 7.4 (m, 5H), 3.95 (s, 2H), 1.44 (s, 9H).

***N*-1-(*tert*-Butyloxycarbonyl)-*N*-2-[4-(pyridin-2-yl)benzyl]hydrazine (9b).** A suspension of **8b** (1655 g, 5.57 mol) in methanol (12 L) was hydrogenated in the presence of Pd/C (10%, 166 g). The catalyst was filtered off, the filtrate concentrated under reduced pressure, and the oily residue crystallized from hexane (3 L). Filtration of the crystallisate, washing twice in hexane (2.5 L), and drying yielded 1478 g (89%) of **9b**: TLC R_f(hexane/ethyl acetate, 1:2) = 0.3; mp 74–77 °C; ^{1}H NMR (DMSO-d_6) δ 8.64 (d, 1H), 8.26 (sb, HN), 8.02 (d, 2H), 7.93 (d, 1H), 7.85 (dd, 1H), 7.42 (d, 2H), 7.32 (dd, 1H), 4.80 (m, HN), 3.92 (d, 2H), 1.38 (s, 9H); FAB MS $(M + H)^+ = 300$. Anal. ($C_{17}H_{21}N_3O_2$) C, H, N.

***N*-1-(*tert*-Butyloxycarbonyl)-*N*-2-[4-(thiazol-2-yl)benzyl]hydrazine (9c).** $NaCNBH_3$ (16.9 g, 95% purity, 256 mmol) was added to an ice-cooled solution of **8c** (77.6 g, 255 mmol) in THF (450 mL). Then a solution of p-TsOH (49.6 g, 0.26 mol) in THF (450 mL) was added dropwise. After 17 h of stirring at r.t., another portion of $NaCNBH_3$ (3.38 g) and p-TsOH (9.9 g) was added, and stirring was continued for 20 h. Then the reaction mixture was diluted with ethyl acetate and water and the aqueous layer separated and extracted twice with ethyl acetate. The organic layers were washed with brine, saturated $NaHCO_3$, and again brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting oil was diluted with dichloroethane (306 mL), then 1 N NaOH in water (306 mL) was added (cooling), and the biphasic mixture was heated for 3.5 h to reflux temperature. After dichloromethane and water were added, the aqueous layer was separated and extracted two times with dichloromethane. The organic phases were dried (Na_2SO_4) and concentrated. Filtration through silica gel (1 kg; toluene/acetone, 9:1) and washing with hexane yielded 60.3 g (77%) of **9c**: TLC R_f(hexane/ethyl acetate 3:2) = 0.30; ^{1}H NMR ($CDCl_3$) δ 7.93 (d, 2H), 7.87 (d, 1H), 7.43 (d, 2H), 7.33 (d, 1H), 6.10 (s, HN), 4.25 (s, HN), 4.03 (d, 2H), 1.47 (s, 9H).

***N*-1-(*tert*-Butyloxycarbonyl)-*N*-2-[4-(thiazol-5-yl)benzyl]hydrazine (9d).** Preparation from **8d** as described for **9c** yielded 20.6 g (80%) of **9d**: mp 93–95 °C; ^{1}H NMR ($CDCl_3$) δ 8.75 (s, 1H), 8.07 (s, 1H), 7.56 (d, 2H), 7.41 (d, 2H), 6.03 (s, HN), 4.25 (s, HN), 4.03 (m, 2H), 1.47 (s, 9H); FAB MS $(M + H)^+ = 306$. Anal. ($C_{15}H_{19}N_3O_2S$) C, H, N, S.

***N*-1-(*tert*-Butyloxycarbonyl)-*N*-2-[4-(2-methyl-2*H*-tetrazol-5-yl)benzyl]hydrazine (9e).** $NaCNBH_3$ (17.6 g, 85% purity, 238 mmol) was added to **8e** (60 g, 198 mmol) in THF (700 mL); then a solution of p-TsOH (45.2 g, 238 mmol) in THF (350 mL) was added dropwise (→ precipitation). After 2 h, the solid was filtered off, washed with ethyl acetate, and discarded. Water and ethyl acetate were added to the filtrate; the aqueous phase was separated off and extracted twice with ethyl acetate. The organic phases were washed with saturated $NaHCO_3$ solution, water, and brine, dried (Na_2SO_4), and concentrated by evaporation. The resulting crystals were taken up in methanol (834 mL) and THF (416 mL), and cooled by an ice bath, and then a solution of $K_2B_4O_7 \cdot 4H_2O$ (254 g, 0.83 mol) in H_2O (834 mL) was added dropwise (→ foam production). The mixture was stirred at r.t. overnight, poured into water (4.4 L), and extracted three times with ethyl acetate. The organic phases were washed with saturated $NaHCO_3$ solution, water, and brine, dried (Na_2SO_4), and concentrated by evaporation. Filtration through silica gel using dichloromethane/THF (10:1) as the eluant, concentration by evaporation to a residual volume of about 0.1 L, and addition of diisopropyl ether (150 mL) yielded 47.9 g (79%) of crystalline **9e**: mp 100–102 °C; ^{1}H NMR (CD_3OD) δ 8.06 (d, 2H), 7.53 (d, 2H), 4.42 (s, 3H), 4.00 (s, 2H), 1.44 (s, 9H). Anal. ($C_{14}H_{20}N_6O_2$) C, H, N.

***N*-1-(*tert*-Butyloxycarbonyl)-*N*-2-[4-(diethylamino)benzyl]hydrazine (9g).** Preparation from **8g** as described for **9b** yielded 72 g (89%) of **9g**: ^{1}H NMR ($CDCl_3$) δ 7.19 (d, 2H), 6.65 (d, 2H), 6.1 (sb, HN), 4.08 (sb, HN), 3.87 (s, 2H), 3.36 (q, 4H), 1.48 (s, 9H), 1.16 (t, 6H).

1-(4-Biphenylyl)-5(*S*)-2,5-bis[(*tert*-butyloxycarbonyl)amino]-4(*S*)-hydroxy-6-phenyl-2-azahexane (12a). Preparation from **9a** as described for **12b** yielded 95 g (86%) of **12a**: mp 184–185 °C; ^{1}H NMR (CD_3OD) δ 7.7–7.1 (m, 14H), 3.90 (s, 2H), 3.7 (m, 2H), 3.0–2.5 (m, 4H), 1.34 (s, 9H), 1.32 (s, 9H); FAB MS $(M + H)^+ = 562$. Anal. ($C_{33}H_{43}N_3O_5$) C, H, N.

1-[4-(Pyridin-2-yl)phenyl]-5(*S*)-2,5-bis[(*tert*-butyloxycarbonyl)amino]-4(*S*)-hydroxy-6-phenyl-2-azahexane (12b). A solution of *N*-(*tert*-butyloxycarbonyl)-2(*S*)-amino-1-phenyl-3(*R*)-3,4-epoxybutane (**10**)[6b,12] (1185 g, 4.5 mol) and **9b** (1230 g, 4.1 mol) in 2-propanol (14 L) was heated to reflux temperature during 16 h. Then ice (15 kg) and water (10 L) were added portionwise. After stirring for 2 h the precipitate was filtered off and washed with water (6 L). The crude product was twice suspended in diethyl ether (5 L), again filtered, and washed with diethyl ether (2 L) each time and finally with diethyl ether/*tert*-butylmethyl ether (1:1) (2 L). Drying in vacuo at 40 °C yielded 1583 g (69%) of **12b**: TLC R_f(hexane/ethyl acetate, 1:2) = 0.45; mp 185–186 °C; $[\alpha]_D = -12°$ ($c = 0.5$, $CHCl_3$); ^{1}H NMR (CD_3OD) δ 8.60 (d, 1H), 7.88 (m, 4H), 7.50 (d, 2H), 7.36 (m, 1H), 7.25 (m, 4H), 7.18 (m, 1H), 3.93 (m, 2H), 3.70 (m, 2H), 3.0–2.6 (m, 4H), 1.33 (s, 9H), 1.30 (s, 9H); HPLC t_R 13.9 min; FAB MS $(M + H)^+ = 563$. Anal. ($C_{32}H_{42}N_4O_5 \cdot 0.14H_2O$) C, H, N, H_2O.

1-[4-(Thiazol-2-yl)phenyl]-5(*S*)-2,5-bis[(*tert*-butyloxycarbonyl)amino]-4(*S*)-hydroxy-6-phenyl-2-azahexane (12c). Preparation from **9c** as described for **12b** yielded 28.7 g (74%) of **12c**: TLC R_f(hexane/acetone, 3:2) = 0.30; ^{1}H NMR ($CDCl_3$) δ 7.92 (d, 2H), 7.86 (d, 1H), 7.40 (d, 2H), 7.32 (d, 1H), 7.25 (m, 5H), 5.29 (s, 1H), 5.10 (d, 1H), 4.51 (s, 1H), 4.01 (d, 1H), 3.88 (d, 1H), 3.63 (m, 2H), 2.93 (d, 2H), 2.82 (m, 1H), 2.46 (m, 1H), 1.38 (s, 9H), 1.34 (s, 9H).

1-[4-(2-Methyl-2*H*-tetrazol-5-yl)phenyl]-5(*S*)-2,5-bis[(*tert*-butyloxycarbonyl)amino]-4(*S*)-hydroxy-6-phenyl-2-azahexane (12e). Preparation from **9e** as described for **12b** yielded 55.6 g (78%) of **12e**: mp 175–178 °C; ^{1}H NMR ($CDCl_3$/CD_3OD mixture) δ 8.07 (d, 2H), 7.43 (d, 2H), 7.21 (m, 5H), 4.39 (s, 3H), 4.01 (d, 1H), 3.87 (d, 1H), 3.62 (m, 2H), 2.92 (d, 2H), 2.78 (m, 1H), 2.47 (m, 1H), 1.36 (s, 9H), 1.30 (s, 9H); FAB MS $(M + H)^+ = 568$. Anal. ($C_{29}H_{41}N_7O_5$) C, H, N.

1-(4-Biphenylyl)-2-[(*tert*-butyloxycarbonyl)amino]-4(*S*)-hydroxy-5(*S*)-[(trifluoroacetyl)amino]-6-phenyl-2-azahexane (13a). A suspension of *N*-(trifluoroacetyl)-2(*S*)-amino-1-phenyl-3(*R*)-3,4-epoxybutane (**11**)[7] (7:1 *threo*:*erythro* mixture;

40.0 g, 154 mmol) and **9a** (46.0 g, 154 mmol) in 2-propanol (800 mL) was heated to 80 °C for 16 h. After concentration of the solution to a volume of ≈0.3 L and cooling to r.t., the product crystallized. Filtration and washing with cold 2-propanol and hexane yielded 54 g (62%) of **13a**: mp 173 °C; ^{1}H NMR (CD_3OD) δ 7.57 (m, 4H), 7.42 (m, 5H), 7.25 (m, 5H), 4.25 (m, 1H), 3.90 (m, 2H), 3.80 (m, 1H), 3.03 (dd, 1H), 2.88 (m, 1H), 2.73 (m, 2H), 1.32 (s, 9H); HPLC t_R 18.6 min; FAB MS $(M + H)^+ = 558$. Anal. ($C_{30}H_{34}N_3O_4F_3$) C, H, N.

1-[4-(Pyridin-2-yl)phenyl]-2-[(*tert*-butyloxycarbonyl)amino]-4(*S*)-hydroxy-5(*S*)-[(trifluoroacetyl)amino]-6-phenyl-2-azahexane (13b). Preparation from **9b** as described for **13a** yielded 16 g (60%) of **13b**: mp 194 °C; ^{1}H NMR (DMSO-d_6) δ 9.12 (d, HN), 8.64 (d, 1H), 8.14 (s, HN), 8.00 (d, 2H), 7.92 (d, 1H), 7.85 (t, 1H), 7.43 (d, 2H), 7.33 (m, 1H), 7.23 (m, 4H), 7.16 (m, 1H), 4.89 (s, HO), 4.21 (m, 1H), 3.94 (AB, 2H), 3.69 (m, 1H), 2.90 (dd, 1H), 2.77 (m, 2H), 2.69 (dd, 1H), 1.28 (s, 9H); HPLC t_R 12.8 min; FAB MS $(M + H)^+ = 559$.

1-[4-(Thiazol-2-yl)phenyl]-2-[(*tert*-butyloxycarbonyl)amino]-4(*S*)-hydroxy-5(*S*)-[(trifluoroacetyl)amino]-6-phenyl-2-azahexane (13c). Preparation from **9c** as described for **13a** yielded 5.1 g (73%) of **13c**: mp 167−168 °C; ^{1}H NMR ($CDCl_3$) δ 7.92 (d, 2H), 7.87 (d, 1H), 7.40 (d, 2H), 7.33 (d, 1H), 7.24 (m, 5H), 6.92 (d, 1H), 5.31 (s, 1H), 4.81 (s, 1H), 4.0 (m, 3H), 3.69 (m, 1H), 3.00 (m, 2H), 2.66 (m, 1H), 2.48 (m, 1H), 1.34 (s, 9H); FAB MS $(M + H)^+ = 565$. Anal. ($C_{27}H_{31}N_4O_4F_3S$) C, H, N, F, S.

1-[4-(Thiazol-5-yl)phenyl]-2-[(*tert*-butyloxycarbonyl)amino]-4(*S*)-hydroxy-5(*S*)-[(trifluoroacetyl)amino]-6-phenyl-2-azahexane (13d). Preparation from **9d** as described for **13a** yielded 14.4 g (52%) of **13d**: ^{1}H NMR ($CDCl_3$) δ 8.77 (s, 1H), 8.07 (s, 1H), 7.55 (d, 2H), 7.36 (d, 2H), 7.25 (m, 5H), 6.87 (d, 1H), 5.30 (s, 1H), 4.78 (s, 1H), 3.98 (m, 3H), 3.67 (m, 1H), 2.99 (m, 2H), 2.63 (m, 1H), 2.45 (m, 1H), 1.35 (s, 9H); FAB MS $(M + H)^+ = 565$.

1-[4-(Diethylamino)phenyl]-2-[(*tert*-butyloxycarbonyl)amino]-4(*S*)-hydroxy-5(*S*)-[(trifluoroacetyl)amino]-6-phenyl-2-azahexane (13g). Preparation from **9g** as described for **13a** yielded 79 g (55%) of **13g**: mp 159−161 °C; ^{1}H NMR (CD_3OD) δ 7.22 (m, 4H), 7.16 (m, 1H), 7.11 (d, 2H), 6.62 (d, 2H), 4.16 (m, 1H), 3.73 (m, 1H), 3.69 (s, 2H), 3.33 (q, 4H), 2.97 (m, 1H), 2.81 (m, 1H), 2.66 (m, 1H), 2.59 (m, 1H), 1.32 (s, 9H), 1.11 (t, 6H); FAB MS $(M + H)^+ = 553$. Anal. ($C_{28}H_{39}N_4O_4F_3$) C, H, N, F.

1-(4-Biphenylyl)-5(*S*)-2,5-diamino-4(*S*)-hydroxy-6-phenyl-2-azahexane Dihydrochloride (14a). A solution of **12a** (95.2 g, 169.5 mmol) in 4 N HCl in dioxane (300 mL) was stirred for 3 h at r.t. and then concentrated in vacuo. Lyophilization from dioxane yielded 74 g (quantitative) of **14a**: FAB MS $(M + H)^+ = 362$.

1-[4-(Pyridin-2-yl)phenyl]-5(*S*)-2,5-diamino-4(*S*)-hydroxy-6-phenyl-2-azahexane Trihydrochloride (14b). A solution of **12b** (1465 g, 2.6 mol) in THF (12 L) and HCl (4 L, 4 N in water) was stirred for 4 h at 50 °C. From the resulting biphasic mixture the aqueous layer was separated and concentrated in vacuo. The residue was diluted with ethanol (4 L), concentrated, again diluted with ethanol/toluene (1:1) (4 L), concentrated, diluted with another 4 L of ethanol, and finally concentrated. Stirring in diisopropyl ether (9 L), filtration, and drying (40 °C, in vacuo) gave 1303 g (quantitative) of crystalline **14b**. Anal. ($C_{22}H_{26}N_4O{\cdot}3.15HCl{\cdot}1.10H_2O$) C, H, N, Cl, O, H_2O.

1-[4-(Thiazol-2-yl)phenyl]-5(*S*)-2,5-diamino-4(*S*)-hydroxy-6-phenyl-2-azahexane (14c). A solution of **12c** (21.7 g, 38.5 mmol) in formic acid (1 L) was stirred for 4 h at r.t. and then concentrated in vacuo. The residue was redissolved in dichloromethane and saturated $NaHCO_3$ solution. The aqueous layer was separated and extracted twice with dichloromethane. The organic layers were washed with brine, dried (Na_2SO_4), and concentrated, yielding 14.6 g of **14c**, which was used without further purification for the next step.

1-[4-(2-Methyl-2*H*-tetrazol-5-yl)phenyl]-5(*S*)-2,5-diamino-4(*S*)-hydroxy-6-phenyl-2-azahexane Dihydrochloride (14e). A solution of **12e** (20 g, 35.2 mmol) in THF (280 mL) and HCl (93 mL, 4 N in water) was stirred for 8 h at 50 °C. The mixture was concentrated in vacuo, and the residue was four times diluted with ethanol and concentrated, yielding 15.5 g (quantitative) of crystalline **14e**: mp 227−230 °C (recrystallized from 2-propanol/diisopropyl ether). Anal. ($C_{19}H_{25}N_7O{\cdot}2HCl{\cdot}0.20H_2O$) C, H, N, Cl, H_2O.

1-[4-(Diethylamino)phenyl]-5(*S*)-2,5-diamino-4(*S*)-hydroxy-6-phenyl-2-azahexane Trihydrochloride (14g). To an ice-cold solution of **15g** (57 g, 125 mmol) in DMF (200 mL) was added 4 N HCl in dioxane (950 mL). After 4 h at ambient temperature, the mixture was concentrated in vacuo. The residue was diluted with dioxane and toluene and again concentrated, giving 58 g (quantitative) of **14g**: FAB MS $(M + H)^+ = 367$.

1-(4-Biphenylyl)-2-[(*tert*-butyloxycarbonyl)amino]-4(*S*)-hydroxy-5(*S*)-amino-6-phenyl-2-azahexane (15a). To a solution of **13a** (54.0 g, 96.8 mmol) in boiling methanol (1.5 L) was added a 1 N aqueous solution of K_2CO_3 (484 mL) dropwise. The resulting suspension was heated at reflux temperature for 3 h (→ solution). The solvent was partially evaporated under reduced pressure and the residue dissolved in ethyl acetate (2 L). This solution was washed with water (0.5 L) and brine (1 L), and the aqueous layers were reextracted with ethyl acetate. Drying (Na_2SO_4) of the organic layers, concentration, and washing with hexane gave 42.6 g (95%) of **15a**: mp 134−136 °C; ^{1}H NMR (CD_3OD) δ 7.58 (m, 4H), 7.5−7.15 (m, 10H), 3.91 (m, 2H), 3.60 (dt, 1H), 3.1−2.7 (m, 4H), 2.63 (dd, 1H), 1.31 (s, 9H); FAB MS $(M + H)^+ = 462$. Anal. ($C_{28}H_{35}N_3O_3$) C, H, N.

1-[4-(Pyridin-2-yl)phenyl]-2-[(*tert*-butyloxycarbonyl)amino]-4(*S*)-hydroxy-5(*S*)-amino-6-phenyl-2-azahexane (15b). Prepared from **13b** as described for **15a** (4.1 g, 75%): ^{1}H NMR (CD_3OD) δ 8.59 (d, 1H), 7.88 (m, 3H), 7.83 (d, 1H), 7.50 (d, 2H), 7.35 (m, 1H), 7.3−7.15 (m, 5H), 3.94 (s, 2H), 3.59 (dt, 1H), 3.02 (m, 1H), 2.90 (m, 2H), 2.81 (m, 1H), 2.66 (dd, 1H), 1.29 (s, 9H); FAB MS $(M + H)^+ = 463$.

1-[4-(Thiazol-2-yl)phenyl]-2-[(*tert*-butyloxycarbonyl)amino]-4(*S*)-hydroxy-5(*S*)-amino-6-phenyl-2-azahexane (15c). Prepared from **13c** as described for **15a** (2.4 g, 91%): HPLC t_R 11.9 min; FAB MS $(M + H)^+ = 469$.

1-[4-(Thiazol-5-yl)phenyl]-2-[(*tert*-butyloxycarbonyl)amino]-4(*S*)-hydroxy-5(*S*)-amino-6-phenyl-2-azahexane (15d). Prepared from **13d** as described for **15a** (4.4 g, 93%): HPLC t_R 11.5 min. Anal. ($C_{25}H_{32}N_4O_3S{\cdot}0.53H_2O$) C, H, N, S, H_2O.

1-[4-(Diethylamino)phenyl]-2-[(*tert*-butyloxycarbonyl)amino]-4(*S*)-hydroxy-5(*S*)-amino-6-phenyl-2-azahexane (15g). Prepared from **13g** as described for **15a** (58 g, 90%): mp 97−98 °C. Anal. ($C_{26}H_{40}N_4O_3$) C, H, N.

1-(4-Biphenylyl)-2-[(*tert*-butyloxycarbonyl)amino]-4(*S*)-hydroxy-5(*S*)-{[*N*-(methoxycarbonyl)-L-valinyl]amino}-6-phenyl-2-azahexane (16a). To a solution of *N*-(methoxycarbonyl)-L-valine[14] (25.9 g, 148 mmol), EDC (53.1 g, 277 mmol), and HOBT (25 g, 185 mmol) in DMF (500 mL) was added triethylamine (77 mL, 554 mmol). The suspension was stirred for 30 min; then a solution of **15a** (42.6 g, 92.2 mmol) in DMF (300 mL) was added dropwise. The ice bath was removed, and stirring was continued at r.t. for 3 h. The reaction mixture then was concentrated in vacuo and the residue taken up in ethyl acetate (2.5 L) and water (1.8 L). For complete dissolution of the remaining solids, methanol (0.2 L) and triethylamine (150 mL) were added optionally. The organic phase was separated and washed three times with water, saturated $NaHCO_3$ solution, water, and brine. The aqueous layers were extracted with ethyl acetate; the organic phases were dried (Na_2SO_4) and concentrated in vacuo. Stirring in diisopropyl ether yielded 45 g (79%) of crystalline **16a**: mp 201 °C; ^{1}H NMR ($CDCl_3$) δ 7.54 (m, 4H), 7.42 (m, 2H), 7.34 (m, 3H), 7.21 (d, 4H), 7.15 (m, 1H), 6.37 (m, HN), 5.28 (sb, HN), 5.09 (m, HN), 4.57 (sb, HO), 4.00 (m, 1H), 3.93 (m, 3H), 3.66 (s, 3H), 3.60 (m, 1H), 2.94 (m, 1H), 2.89 (m, 1H), 2.73 (m, 1H), 2.38 (m, 1H), 1.97 (m, 1H), 1.33 (s, 9H), 0.81 (d, 3H), 0.74 (d, 3H); HPLC t_R 17.9 min; FAB MS $(M + H)^+ = 619$. Anal. ($C_{35}H_{46}N_4O_6{\cdot}0.33H_2O$) C, H, N.

1-[4-(Pyridin-2-yl)phenyl]-2-[(*tert*-butyloxycarbonyl)amino]-4(*S*)-hydroxy-5(*S*)-{[*N*-(methoxycarbonyl)-L-valinyl]amino}-6-phenyl-2-azahexane (16b). Preparation from **15b** as described for **16a** yielded 5.1 g (92%) of **16b**: ^{1}H NMR (CD_3OD) δ 8.59 (d, 1H), 7.88 (m, 3H), 7.83 (d, 1H), 7.48 (d, 2H), 7.34 (m, 1H), 7.22 (m, 4H), 7.14 (m, 1H), 4.10 (m, 1H), 3.91 (s, 2H), 3.83 (d, 1H), 3.69 (m, 1H), 3.63 (s, 3H), 2.95 (dd, 1H), 2.83 (dd, 1H), 2.76 (m, 1H), 2.57 (m, 1H), 1.87 (m, 1H), 1.30 (s, 9H), 0.78 (d, 3H), 0.76 (d, 3H); HPLC t_R 11.9 min; FAB MS $(M + H)^+ = 620$.

1-[4-(Thiazol-2-yl)phenyl]-2-[(*tert*-butyloxycarbonyl)amino]-4(*S*)-hydroxy-5(*S*)-{[*N*-(methoxycarbonyl)-L-valinyl]amino}-6-phenyl-2-azahexane (16c). Preparation from **15c** as described for **16a** yielded 2.7 g (86%) of **16c**: mp 178−179 °C; ^{1}H NMR ($CDCl_3$) δ 7.92 (d, 2H), 7.87 (d, 1H), 7.40 (d, 2H), 7.33 (d, 1H), 7.23 (m, 5H), 6.38 (d, 1H), 5.31 (s, 1H), 5.12 (m, 1H), 4.60 (s, 1H), 4.02 (m, 1H), 3.93 (m, 3H), 3.66 (s, 3H), 3.59 (m, 1H), 2.93 (m, 2H), 2.73 (m, 1H), 2.39 (m, 1H), 1.94 (m, 1H), 1.33 (s, 9H), 0.80 (d, 3H), 0.73 (d, 3H); HPLC t_R 15.9 min; FAB MS $(M + H)^+ = 626$.

1-[4-(Thiazol-5-yl)phenyl]-2-[(*tert*-butyloxycarbonyl)amino]-4(*S*)-hydroxy-5(*S*)-{[*N*-(methoxycarbonyl)-L-valinyl]amino}-6-phenyl-2-azahexane (16d). Preparation from **15d** as described for **16a** yielded 4.5 g (75%) of **16d**: mp 114−115 °C; ^{1}H NMR ($CDCl_3$) δ 8.75 (s, 1H), 8.07 (s, 1H), 7.53 (d, 2H), 7.36 (d, 2H), 7.22 (m, 5H), 6.40 (d, 1H), 5.31 (s, 1H), 5.12 (m, 1H), 4.58 (s, 1H), 4.02 (m, 1H), 3.93 (m, 3H), 3.68 (s, 3H), 3.61 (m, 1H), 2.93 (m, 2H), 2.73 (m, 1H), 2.37 (m, 1H), 1.97 (m, 1H), 1.35 (s, 9H), 0.82 (d, 3H), 0.74 (d, 3H); HPLC t_R 15.1 min; FAB MS $(M + H)^+ = 626$. Anal. ($C_{32}H_{43}N_5O_6S\cdot0.27H_2O$) C, H, N, S, H_2O.

1-(4-Biphenylyl)-2-[(*tert*-butyloxycarbonyl)amino]-4(*S*)-hydroxy-5(*S*)-{[*N*-(methoxycarbonyl)-L-*tert*-leucinyl]amino}-6-phenyl-2-azahexane (17a). Preparation as described for **16a** starting from **29** yielded 900 mg (90%) of **17a**: TLC R_f(dichloromethane/methanol, 19:1) = 0.57; ^{1}H NMR (CD_3OD) δ 7.58 (m, 4H), 7.43 (m, 5H), 7.23 (m, 4H), 7.18 (m, 1H), 4.10 (m, 1H), 3.89 (s, 3H), 3.70 (m, 1H), 3.65 (s, 3H), 2.9 (m, 2H), 2.76 (m, 1H), 2.55 (m, 1H), 1.31 (s, 9H), 0.85 (s, 9H); HPLC t_R 18.2 min; FAB MS $(M + H)^+ = 633$.

1-[4-(Pyridin-2-yl)phenyl]-2-[(*tert*-butyloxycarbonyl)amino]-4(*S*)-hydroxy-5(*S*)-{[*N*-(methoxycarbonyl)-L-*tert*-leucinyl]amino}-6-phenyl-2-azahexane (17b). Preparation from **15b** and **29** as described for **16a** yielded 4.4 g (81%) of **17b**: ^{1}H NMR (CD_3OD) δ 8.59 (d, 1H), 7.88 (m, 3H), 7.83 (d, 1H), 7.48 (d, 2H), 7.35 (m, 1H), 7.21 (m, 4H), 7.13 (m, 1H), 4.10 (m, 1H), 3.91 (s, 2H), 3.87 (s, 1H), 3.70 (m, 1H), 3.64 (s, 3H), 2.94 (dd, 1H), 2.83 (dd, 1H), 2.78 (m, 1H), 2.58 (m, 1H), 1.30 (s, 9H), 0.85 (s, 9H); HPLC t_R 12.5 min; FAB MS $(M + H)^+ = 634$. Anal. ($C_{35}H_{47}N_5O_6$) C, H, N.

1-[4-(Thiazol-5-yl)phenyl]-2-[(*tert*-butyloxycarbonyl)amino]-4(*S*)-hydroxy-5(*S*)-{[*N*-(methoxycarbonyl)-L-*tert*-leucinyl]amino}-6-phenyl-2-azahexane (17d). Preparation from **15d** and **29** as described for **16a** yielded 2.2 g (76%) of **17d**: ^{1}H NMR (CD_3OD) δ 8.96 (s, 1H), 8.15 (s, 1H), 7.60 (d, 2H), 7.45 (d, 2H), 7.2 (m, 5H), 4.11 (m, 1H), 3.89 (m, 3H), 3.7 (m, 1H), 3.66 (s, 3H), 3.0−2.7 (m, 3H), 2.56 (m, 1H), 1.30 (s, 9H), 0.83 (s, 9H); HPLC t_R 16.0 min; FAB MS $(M + H)^+ = 640$.

1-[4-(Pyridin-2-yl)phenyl]-2-[(*tert*-butyloxycarbonyl)amino]-4(*S*)-hydroxy-5(*S*)-{[*N*-(methoxycarbonyl)-L-isoleucinyl]amino}-6-phenyl-2-azahexane (18b). Preparation as described for **16a**, starting from **15b** and *N*-(methoxycarbonyl)-L-isoleucine[14] yielded 1.6 g (72%) of **18b**: ^{1}H NMR (CD_3OD) δ 8.58 (d, 1H), 7.88 (m, 3H), 7.83 (d, 1H), 7.48 (d, 2H), 7.34 (m, 1H), 7.23 (m, 4H), 7.14 (m, 1H), 4.12 (m, 1H), 3.91 (m, 2H), 3.87 (d, 1H), 3.70 (m, 1H), 3.63 (s, 3H), 2.95 (m, 1H), 2.87−2.75 (m, 2H), 2.58 (m, 1H), 1.67 (m, 1H), 1.34 (m, 1H), 1.29 (s, 9H), 1.05 (m, 1H), 0.79 (t, 3H), 0.73 (d, 3H); HPLC t_R 12.5 min; FAB MS $(M + H)^+ = 634$.

1-(4-Biphenylyl)-2-amino-4(*S*)-hydroxy-5(*S*)-{[*N*-(methoxycarbonyl)-L-valinyl]amino}-6-phenyl-2-azahexane Hydrochloride (19a). A solution of **16a** (57.2 g, 92.4 mmol) in 4 N HCl in dioxane (200 mL) and methanol (20 mL) was stirred for 3 h at r.t. and then concentrated in vacuo. Lyophilization from dioxane then yielded 56.4 g (quantitative) of **19a**: FAB MS $(M + H)^+ = 519$; HPLC t_R 12.7 min.

1-[4-(Pyridin-2-yl)phenyl]-2-amino-4(*S*)-hydroxy-5(*S*)-{[*N*-(methoxycarbonyl)-L-valinyl]amino}-6-phenyl-2-azahexane Dihydrochloride (19b). Prepared from **16b** as described for **19a** (4.0 g, quantitative): FAB MS $(M + H)^+ = 520$; HPLC t_R 8.0 min.

1-[4-(Thiazol-2-yl)phenyl]-2-amino-4(*S*)-hydroxy-5(*S*)-{[*N*-(methoxycarbonyl)-L-valinyl]amino}-6-phenyl-2-azahexane (19c). Deprotection of **16c** by formic acid as described for **14c** (552 mg, 70%): FAB MS $(M + H)^+ = 526$; HPLC t_R 10.6 min.

1-[4-(Thiazol-5-yl)phenyl]-2-amino-4(*S*)-hydroxy-5(*S*)-{[*N*-(methoxycarbonyl)-L-valinyl]amino}-6-phenyl-2-azahexane (19d). Deprotection of **16d** by formic acid as described for **14c** (903 mg): FAB MS $(M + H)^+ = 526$; HPLC t_R 10.0 min.

1-(4-Biphenylyl)-2-amino-4(*S*)-hydroxy-5(*S*)-{[*N*-(methoxycarbonyl)-L-*tert*-leucinyl]amino}-6-phenyl-2-azahexane Hydrochloride (20a). Deprotection of **17a** as described for **19a** (820 mg, 97%): FAB MS $(M + H)^+ = 533$; HPLC t_R 13.2 min.

1-[4-(Pyridin-2-yl)phenyl]-2-amino-4(*S*)-hydroxy-5(*S*)-{[*N*-(methoxycarbonyl)-L-*tert*-leucinyl]amino}-6-phenyl-2-azahexane Dihydrochloride (20b). Prepared from **17b** as described for **19a** (4.4 g, ≈ quantitative): FAB MS $(M + H)^+ = 534$; HPLC t_R 8.5 min.

1-[4-(Thiazol-5-yl)phenyl]-2-amino-4(*S*)-hydroxy-5(*S*)-{[*N*-(methoxycarbonyl)-L-*tert*-leucinyl]amino}-6-phenyl-2-azahexane (20d). Deprotection of **17d** by formic acid as described for **14c** (882 mg, quantitative): FAB MS $(M + H)^+ = 540$.

1-[4-(Pyridin-2-yl)phenyl]-2-amino-4(*S*)-hydroxy-5(*S*)-{[*N*-(methoxycarbonyl)-L-isoleucinyl]amino}-6-phenyl-2-azahexane dihydrochloride (21b). Prepared from **18b** as described for **19a** (1.6 g, quantitative): FAB MS $(M + H)^+ = 534$; HPLC t_R 8.8 min.

1-(4-Biphenylyl)-5(*S*)-2,5-bis{[*N*-(methoxycarbonyl)-L-valinyl]amino}-4(*S*)-hydroxy-6-phenyl-2-azahexane (22a). To an ice-cooled suspension of *N*-(methoxycarbonyl)-L-valine[14] (48.4 g, 276 mmol) and EDC (101.8 g, 530.9 mmol) in DMF (1 L) was added HOBT (43 g, 318.5 mmol), followed by triethylamine (82.9 mL, 594.6 mmol). After 20 min of stirring, 1-(4-biphenylyl)-5(*S*)-2,5-diamino-4(*S*)-hydroxy-6-phenyl-2-azahexane dihydrochloride (**14a**) (46 g, 106 mmol) was added portionwise. The ice bath was removed, and stirring was continued overnight. The reaction mixture then was concentrated in vacuo and the residue redissolved in dichloromethane and washed with aqueous solutions of $NaHCO_3$, citric acid, and NaCl. The aqueous layers were extracted three times with dichloromethane; the organic phases were dried (Na_2SO_4) and concentrated in vacuo. Recrystallization from methanol/diisopropyl ether yielded 43.8 g (61%) of **22a**: TLC R_f(ethyl acetate) = 0.37; mp 214−216 °C; ^{1}H NMR (CD_3OD) δ 7.57 (m, 2H), 7.52 (d, 2H), 7.43 (d, 2H), 7.41 (t, 2H), 7.31 (t, 1H), 7.21 (m, 4H), 7.13 (m, 1H), 4.13 (m, 1H), 3.98 (m, 1H), 3.88 (m, 1H), 3.79 (d, 1H), 3.73 (m, 1H), 3.64 (s, 3H), 3.63 (m, 1H), 3.61 (s, 3H), 2.93 (dd, 1H), 2.84 (m, 2H), 2.64 (d, 1H), 1.85 (m, 1H), 1.67 (m, 1H), 0.77 (d, 3H), 0.75 (d, 3H), 0.64 (d, 3H), 0.60 (d, 3H); HPLC t_R 15.5 min; FAB MS $(M + H)^+ = 676$. Anal. ($C_{37}H_{49}N_5O_7$) C, H, N.

1-[4-(Pyridin-2-yl)phenyl]-5(*S*)-2,5-bis{[*N*-(methoxycarbonyl)-L-valinyl]amino}-4(*S*)-hydroxy-6-phenyl-2-azahexane (22b). Preparation from **14b** as described for **22a** yielded 295 mg (44%) of **22b**: mp 210−212 °C; ^{1}H NMR (DMSO-d_6) δ 9.06 (s, HN), 8.64 (d, 1H), 7.97 (d, 2H), 7.90 (d, 1H), 7.85 (td, 1H), 7.50 (d, 1H), 7.41 (d, 2H), 7.32 (m, 1H), 7.18 (m, 4H), 7.12 (m, 1H), 7.04 (d, 1H), 6.96 (d, 1H), 5.00 (s, 1H), 4.00 (m, 1H), 3.96 (d, 1H), 3.90 (d, 1H), 3.73 (t, 1H), 3.57 (m, 2H), 3.50 (s, 6H), 2.78 (dd, 1H), 2.70 (m, 2H), 2.61 (d, 1H), 1.77 (m, 1H), 1.59 (m, 1H), 0.68 (d, 3H), 0.63 (d, 3H), 0.55 (d, 3H), 0.48 (d, 3H); FAB MS $(M + H)^+ = 677$. Anal. ($C_{36}H_{48}N_6O_7\cdot0.6H_2O$) C, H, N, H_2O.

1-[4-(Thiazol-5-yl)phenyl]-5(*S*)-2,5-bis{[*N*-(methoxycarbonyl)-L-valinyl]amino}-4(*S*)-hydroxy-6-phenyl-2-azahexane (22d). Preparation as described for **23b** starting from *N*-(methoxycarbonyl)-L-valine[14] and 1-[4-(thiazol-5-yl)phenyl]-2-amino-4(*S*)-hydroxy-5(*S*)-{[*N*-(methoxycarbonyl)-L-valinyl]amino}-6-phenyl-2-azahexane (**19d**) yielded 124 mg (36%) of **22d**: mp 207−208 °C; ^{1}H NMR ($CDCl_3$) δ 8.75 (s, 1H), 8.05 (s, 1H), 7.50 (d, 2H), 7.36 (d, 2H), 7.2 (m, 5H), 6.90 (s, 1H), 6.60 (d, 1H), 5.15 (m, 2H), 4.83 (s, 1H), 4.2−3.8 (m, 4H), 3.68 (s, 3H), 3.63 (s, 3H), 3.6 (m, 2H), 2.95 (d, 2H), 2.83 (m, 1H), 2.56 (m, 1H), 2.01 (m, 1H), 1.82 (m, 1H), 0.84 (d, 3H), 0.74 (d, 3H), 0.67 (d, 3H), 0.63 (d, 3H); HPLC t_R 13.3 min; FAB MS $(M + H)^+ = 683$. Anal. ($C_{34}H_{46}N_6O_7S{\cdot}0.66H_2O$) C, H, N, S, H_2O.

1-(4-Biphenylyl)-2-{[*N*-(methoxycarbonyl)-L-*tert*-leucinyl]amino}-4(*S*)-hydroxy-5(*S*)-{[*N*-(methoxycarbonyl)-L-valinyl]amino}-6-phenyl-2-azahexane (23a). A solution of *N*-(methoxycarbonyl)-L-*tert*-leucine (**29**) (18.04 g, 95.3 mmol) and TPTU (28.4 g, 95.3 mmol) in DMF (180 mL) was stirred for 15 min. Then a solution of 1-(4-biphenylyl)-2-amino-4(*S*)-hydroxy-5(*S*)-{[*N*-(methoxycarbonyl)-L-valinyl]amino}-6-phenyl-2-azahexane hydrochloride (**19a**) (52.8 g, 95.3 mmol) and NMM (31.4 mL, 286 mmol) in DMF (560 mL) was added dropwise. After stirring for 16 h, the reaction mixture was poured into water (7 L) and the resulting precipitate filtered off and washed with water. The crude product was redissolved in ethyl acetate (2.5 L) and washed with water and brine. The aqueous layers were extracted with ethyl acetate and the organic phases dried (Na_2SO_4) and concentrated to a volume of ≈1 L. Crystallization by adding hexane (2 L), filtration, and recrystallization from methanol afforded 33 g (50%) of **23a**: mp 206−207 °C; $[\alpha]_D = -42°$ (c = 1, EtOH); ^{1}H NMR (DMSO-d_6) δ 8.82 (s, 1H), 7.58 (d, 2H), 7.50 (d, 2H), 7.44 (t, 2H), 7.40 (t, 2H), 7.30 (m, 2H), 7.19 (m, 4H), 7.12 (m, 1H), 6.57 (m, 1H), 6.35 (m, 1H), 4.78 (s, 1H), 4.05 (q, 1H), 3.95 (m, 2H), 3.77 (dd, 1H), 3.66 (d, 1H), 3.63 (m, 1H), 3.53 (s, 3H), 3.51 (s, 3H), 2.84 (dd, 1H), 2.74 (m, 3H), 1.85 (oct, 1H), 0.75 (d, 3H), 0.72 (d, 3H), 0.70 (s, 9H); HPLC t_R 16.7 min; FAB MS $(M + H)^+ = 690$. Anal. ($C_{38}H_{51}N_5O_7$) C, H, N.

1-[4-(Pyridin-2-yl)phenyl]-2-{[*N*-(methoxycarbonyl)-L-*tert*-leucinyl]amino}-4(*S*)-hydroxy-5(*S*)-{[*N*-(methoxycarbonyl)-L-valinyl]amino}-6-phenyl-2-azahexane (23b). To an ice-cooled solution of **29** (152 mg, 0.80 mmol), EDC (287 mg, 1.5 mmol), and HOBT (135 mg, 1.0 mmol) in DMF (3 mL) was added triethylamine (0.49 mL, 3.5 mmol). The suspension was stirred for 10 min; then a solution of 1-[4-(pyridin-2-yl)-phenyl]-2-amino-4(*S*)-hydroxy-5(*S*)-{[*N*-(methoxycarbonyl)-L-valinyl]amino}-6-phenyl-2-azahexane dihydrochloride (**19b**) (296 mg, 0.50 mmol) in DMF (3 mL) was added. The ice bath was removed, and stirring was continued at r.t. for 3 h. The reaction mixture then was concentrated in vacuo and the residue redissolved in dichloromethane/water. The aqueous phase was separated and extracted twice with dichloromethane. The organic layers were washed with saturated $NaHCO_3$ solution, water, and brine, dried (Na_2SO_4), and concentrated in vacuo. Medium-pressure liquid chromatography (SiO_2, ethyl acetate/hexane, 4:1) and stirring in diisopropyl ether yielded 105 mg (30%) of **23b**: TLC R_f(ethyl acetate) = 0.35; ^{1}H NMR (CD_3OD) δ 8.58 (d, 1H), 7.87 (m, 3H), 7.82 (d, 1H), 7.51 (d, 2H), 7.34 (m, 1H), 7.22 (m, 4H), 7.13 (m, 1H), 4.13 (m, 1H), 3.99 (m, 2H), 3.79 (d, 1H), 3.74 (m, 1H), 3.68 (s, 1H), 3.62 (s, 3H), 3.59 (s, 3H), 2.93 (dd, 1H), 2.84 (m, 2H), 2.67 (m, 1H), 1.86 (m, 1H), 0.76 (d, 3H), 0.74 (d, 3H), 0.70 (s, 9H); HPLC t_R 11.1 min; FAB MS $(M + H)^+ = 691$.

1-[4-(Thiazol-2-yl)phenyl]-2-{[*N*-(methoxycarbonyl)-L-*tert*-leucinyl]amino}-4(*S*)-hydroxy-5(*S*)-{[*N*-(methoxycarbonyl)-L-valinyl]amino}-6-phenyl-2-azahexane (23c). Preparation from **19c** as described for **23b** yielded 95 mg (39%) of **23c**: ^{1}H NMR (CD_3OD) δ 7.88 (d, 2H), 7.85 (d, 1H), 7.60 (d, 1H), 7.52 (d, 2H), 7.2 (m, 5H), 4.15 (m, 1H), 4.00 (s, 2H), 3.77 (m, 3H), 3.64 (s, 3H), 3.61 (s, 3H), 3.0−2.6 (m, 4H), 1.86 (m, 1H), 0.78 (d, 3H), 0.75 (d, 3H), 0.71 (s, 9H); HPLC t_R 14.5 min; FAB MS $(M + H)^+ = 697$. Anal. ($C_{35}H_{48}N_6O_7S{\cdot}0.7H_2O$) C, H, N, S, H_2O.

1-[4-(Thiazol-5-yl)phenyl]-2-{[*N*-(methoxycarbonyl)-L-*tert*-leucinyl]amino}-4(*S*)-hydroxy-5(*S*)-{[*N*-(methoxycarbonyl)-L-valinyl]amino}-6-phenyl-2-azahexane (23d). Preparation from **19d** as described for **23b** yielded 67 mg (9%) of **23d**: mp 200−201 °C; ^{1}H NMR (CD_3OD) δ 8.95 (s, 1H), 8.15 (s, 1H), 7.58 (d, 2H), 7.47 (d, 2H), 7.23 (m, 4H), 7.15 (m, 1H), 4.13 (m, 1H), 3.96 (m, 2H), 3.79 (d, 1H), 3.75 (m, 1H), 3.66 (s, 1H), 3.64 (s, 3H), 3.61 (s, 3H), 2.87 (m, 3H), 2.67 (m, 1H), 1.86 (m, 1H), 0.76 (d, 3H), 0.74 (d, 3H), 0.70 (s, 9H); HPLC t_R 14.0 min; FAB MS $(M + H)^+ = 697$.

1-(4-Biphenylyl)-2-{[*N*-(methoxycarbonyl)-L-valinyl]amino}-4(*S*)-hydroxy-5(*S*)-{[*N*-(methoxycarbonyl)-L-*tert*-leucinyl]amino}-6-phenyl-2-azahexane (24a). Preparation as described for **23a** starting from *N*-(methoxycarbonyl)-L-valine[14] and **20a** yielded 564 mg (61%) of **24a**: ^{1}H NMR (CD_3OD) δ 7.6−7.1 (m, 14H), 4.15 (m, 1H), 3.96 (m, 2H), 3.88 (s, 1H), 3.76 (d, 1H), 3.65 (s, 3H), 3.62 (s, 3H), 3.6 (m, 1H), 2.9 (m, 3H), 2.67 (m, 1H), 1.70 (oct, 1H), 0.84 (s, 9H), 0.66 (d, 3H), 0.60 (d, 3H); HPLC t_R 16.5 min; FAB MS $(M + H)^+ = 690$. Anal. ($C_{38}H_{51}N_5O_7{\cdot}0.21H_2O$) C, H, N, H_2O.

1-[4-(Pyridin-2-yl)phenyl]-2-{[*N*-(methoxycarbonyl)-L-valinyl]amino}-4(*S*)-hydroxy-5(*S*)-{[*N*-(methoxycarbonyl)-L-*tert*-leucinyl]amino}-6-phenyl-2-azahexane (24b). Preparation as described for **23b** starting from *N*-(methoxycarbonyl)-L-valine[14] and **20b** yielded 310 mg (30%) of **24b**: TLC R_f(ethyl acetate) = 0.35; ^{1}H NMR (CD_3OD) δ 8.58 (d, 1H), 7.87 (m, 3H), 7.81 (d, 1H), 7.50 (d, 2H), 7.35 (m, 1H), 7.21 (m, 4H), 7.12 (m, 1H), 4.15 (m, 1H), 4.02 (d, 1H), 3.94 (d, 1H), 3.85 (s, 1H), 3.75 (m, 1H), 3.63 (m, 4H), 3.60 (s, 3H), 2.93 (dd, 1H), 2.86 (m, 2H), 2.68 (m, 1H), 1.69 (m, 1H), 0.83 (s, 9H), 0.66 (d, 3H), 0.60 (d, 3H); HPLC t_R 10.9 min; FAB MS $(M + H)^+ = 691$. Anal. ($C_{37}H_{50}N_6O_7{\cdot}0.59H_2O$) C, H, N, H_2O.

1-[4-(Thiazol-5-yl)phenyl]-2-{[*N*-(methoxycarbonyl)-L-valinyl]amino}-4(*S*)-hydroxy-5(*S*)-{[*N*-(methoxycarbonyl)-L-*tert*-leucinyl]amino}-6-phenyl-2-azahexane (24d). Preparation as described for **23a** starting from *N*-(methoxycarbonyl)-L-valine[14] and **20d** yielded 174 mg (43%) of **24d**: mp 134−135 °C; ^{1}H NMR (CD_3OD) δ 8.96 (s, 1H), 8.15 (s, 1H), 7.59 (d, 2H), 7.47 (d, 2H), 7.22 (m, 4H), 7.17 (m, 1H), 4.15 (m, 1H), 3.96 (m, 2H), 3.86 (s, 1H), 3.75 (m, 1H), 3.65 (s, 3H), 3.62 (s, 3H), 3.57 (m, 1H), 2.9 (m, 3H), 2.67 (m, 1H), 1.70 (m, 1H), 0.83 (s, 9H), 0.68 (d, 3H), 0.62 (d, 3H); HPLC t_R 14.0 min; FAB MS $(M + H)^+ = 697$. Anal. ($C_{35}H_{48}N_6O_7S$) C, H, N, S.

1-(4-Biphenylyl)-5(*S*)-2,5-bis{[*N*-(methoxycarbonyl)-L-*tert*-leucinyl]amino}-4(*S*)-hydroxy-6-phenyl-2-azahexane (25a, CGP 75355). Preparation from **14a** as described for **25b** yielded 45.1 g (44%) of **25a** (CGP 75355): mp 210−211 °C; $[\alpha]_D = -58°$ (c = 1, EtOH); ^{1}H NMR (CD_3OD) δ 7.56 (d, 2H), 7.51 (d, 2H), 7.44 (d, 2H), 7.41 (t, 2H), 7.31 (t, 1H), 7.20 (m, 4H), 7.12 (m, 1H), 4.13 (t, 1H), 3.96 (m, 2H), 3.85 (s, 1H), 3.75 (d, 1H), 3.69 (s, 1H), 3.63 (s, 3H), 3.60 (s, 3H), 2.92 (dd, 1H), 2.85 (m, 2H), 2.66 (d, 1H), 0.83 (s, 9H), 0.71 (s, 9H); HPLC t_R 12.1 min; FAB MS $(M + H)^+ = 704$. Anal. ($C_{39}H_{53}N_5O_7{\cdot}0.22H_2O$) C, H, N, O, H_2O.

1-[4-(Pyridin-2-yl)phenyl]-5(*S*)-2,5-bis{[*N*-(methoxycarbonyl)-L-*tert*-leucinyl]amino}-4(*S*)-hydroxy-6-phenyl-2-azahexane (25b, CGP 73547). To an ice-cooled suspension of *N*-(methoxycarbonyl)-L-*tert*-leucine (**29**) (567 g, 3.0 mol) and TPTU (891 g, 3.0 mol) in dichloromethane (3 L) was added dropwise *N*-ethyldiisopropylamine (775 g, 6 mol). Stirring for 20 min produced a solution. Then a suspension of 1-[4-(pyridin-2-yl)phenyl]-5(*S*)-2,5-diamino-4(*S*)-hydroxy-6-phenyl-2-azahexane trihydrochloride (**14b**) (472 g, 1.0 mol) in dichloromethane (3 L) was added portionwise at 0−5 °C. The ice bath was removed, and stirring was continued overnight. The reaction mixture then was washed with water (10 L), saturated $NaHCO_3$ solution (10 L), and brine (5 L). The aqueous layers were extracted twice with dichloromethane (5 L); the organic phases were dried (Na_2SO_4) and concentrated in vacuo. The residue was dissolved in ethyl acetate (6 L) and filtered through silica gel (500 g); the column was eluted with ethyl acetate (6 L) and the eluate concentrated under reduced pressure. The resulting material was stirred for 1 h in boiling diisopropyl ether with 2% ethanol (9 L). Cooling to r.t.,

filtration, and washing with diisopropyl ether (+2% ethanol) afforded 513 g (73%) of crude **25b**: TLC R_f(ethyl acetate) = 0.53; mp 201−203 °C. Redissolving at 70 °C in ethanol (70% in water), filtration, and crystallization by adding water and cooling to 5 °C gave pure **25b** (CGP 73547) in 67% yield: mp 207−209 °C; $[\alpha]_D = -47°$ ($c = 1$, EtOH); ^{1}H NMR (CD_3OD) δ 8.58 (d, 1H), 7.86 (m, 3H), 7.81 (d, 1H), 7.50 (d, 2H), 7.35 (dd, 1H), 7.20 (m, 4H), 7.12 (m, 1H), 4.15 (t, 1H), 3.99 (m, 2H), 3.85 (s, 1H), 3.76 (d, 1H), 3.68 (s, 1H), 3.63 (s, 3H), 3.59 (s, 3H), 2.93 (dd, 1H), 2.86 (m, 2H), 2.69 (d, 1H), 0.83 (s, 9H), 0.71 (s, 9H); HPLC t_R 11.9 min; FAB MS $(M + H)^+ = 705$. Anal. ($C_{38}H_{52}N_6O_7{\cdot}0.18H_2O$) C, H, N, O, H_2O.

1-[4-(Thiazol-2-yl)phenyl]-2,5-bis{[*N*-(methoxycarbonyl)-L-*tert*-leucinyl]amino}-4(*S*)-hydroxy-6-phenyl-2-azahexane (25c, CGP 75136). Preparation from **14c** as described for **25b** (solvent: DMF) yielded 17.1 g (62%) of **25c** (CGP 75136): mp 134−136 °C; TLC R_f(hexane/ethyl acetate, 1:3) = 0.22; $[\alpha]_D = -46°$ ($c = 0.6$, EtOH); ^{1}H NMR (CD_3OD) δ 7.86 (d, 2H), 7.84 (d, 1H), 7.58 (d, 1H), 7.51 (d, 2H), 7.20 (m, 4H), 7.12 (m, 1H), 4.15 (m, 1H), 3.98 (s, 2H), 3.84 (s, 1H), 3.75 (m, 1H), 3.68 (s, 1H), 3.63 (s, 3H), 3.60 (s, 3H), 2.92 (dd, 1H), 2.85 (m, 2H), 2.69 (m, 1H), 0.82 (s, 9H), 0.72 (s, 9H); FAB MS $(M + H)^+ = 711$. Anal. ($C_{36}H_{50}N_6O_7S{\cdot}0.23H_2O$) C, H, N, S, H_2O.

1-[4-(Thiazol-5-yl)phenyl]-2,5-bis{[*N*-(methoxycarbonyl)-L-*tert*-leucinyl]amino}-4(*S*)-hydroxy-6-phenyl-2-azahexane (25d). Preparation as described for **23a** starting from 1-[4-(thiazol-5-yl)phenyl]-2-amino-4(*S*)-hydroxy-5(*S*)-{[*N*-(methoxycarbonyl)-L-*tert*-leucinyl]amino}-6-phenyl-2-azahexane (**20d**) yielded 105 mg (34%) of **25d**: mp 207−209 °C; ^{1}H NMR (CD_3OD) δ 8.96 (s, 1H), 8.15 (s, 1H), 7.59 (d, 2H), 7.47 (d, 2H), 7.2 (m, 5H), 4.15 (m, 1H), 3.97 (s, 2H), 3.85 (s, 1H), 3.75 (m, 1H), 3.69 (s, 1H), 3.64 (s, 3H), 3.62 (s, 3H), 2.9 (m, 3H), 2.67 (m, 1H), 0.82 (s, 9H), 0.72 (s, 9H); HPLC t_R 14.7 min; FAB MS $(M + H)^+ = 711$. Anal. ($C_{36}H_{50}N_6O_7S{\cdot}0.25H_2O$) C, H, N, S, H_2O.

1-[4-(2-Methyl-2*H*-tetrazol-5-yl)phenyl]-2,5-bis{[*N*-(methoxycarbonyl)-L-*tert*-leucinyl]amino}-4(*S*)-hydroxy-6-phenyl-2-azahexane (25e, CGP 75176). Preparation from **14e** as described for **25b** (solvent: DMF) yielded 16 g (64%) of **25e** (CGP 75176): mp 191−192 °C; $[\alpha]_D = -46°$ ($c = 0.5$, EtOH); ^{1}H NMR (DCl_2C-CCl_2D, 80 °C) δ 8.09 (d, 2H), 7.47 (d, 2H), 7.3−7.15 (m, 5H), 6.6 (sb, 1H), 6.24 (d, 1H), 5.13 (m, 2H), 4.39 (s, 3H), 4.08 (m, 2H), 4.01 (d, 1H), 3.75 (d, 1H), 3.8−3.55 (m, 3H), 3.68 (s, 3H), 3.64 (s, 3H), 2.95 (m, 2H), 2.89 (m, 1H), 2.68 (m, 1H), 0.91 (s, 9H), 0.83 (s, 9H); HPLC t_R 14.4 min; FAB MS $(M + H)^+ = 710$. Anal. ($C_{35}H_{51}N_9O_7$) C, H, N, O.

1-[4-(2-*tert*-Butyl-2*H*-tetrazol-5-yl)phenyl]-2,5-bis{[*N*-(methoxycarbonyl)-L-*tert*-leucinyl]amino}-4(*S*)-hydroxy-6-phenyl-2-azahexane (25f). A solution of *N*-(methoxycarbonyl)-L-*tert*-leucine (**29**) (54 mg, 0.283 mmol) and TPTU (84 mg, 0.283 mmol) in DMF (1 mL) was stirred for 10 min. Then a solution of 1-[4-(2-*tert*-butyl-2*H*-tetrazol-5-yl)phenyl]-2-{[*N*-(methoxycarbonyl)-L-*tert*-leucinyl]amino}-4(*S*)-hydroxy-5(*S*)-amino-6-phenyl-2-azahexane hydrochloride (**36**) (175 mg, 0.283 mmol) and NMM (94 μL, 0.85 mmol) in DMF (2 mL) was added. After stirring for 16 h, the reaction mixture was poured into water (40 mL) and extracted with three portions of dichloromethane. The organic layers were washed with brine, dried (Na_2SO_4), and concentrated. Column chromatography (CH_2Cl_2/methanol, 25:1) gave 79 mg (37%) of **25f**: mp 140 °C (crystallized from toluene/hexane); $[\alpha]_D = -41.5°$ ($c = 0.9$, EtOH); TLC R_f(CH_2Cl_2/methanol, 19:1) = 0.48; ^{1}H NMR (CD_3OD) δ 8.02 (d, 2H), 7.55 (d, 2H), 7.23 (m, 4H), 7.16 (m, 1H), 4.17 (m, 1H), 4.01 (s, 2H), 3.86 (s, 1H), 3.78 (m, 1H), 3.7 (s, 1H), 3.63 (s, 3H), 3.62 (s, 3H), 2.9 (m, 3H), 2.70 (m, 1H), 1.82 (s, 9H), 0.84 (s, 9H), 0.73 (s, 9H); FAB MS $(M + H)^+ = 752$. Anal. ($C_{38}H_{57}N_9O_7$) C, H, N, O.

1-[4-(Diethylamino)phenyl]-2,5-bis{[*N*-(methoxycarbonyl)-L-*tert*-leucinyl]amino}-4(*S*)-hydroxy-6-phenyl-2-azahexane (25g). Preparation from **14g** as described for **25b** (solvent: DMF) yielded 69 g (82%) of **25g**: mp 155 °C; $[\alpha]_D = -54°$ ($c = 0.55$, EtOH); ^{1}H NMR (CD_3OD) δ 7.2 (m, 4H), 7.13 (m, 1H), 7.13 (d, 2H), 6.61 (d, 2H), 4.07 (t, 1H), 3.86 (s, 1H), 3.78 (m, 2H), 3.71 (s, 1H), 3.70 (m, 1H), 3.65 (s, 3H), 3.64 (s, 3H), 3.33 (q, 4H), 2.90 (dd, 1H), 2.84 (dd, 1H), 2.81 (m, 1H), 2.56 (d, 1H), 1.12 (t, 6H), 0.84 (s, 9H), 0.75 (s, 9H); HPLC t_R 11.8 min; FAB MS $(M + H)^+ = 699$. Anal. ($C_{37}H_{58}N_6O_7{\cdot}0.55H_2O$) C, H, N, H_2O.

1-[4-(Pyridin-2-yl)phenyl]-2-{[*N*-(methoxycarbonyl)-L-valinyl]amino}-4(*S*)-hydroxy-5(*S*)-{[*N*-(methoxycarbonyl)-L-isoleucinyl]amino}-6-phenyl-2-azahexane (26b). Preparation as described for **23a** starting from *N*-(methoxycarbonyl)-L-valine[14] and **21b** yielded 465 mg (45%) of **26b**: TLC R_f(ethyl acetate) = 0.4; ^{1}H NMR (CD_3OD) δ 8.58 (d, 1H), 7.88 (m, 3H), 7.82 (d, 1H), 7.51 (d, 2H), 7.34 (m, 1H), 7.21 (m, 4H), 7.13 (m, 1H), 4.15 (m, 1H), 4.04 (d, 1H), 3.92 (d, 1H), 3.84 (d, 1H), 3.74 (m, 1H), 3.63 (m, 4H), 3.61 (s, 3H), 2.92 (dd, 1H), 2.86 (m, 2H), 2.67 (m, 1H), 1.66 (m, 2H), 1.29 (m, 1H), 1.03 (m, 1H), 0.79 (t, 3H), 0.71 (d, 3H), 0.63 (d, 3H), 0.58 (d, 3H); HPLC t_R 11.1 min; FAB MS $(M + H)^+ = 691$. Anal. ($C_{37}H_{50}N_6O_7{\cdot}0.18H_2O$) C, H, N, H_2O.

1-[4-(Pyridin-2-yl)phenyl]-2-{[*N*-(ethoxycarbonyl)-L-valinyl]amino}-4(*S*)-hydroxy-5(*S*)-{[*N*-(methoxycarbonyl)-L-valinyl]amino}-6-phenyl-2-azahexane (27b). Preparation as described for **23b** starting from *N*-(ethoxycarbonyl)-L-valine[17] yielded 310 mg (45%) of **27b**: TLC R_f(ethyl acetate) = 0.33; ^{1}H NMR (CD_3OD) δ 8.59 (d, 1H), 7.87 (m, 3H), 7.82 (d, 1H), 7.50 (d, 2H), 7.34 (m, 1H), 7.21 (m, 4H), 7.13 (m, 1H), 4.14 (m, 1H), 4.03 (m, 3H), 3.93 (d, 1H), 3.79 (d, 1H), 3.75 (m, 1H), 3.64 (d, 1H), 3.63 (s, 3H), 2.92 (dd, 1H), 2.85 (m, 2H), 2.67 (m, 1H), 1.85 (m, 1H), 1.68 (m, 1H), 1.20 (t, 3H), 0.76 (d, 3H), 0.74 (d, 3H), 0.65 (d, 3H), 0.59 (d, 3H); HPLC t_R 11.1 min; FAB MS $(M + H)^+ = 691$. Anal. ($C_{37}H_{50}N_6O_7{\cdot}0.25H_2O$) C, H, N, H_2O.

1-[4-(Thiazol-5-yl)phenyl]-2-{[*N*-(ethoxycarbonyl)-L-valinyl]amino}-4(*S*)-hydroxy-5(*S*)-{[*N*-(methoxycarbonyl)-L-*tert*-leucinyl]amino}-6-phenyl-2-azahexane (28d). Preparation as described for **23a** starting from *N*-(ethoxycarbonyl)-L-valine[17] and **20d** yielded 229 mg (55%) of **28d**: mp 168−169 °C; ^{1}H NMR (CD_3OD) δ 8.97 (s, 1H), 8.15 (s, 1H), 7.60 (d, 2H), 7.47 (d, 2H), 7.22 (m, 4H), 7.15 (m, 1H), 4.15 (m, 1H), 4.06 (q, 2H), 3.96 (m, 2H), 3.87 (s, 1H), 3.77 (m, 1H), 3.65 (s, 3H), 3.62 (m, 1H), 2.9 (m, 3H), 2.69 (m, 1H), 1.70 (m, 1H), 1.21 (t, 3H), 0.82 (s, 9H), 0.68 (d, 3H), 0.62 (d, 3H); HPLC t_R 14.7 min; FAB MS $(M + H)^+ = 711$. Anal. ($C_{36}H_{50}N_6O_7S$) C, H, N, S.

***N*-(Methoxycarbonyl)-L-*tert*-leucine (29).** To a solution of L-*tert*-leucine (1250 g, 9.5 mol) in dioxane (5 L) and 2 N aqueous sodium hydroxide (15.7 L) was added methyl chloroformiate (1470 mL, 18.9 mol) during 1.5 h. Then the clear solution was stirred for 18 h at 60 °C, cooled to r.t., and extracted twice with dichloromethane (15 L). The aqueous phase was acidified by addition of 4 N HCl (8 L, pH ≈ 2) and extracted three times with ethyl acetate (10 L). Drying (Na_2SO_4) of the ethyl acetate layers, concentration in vacuo, stirring in cold hexane (5 L), and filtration afforded 1622 g (90%) **29**: mp 108−109 °C; ^{1}H NMR (CD_3OD) δ 7.00 (d, HN), 4.00 (m, 1H), 3.66 (s, 3H), 1.02 (s, 9H). Anal. ($C_8H_{15}NO_4$) C, H, N, O.

***N*-1-(*tert*-Butyloxycarbonyl)-*N*-2-[*N*-(methoxycarbonyl)-L-*tert*-leucinyl]hydrazine (30).** To **29** (10 g, 52.8 mmol), EDC (11.1 g, 58.1 mmol), and HOBT (7.85 g, 58.1 mmol) in ethyl acetate (130 mL) was added NMM (7.0 mL, 63.7 mmol). After 30 min, *tert*-butyl carbazate (7.69 g, 58.1 mmol) was added, and stirring was continued for 16 h. Then the reaction mixture was diluted with ethyl acetate (0.3 L) and washed with saturated $NaHCO_3$ solution, water, and brine. The inorganic layers were reextracted twice with ethyl acetate; the combined organic phases were dried (Na_2SO_4) and concentrated, yielding 16 g of **30** (≈ quantitative): ^{1}H NMR (CD_3OD) δ 3.98 (s, 1H), 3.66 (s, 3H), 1.47 (s, 9H), 1.03 (s, 9H); FAB MS $(M + H)^+ = 304$.

[*N*-(Methoxycarbonyl)-L-*tert*-leucinyl]hydrazine (31). A solution of **30** (16 g, 52.8 mmol) in 4 N HCl in dioxane (100 mL) was stirred for 18 h at r.t. and then concentrated in vacuo. The residue was diluted with saturated $NaHCO_3$ solution and extracted four times with dichloromethane (800 mL). The organic layers were washed with brine, dried (Na_2SO_4), and concentrated, yielding 6.5 g (60%) of **31**: ^{1}H NMR (CD_3OD) δ 3.89 (s, 1H), 3.65 (s, 3H), 0.98 (s, 9H); FAB MS $(M + H)^+ = 204$.

***N*-1-[*N*-(Methoxycarbonyl)-L-*tert*-leucinyl] *N*-2-[4-(Tetrazol-5-yl)benzylidene] Hydrazone (32).** A solution of 4-(tetrazol-5-yl)benzaldehyde (**6**) (2.57 g, 14.8 mmol) and **31** (3.0 g, 14.8 mmol) in 2-propanol (30 mL) was heated to reflux temperature during 18 h. Addition of water (100 mL) and filtration afforded 4.3 g (80%) of **32**: ^{1}H NMR (CD_3OD) δ 8.23 (s, 1H), 8.1 (m, 2H), 8.0 (m, 2H), 4.08 (s, 1H), 3.68 (s, 3H), 1.06 (s, 9H); FAB MS $(M + H)^+ = 360$.

***N*-1-[*N*-(Methoxycarbonyl)-L-*tert*-leucinyl] *N*-2-[4-(2-*tert*-Butyl-2*H*-tetrazol-5-yl)benzylidene] Hydrazone (33).** In a sealed tube, **32** (3.0 g, 8.34 mmol), toluene (25 mL), methanesulfonic acid (0.08 g, 0.83 mmol), and isobutene (1.2 g) were heated to 110 °C for 1 h. The reaction mixture was cooled to r.t. and then diluted with ethyl acetate and saturated $NaHCO_3$ solution. The aqueous phase was separated and extracted twice with ethyl acetate. The organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Column chromatography (hexane/ethyl acetate, 1:1) gave 2.35 g (68%) of **33**: TLC R_f(hexane/ethyl acetate, 1:1) = 0.22; ^{1}H NMR (CD_3OD) δ 8.21 (s, 1H), 8.17 (m, 2H), 7.94 (m, 2H), 4.07 (m, 1H), 3.68 (s, 3H), 1.82 (s, 9H), 1.08 (s, 9H); FAB MS $(M + H)^+ = 416$.

***N*-1-[*N*-(Methoxycarbonyl)-L-*tert*-leucinyl]-*N*-2-[4-(2-*tert*-butyl-2*H*-tetrazol-5-yl)benzyl]hydrazine (34).** $NaCNBH_3$ (317 mg, 5.05 mmol) was added to **33** (2.0 g, 4.81 mmol) in THF (9 mL); then a solution of p-TsOH (915 mg, 4.81 mmol) in THF (9 mL) was added dropwise. After 18 h, the reaction mixture was diluted with ethyl acetate. The aqueous layer was separated and extracted twice with ethyl acetate. The organic phases were washed with saturated $NaHCO_3$ solution and brine, dried (Na_2SO_4), and concentrated by evaporation. The residue was taken up in water (20 mL) and THF (20 mL), then $K_2B_4O_7 \cdot 4H_2O$ (6.1 g, 20 mmol) was added, and the mixture stirred at r.t. overnight. After dilution with ethyl acetate and saturated $NaHCO_3$ solution, the aqueous phase was separated and extracted twice with ethyl acetate. The organic layers were washed with brine, dried (Na_2SO_4), and concentrated by evaporation. Column chromatography (hexane/ethyl acetate, 1:2) gave 1.17 g (58%) of **34**: TLC R_f-(CH_2Cl_2/methanol, 30:1) = 0.33; ^{1}H NMR (CD_3OD) δ 8.07 (d, 2H), 7.53 (d, 2H), 4.04 (s, 2H), 3.83 (s, 1H), 3.64 (s, 3H), 1.82 (s, 9H), 0.92 (s, 9H); FAB MS $(M + H)^+ = 418$.

1-[4-(2-*tert*-Butyl-2*H*-tetrazol-5-yl)phenyl]-2-{[*N*-(methoxycarbonyl)-L-*tert*-leucinyl]amino}-4(*S*)-hydroxy-5(*S*)-[(*tert*-butyloxycarbonyl)amino]-6-phenyl-2-azahexane (35). A solution of *N*-(*tert*-butyloxycarbonyl)-2(*S*)-amino-1-phenyl-3(*R*)-3,4-epoxybutane (**10**)[6b,12] (737 mg, 2.8 mmol) and **34** (1.17 g, 2.8 mmol) in 2-propanol (15 mL) was heated to reflux temperature during 16 h. Addition of water (100 mL) and filtration gave the crude product. Recrystallization from CH_2Cl_2 by addition of diisopropyl ether/hexane afforded 803 mg (42%) of **35**: TLC R_f(CH_2Cl_2/methanol, 30:1) = 0.34; ^{1}H NMR (CD_3OD) δ 8.01 (d, 2H), 7.55 (d, 2H), 7.23 (m, 4H), 7.15 (m, 1H), 4.00 (s, 2H), 3.74 (m, 2H), 3.68 (s, 1H), 3.59 (s, 3H), 2.8 (m, 4H), 1.80 (s, 9H), 1.30 (s, 9H), 0.72 (s, 9H); FAB MS $(M + H)^+ = 681$.

1-[4-(2-*tert*-Butyl-2*H*-tetrazol-5-yl)phenyl]-2-{[*N*-(methoxycarbonyl)-L-*tert*-leucinyl]amino}-4(*S*)-hydroxy-5(*S*)-amino-6-phenyl-2-azahexane Hydrochloride (36). A suspension of **35** (200 mg, 0.294 mmol) in THF (2.3 mL) and HCl (1.6 mL, 2 N in water) was stirred for 8 h at 50 °C. The resulting solution was concentrated in vacuo. The residue was four times diluted with ethanol and again concentrated, giving 182 mg (quantitative) of **36**: TLC R_f(CH_2Cl_2/methanol/H_2O/CH_3COOH, 170:26:3:1) = 0.28; ^{1}H NMR (CD_3OD) δ 8.03 (d, 2H), 7.50 (d, 2H), 7.32 (m, 5H), 4.18 (d, 1H), 3.92 (d, 1H), 3.80 (m, 1H), 3.68 (s, 1H), 3.58 (s, 3H), 3.58 (m, 1H), 3.2–2.9 (m, 4H), 1.81 (s, 9H), 0.76 (s, 9H); FAB MS $(M + H)^+ = 581$.

Acknowledgment. The authors would like to thank Mr. B. Bohler, Mrs. P. Frei, Mr. G. Goutte, Mr. P. Hauser, Mrs. D. Kempf, Mrs. C. Kowalik, Mrs. C. Sonderegger, and Mr. F. Stauffer for their capable technical assistance in biological testing and Dr. U. Schneider and Mr. W. Salamin for spectral measurements.

References

(1) Kohl, N. E.; Emini, E. A.; Schleif, W. A.; Davis, L. J.; Heimbach, J. C.; Dixon, R. A. F.; Scolnick, E. M.; Sigal, I. S. Active Human Immunodeficiency Virus Protease is Required for Viral Infectivity. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 4686–4690.

(2) (a) Steele, F. R. New Protease Inhibitors, with Combination Drug Therapy, and Early Intervention to Reduce 'Viral Load' Show Real Promise in Treating AIDS. *Nature Med.* **1996**, *2*, 257–258. (b) Deeks, St. G.; Smith, M.; Holodniy, M.; Kahn, J. O. HIV-1 Protease Inhibitors: A Review for Clinicians. *J. Am. Med. Assoc.* (*U.S.*) **1997**, *277*, 145–153. (c) Phillips, K. D. Protease Inhibitors: A New Weapon and a New Strategy Against HIV. *J. Assoc. Nurses AIDS Care* **1996**, *7*, 57–71. (d) Boudes, P.; Geiger, J.-M. Les inhibiteurs de la protéase du VIH: revue générale. *Thèrapie* (*France*) **1996**, *51*, 319–325.

(3) For recent reviews, see: (a) Chrusciel, R. A.; Romines, K. R. Recent developments in HIV protease inhibitor research. *Exp. Opin. Ther. Patents* **1997**, *7*, 111–121. (b) Vacca, J. P.; Condra, J. H. Clinically effective HIV-1 protease inhibitors. *Drug Discovery Today* **1997**, *2*, 261–272. (c) Chong, K. T. Recent Advances in HIV-1 Protease Inhibitors. *Exp. Opin. Invest. Drugs* **1996**, *5*, 115–124. (d) Kempf, D. J.; Sham, H. L. HIV Protease Inhibitors. *Curr. Pharm. Des.* **1996**, *2*, 225–246. (e) Mansour, T. S. Emerging Anti-HIV Agents and Targets. *Exp. Opin. Ther. Patents* **1996**, *6*, 137–159. (f) Martin, J. A.; Redshaw, S.; Thomas, G. J. Inhibitors of HIV Proteinase. *Prog. Med. Chem.* **1995**, *32*, 239–287. (g) West, M. L.; Fairlie, D. P. Targeting HIV-1 Protease; a Test of Drug-design Methodologies. *Trends Pharmacol. Sci.* **1995**, *16*, 67–75. (h) De Clercq, E. Toward Improved Anti-HIV Chemotherapy: Therapeutic Strategies for Intervention with HIV Infections. *J. Med. Chem.* **1995**, *38*, 2491–2517. (i) Darke, P. L.; Huff, J. R. HIV Protease as an Inhibitor Target for the Treatment of AIDS. *Adv. Pharmacol.* **1994**, *25*, 399–454. (j) De Lucca, G. V.; Erickson-Viitanen, S.; Lam, P. Y. S. Cyclic HIV Protease Inhibitors Capable of Displacing the Active Site Structural Water Molecule. *Drug Discovery Today* **1997**, *2*, 6–18.

(4) (a) Zurer, P. Protease Inhibitors: Studies Probe HIV Resistance to Drugs. *Chem. Eng. News* **1996**, 6. (b) Mayers, D. L. Prevalence and Incidence of Resistance to Zidovudine and Other Antiretroviral Drugs. *Am. J. Med.* **1997**, *102*, 70–75.

(5) (a) Navia, M. A.; Fitzgerald, P. M. D.; McKeever, B. M.; Leu, C.-T.; Heimbach, J. C.; Herber, W. K.; Sigal, I. S.; Darke, P. L.; Springer, J. P. Three-dimensional Structure of Aspartyl Protease from Human Immunodeficiency Virus HIV-1. *Nature* **1989**, *337*, 615–620. (b) Wlodawer, A.; Miller, M.; Jaskólski, M.; Sathyanarayana, B. K.; Baldwin, E.; Weber, I. T.; Selk, L. M.; Clawson, L.; Schneider, J.; Kent, St. B. H. Conserved Folding in Retroviral Proteases: Crystal Structure of a Synthetic HIV-1 Protease. *Science* **1989**, *245*, 616–621. (c) Lapatto, R.; Blundell, T.; Hemmings, A.; Overington, J.; Wilderspin, A.; Wood, St.; Merson, J. R.; Whittle, P. J.; Danley, D. E.; Geoghegan, K. F.; Hawrylik, St. J.; Lee, S. E.; Scheld, K. G.; Hobart, P. M. X-ray Analysis of HIV-1 Proteinase at 2.7 Å Resolution Confirms Structural Homology among Retroviral Enzymes. *Nature* **1989**, *342*, 299–302.

(6) (a) Fässler, A.; Bold, G.; Lang, M.; Schneider, P. Pharmakologisch wirksame Hydrazinderivate und Verfahren zu deren Herstellung. EP-521827-A1, priority date July 3, 1991; publication date Jan 7, 1993. (b) Fässler, A.; Rösel, J.; Grütter, M.; Tintelnot-Blomley, M.; Alteri, E.; Bold, G.; Lang, M. Novel Pseudosymmetric Inhibitors of HIV-1 Protease. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2837–2842. (c) Sham. H. L.; Zhao, Ch.; Marsh, K. C.; Betebenner, D. A.; Lin, S.; McDonald, E.; Vasavanonda, S.; Wideburg, N.; Saldivar, A.; Robins, T.; Kempf, D. J.; Plattner, J. J.; Norbeck, D. W. Potent Inhibitors of the HIV-1 Protease with Good Oral Bioavailabilities. *Biochem. Biophys. Res. Commun.* **1995**, *211*, 159–165. (d) Grobelny, D.; Chen, Q.; Tyssen, D.; Tachedjian, G.; Sebire, K.; Buchanan, L.; Birch, C. Antiviral activity of DG-35-VIII, a potent inhibitor of the protease of human immunodeficiency virus. *Antiviral Chem. Chemother.* **1997**, *8*, 99–106.

(7) Fässler, A.; Bold, G.; Capraro, H.-G.; Cozens, R.; Mestan, J.; Poncioni, B.; Rösel, J.; Tintelnot-Blomley, M.; Lang, M. Aza-Peptide Analogues as Potent Human Immunodeficiency Virus Type-1 Protease Inhibitors with Oral Bioavailability. *J. Med. Chem.* **1996**, *39*, 3203–3216.

(8) Priestle, J. P.; Fässler, A.; Rösel, J.; Tintelnot-Blomley, M.; Strop, P.; Grütter, M. G. Comparative Analysis of the X-ray Structures of HIV-1 and HIV-2 Proteases in Complex with CGP 53820, a Novel Pseudosymmetric Inhibitor. *Structure* **1995**, *3*, 381–389.

(9) Creary, X.; Aldridge, T. Variable Electronic Properties of the $CSNMe_2$ Group. *J. Org. Chem.* **1991**, *56*, 4280–4285.

(10) Rutjes, F. P. J. T.; Teerhuis, N. M.; Hiemstra, H.; Speckamp, W. N. Synthesis of Cyclic α-Hydrazino Acid Derivatives via *N*-Acylhydrazonium Ions. *Tetrahedron* **1993**, *49*, 8605−8628.

(11) Hydrogenation of **8e** in the presence of Pd/C led to partial hydrogenolytical cleavage of the tetrazole ring, yielding *N*-1-(*tert*-butyloxycarbonyl)-*N*-2-(4-methylbenzyl)hydrazine. However, hydrogenation with Lindlar's catalyst gave pure **9e**.

(12) Thompson, W. J.; Fitzgerald, P. M. D.; Holloway, M. K.; Emini, E. A.; Darke, P. L.; McKeever, B. M.; Schleif, W. A.; Quintero, J. C.; Zugay, J. A.; Tucker, T. J.; Schwering, J. E.; Homnick, C. F.; Nunberg, J.; Springer, J. P.; Huff, J. R. Synthesis and Antiviral Activity of a Series of HIV-1 Protease Inhibitors with Functionality Tethered to the P_1 or P_1' Phenyl Substituents: X-ray Crystal Structure Assisted Design. *J. Med. Chem.* **1992**, *35*, 1685−1701.

(13) Luly, J. R.; Dellaria, J. F.; Plattner, J. J.; Soderquist, J. L.; Yi, N. A Synthesis of Protected Aminoalkyl Epoxides from α-Amino Acids. *J. Org. Chem.* **1987**, *52*, 1487−1492.

(14) Irie, H.; Nakanishi, H.; Fujii, N.; Mizuno, Y.; Fushimi, T.; Funakoshi, S.; Yajima, H. Validity of Methoxycarbonyl as an *N*-Protecting Group in Peptide Synthesis: New Synthesis of MSH-Release Inhibiting Factor. *Chem. Lett.* **1980**, 705−708.

(15) (a) Jadhav, P. K.; Ala, P.; Woerner, F. J.; Chang, C.-H.; Garber, S. S.; Anton, E. D.; Bacheler, L. T. Cyclic Urea Amides: HIV-1 Protease Inhibitors with Low Nanomolar Potency against both Wild-Type and Protease Inhibitor Resistant Mutants of HIV. *J. Med. Chem.* **1997**, *40*, 181−191. (b) Ala, P. J.; Huston, E. E.; Klabe, R. M.; McCabe, D. D.; Duke, J. L.; Rizzo, C. J.; Korant, B. D.; DeLoskey, R. J.; Lam, P. Y. S.; Hodge, C. N.; Chang, C.-H. Molecular Basis of HIV-1 Protease Drug Resistance: Structural Analysis of Mutant Proteases Complexed with Cyclic Urea Inhibitors. *Biochemistry* **1997**, *36*, 1573−1580.

(16) (a) Capraro, H.-G.; Bold, G.; Fässler, A.; Cozens, R.; Klimkait, Th.; Lazdins, J.; Mestan, J.; Poncioni, B.; Rösel, J. L.; Stover, D.; Lang, M. Synthesis of Potent and Orally Active HIV-Protease Inhibitors. *Arch. Pharm., Pharm. Med. Chem.* **1996**, *329*, 273−278. (b) Cozens, R. M.; Bold, G.; Capraro, H.-G.; Fässler, A.; Mestan, J.; Lang, M.; Poncioni, B.; Stover, D.; Rösel, J. L. Synthesis and pharmacological evaluation of CGP 57813 and CGP 61755, HIV-1 protease inhibitors from the Phe-c-Phe dipetidomimetic class. *Antiviral Chem. Chemother.* **1996**, *7*, 294−299.

(17) Langer, K.; Mattay, J. Stereoselective Intramolecular Copper(I)-Catalyzed [2+2]-Photocycloadditions. Enantioselective Synthesis of (+)- and (−)-Grandisol. *J. Org. Chem.* **1995**, *60*, 7256−7266.

JM970873C