HIV-1 Protease Inhibitors Based on Hydroxyethylene Dipeptide Isosteres: An Investigation into the Role of the P_1' Side Chain on Structure-Activity

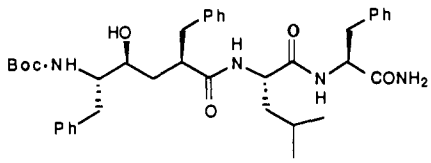
Steven D. Young,*,† Linda S. Payne,† Wayne J. Thompson,† Neil Gaffin,† Terry A. Lyle,† Susan F. Britcher,† Samuel L. Graham,† Thomas H. Schultz,† Albert A. Deana,† Paul L. Darke,‡ Joan Zugay,‡ William A. Schleif,§ Julio C. Quintero,§ Emilio A. Emini,§ Paul S. Anderson,† and Joel R. Huff†

Departments of Medicinal Chemistry, Molecular Biology, and Virus and Cell Biology, Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486. *Received November 5, 1991*

A systematic investigation was undertaken to determine the role of the P_1' sidechain in a series of hydroxyethylene isostere based inhibitors of HIV-1 protease. Substitution and homologation of the benzyl P_1' side chain of the Phe-Phe isostere based pseudo peptides 1 (L-682,679) and 2 (L-685,434) with various heteroalkyl groups leads to a series of extremely potent inhibitors of the enzyme. Several examples of the most potent inhibitors were very effective in an ex vivo cell based viral spread assay using human H9 T-lymphocytes and the IIIb isolate of HIV-1. Compound 19 is 120 times more potent than 1 and 16 times more potent than 2 in inhibiting the spread of infection in this assay.

The virally encoded protease from human immunodeficiency virus-1 (HIVP-1) has become a target for chemotherapeutic intervention in the treatment of AIDS.[1] HIVP was identified as a homodimeric endopeptidase of the aspartyl proteinase family, with each monomer contributing one of the two catalytic Asp-Thr-Gly triads.[2] HIVP functions as a post-translational processing enzyme, serving to cleave the large $p160^{gag\text{-}pol}$ polyprotein into the enzymes integrase, reverse transcriptase, protease itself, along with the *gag* gene 55 kDa polyprotein.[3] The p55 polyprotein is further processed by HIVP into the structural proteins p17, p24, p7, and p6.[4] Preparation of HIVP containing the point mutation Asp^{25} to Asn^{25} by recombinant methods results in an enzyme devoid of catalytic activity. Incorporation of this mutant enzyme into proviral DNA and subsequent transfection into human colon carcinoma cells produces incompetent virons which contain unprocessed proteins. These virons were shown to be incapable of infecting MT-4 cells.[5] We[6] and others[7] have established that inhibition of HIVP by pseudopeptides containing a transition-state mimic of the scissile bond is effective in inhibiting the spread of viral infection through a tissue culture of human T-lymphocytes. Further, infected cells exposed to HIVP inhibitors have been shown to accumulate high concentrations of unprocessed p55 with an associated reduction in the concentration of the cleavage proteins.[6a]

The lead compound for our entry into the development of HIVP inhibitors is the pseudo pentapeptide 1, a truncated analogue of a previously prepared renin inhibitor.[6b,8] Early work directed toward finding replacements for the two C-terminal amino acid residues has shown that 2-amino-3-hydroxyindan is an effective substitute for the Leu-Phe-NH_2 portion of 1. Compound 2 retains the intrinsic potency of 1 and has much improved activity in a viral spread assay.[6c] Concurrent with this work we sought to examine the replacement and substitution of the P_1' Phe side chain (residue nomenclature of Schechter and Berger[9]) of our hydroxyethylene isostere with groups which might lend enhanced potency and solubility to the molecule.



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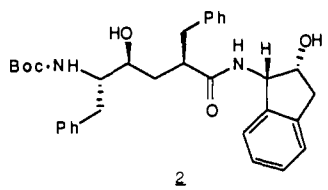

2
(L-685,434)

† Department of Medicinal Chemistry.
‡ Department of Molecular Biology.
§ Department of Virus and Cell Biology.

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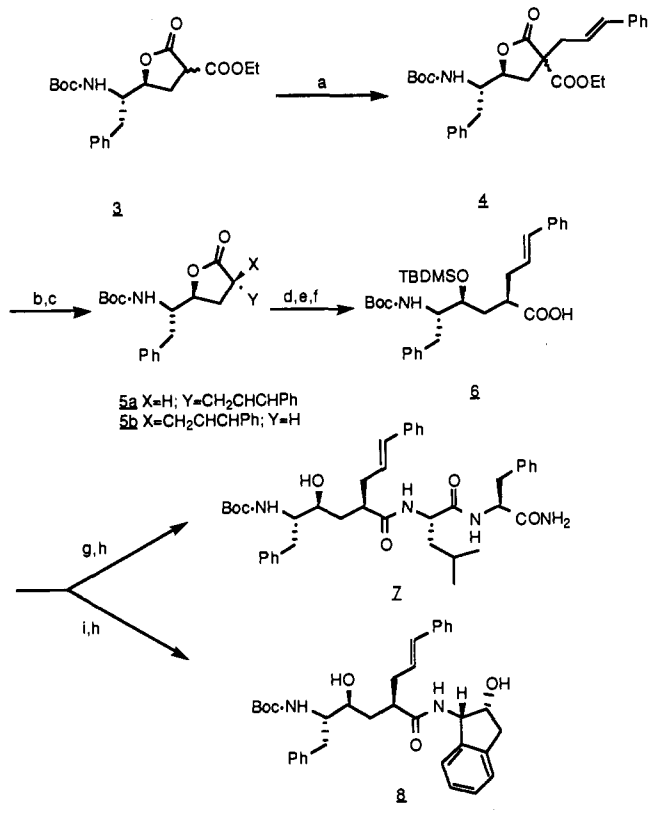
In this paper we describe modifications to the P_1' side chain in both series of molecules, ie., **1** and **2**, differing in the C-terminal amino acid residue(s). Once it was established that the enzyme would tolerate P_1' side chains not related to natural amino acids, the emphasis of the work concentrated on modifications that would improve cell penetration. Overall, it was felt that improvements in solubility, coupled with increased intrinsic potency, would result in compounds greater potency in the cell-based viral spread assay.

Results and Discussion

Synthesis. All compounds prepared here were synthesized from carboxy-lactone **3**, an intermediate described by Evans et al.[8] This intermediate proved particularly useful in the introduction of a wide variety of side-chain functional groups. The general strategy for elaboration of the alkylated material **4** into the final products is consistent with the methodology used in the preparation of compounds **1** and **2**. The diastereomeric esters **4** were hydrolyzed and thermally decarboxylated to give a mixture of lactones **5a,b** which could be separated chromatographically. The undesired lactone **5b** could often be recycled by equilibration with base followed again by chromatographic separation. The lactone **5a** was then hydrolyzed, silylated, and partially deprotected to give the general intermediate, γ-silyloxy acid **6**. The final products **7** and **8** were obtained by coupling silyloxy acid **6** with the appropriate C-terminus using EDC–HOBt coupling conditions and then unmasking the hydroxyl group by treatment with tetrabutylammonium fluoride in THF (Scheme I).

Scheme I[a]



[a] (a) $PhCH{=}CHCH_2Br$/NaOEt/EtOH, RT. (b) 1 M LiOH/DME, RT, 18 h; and then 10% aqueous citric acid. (c) $PhCH_3$, reflux, 24 h; and then chromatography on silica gel. (d) 1 M LiOH/DME, RT, 3 h. (e) *tert*-Butyldimethylsilyl chloride, imidazole, DMF, RT, 18 h. (f) MeOH, RT, 4 h. (g) EDC·HCl, HOBt, H_2N-Leu-Phe-NH_2, Et_3N, DMF, RT, 24 h. (h) 1 M tetrabutylammonium fluoride in THF, RT, 18 h. (i) EDC·HCl, HOBt, 2-(*S*)-amino-3(*R*)-hydroxyindan, Et_3N, DMF, RT, 24 h.

p-Aminoalkyl derivatives of compound **2** required manipulation of the alkylated lactone **5a** prior to elaboration to the coupled product **8**. The general strategy is shown in Scheme II. A suitable 4-(hydroxyalkyl)benzyl alcohol[10] was converted into the benzyl bromide with anhydrous hydrogen bromide in ether. These bromides were used to prepare the desired lactone **14** in the usual manner. At this point, the primary carbinol was oxidized to the aldehyde and protected as the dimethyl acetal. The acetal was then transformed as before to the silyloxy amide **15** whereupon the aldehyde functionality was unmasked and reductively aminated with the appropriate amine. The amine obtained in this manner was desilylated as above to give the desired product **16**. Compound **16** was subsequently treated with methyl iodide to give quaternary ammonium salt **17**.

Synthesis of the 4-hydroxyalkyl- and 4-alkoxyalkyl-substituted derivatives of compound **2** required minor modification to the general synthesis. Alkylation product **14** (see Scheme II) was hydrolyzed with lithium hydroxide and silylated with an excess of silyl chloride. Treatment of the bis(silyloxy) ester with methanol gave the bissilyl acid **18**. The usual coupling procedure followed by desilylation with tetrabutylammonium fluoride gave the 4-hydroxypropyl compound **19**. Compound **19** was selec-

(7) (a) Meek, T. D.; Lambert, D. M.; Carr, T. J.; Tomaszek, T. A., Jr.; Moore, M. L.; Strickler, J. E.; Debouck, C.; Hyland, L. J.; Matthews, T. J.; Metcalf, B. W.; Petteway, S. R. Inhibition of HIV-1 Protease in Infected T-lymphocytes by Synthetic Peptide Analogues. *Nature* **1990**, *343*, 90–92. (b) McQuade, T. J.; Tomasselli, A. G.; Liu, L.; Karacostas, V.; Moss, B.; Sawyer, T. K.; Heinrikson, R. L.; Tarpley, W. G. A Synthetic HIV-1 Protease Inhibitor with Antiviral Activity Arrests HIV-Like Particle Maturation. *Science* **1990**, *247*, 454–410. (c) Roberts, N. A.; Martin, J. A.; Kinchington, D.; Broadhurst, A. V.; Craig, J. C.; Duncan, I. B.; Galpin, S. A.; Handa, B. K.; Kay, J.; Krohn, A.; Lambert, R. W.; Merrett, J. H.; Mills, J. S.; Parkes, K. E. B.; Redshaw, S.; Ritchie, A. J.; Taylor, D. L.; Thomas, G. J.; Machin, P. J. Rational Design of Peptide-Based HIV Proteinase Inhibitors. *Science* **1990**, *248*, 358–361. (d) Tomasselli, A. G.; Olsen, M. K.; Hui, J. O.; Staples, D. J.; Sawyer, T. K.; Heinrikson, R. L.; Tomich, C.-H. C. Substrate Analogue Inhibition and Active Site Titration of Purified Recombinant HIV-1 Protease. *Biochemistry* **1990**, *29*, 264–269. (e) Dreyer, G. B.; Metcalf, B. W.; Tomaszek, T. A.; Carr, T. J.; Chandler, A. C. III; Hyland, L.; Fakhoury, S. A.; Magaard, V. W.; Moore, M. L.; Strickler, J. A.; Debouck, C.; Meek, T. D. Inhibition of Human Immunodeficiency Virus 1 Protease In Vitro: Rational Design of Substrate Analogue Inhibitors. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 9752–9756. (f) Rich, D. H.; Green, J.; Toth, M. V.; Marshall, G. R.; Kent, S. B. H. Hydroxyethylamine Analogues of the p17/p24 Substrate Cleavage Site Are Tight-Binding Inhibitors of HIV Protease. *J. Med. Chem.* **1990**, *33*, 1285–1288. (g) Grobelny, D.; Wondrak, E. M.; Galardy, R. E.; Oroszlan, S. Selective Phosphinate Transition-State Analogue Inhibitors of the Protease of Human Immunodeficiency Virus. *Biochem. Biophys. Res. Commun.* **1990**, *169*, 1111–1116.

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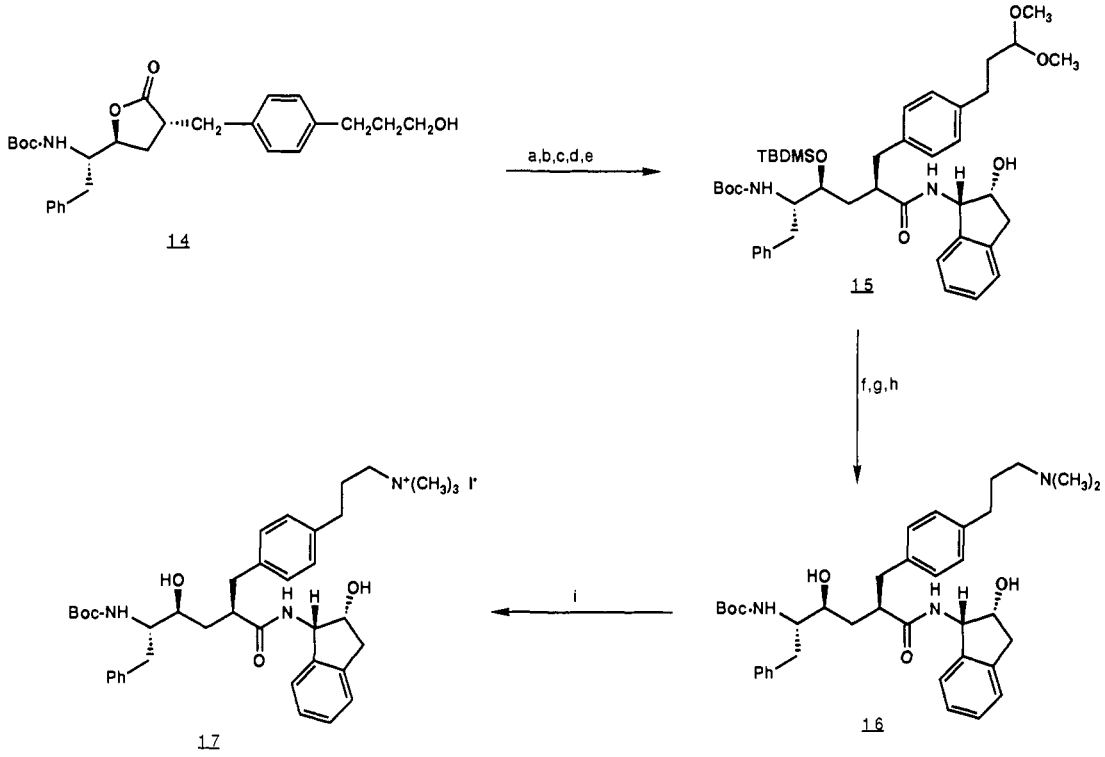
(10) Matsuoka, T.; Negi, T.; Otsubo, T.; Sakata, Y.; Misumi, S. Layered Compounds. V. Synthesis and Properties of [m.n] Paracyclophadiynes. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 1825–1833.

Scheme II[a]



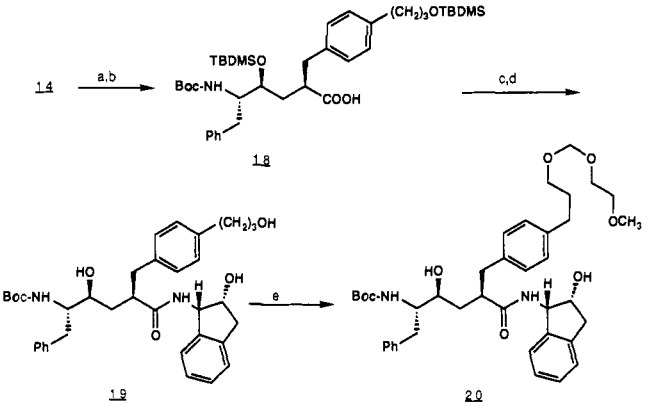
[a] (a) SO_3·Pyr, Et_3N, DMSO, 0 °C. (b) $HC(OMe)_3$, MeOH, pTSA, RT. (c) 1 M LiOH, DME, RT, 3 h. (d) *tert*-Butyldimethylsilyl chloride, imidazole, DMF, RT, 18 h; and then MeOH, RT, 5 h. (e) EDC·HCl, HOBt, 2(*S*)-amino-3(*R*)-hydroxyindan, Et_3N, DMF, RT, 24 h. (f) acetone, H_2O, PPTS, reflux, 4 h. (g) Me_2NH, MeOH, Al–Hg, RT, 18 h. (h) 1 M tetrabutylammonium fluoride in THF, RT, 24 h. (i) MeI, MeOH, RT, 24 h.

tively alkylated on the primary hydroxyl group to give ether **20** using a single equivalent of alkylating agent (Scheme III).

Preparation of the 3-(4-hydroxyphenyl)-2-propenyl and 3-[4-[2-(4-morpholino)ethoxy]phenyl]-2-propenyl compounds **24** and **25** required the preparation of the cinnamyl bromide **23**. Trans 4-hydroxycinnamic acid **21**, was bissiylated with *tert*-butyldimethylsilyl chloride then reduced with Dibal-H in ether to the cinnamyl alcohol **22**. Treatment of **22** with phosphorous tribromide in ether at 0 °C gave the unstable bromide **23**, which was used without purification. The reactive bromide was used in the same sequence of reactions outlined in Scheme I, to produce **24**. Further alkylation of **24** with (2-chloroethyl)morpholine[11] gave the potent inhibitor **25** (Scheme IV).

Enzyme Inhibition Activity. Measurement of inhibitory potency was carried out as described by Darke et al.[12] Briefly, a peptide substrate H_2N-Val-Ser-Asn-(β-naphthylalanine)-Pro-Ile-Val-OH in pH 5.5 buffer is incubated with enzyme and BSA along with the inhibitor at 30 °C. The reaction is quenched with H_3PO_4 and the products are analyzed by HPLC at 225 nm. The reaction is run only to 10% completion to insure linearity. The HPLC determination of product can detect 20 pmol of product as a 10:1 signal to noise ratio. IC_{50} values reported are the concentration of compound required to halve the amount of substrate cleaved during the allotted reaction period. The results of these measurements are shown in Tables I and II.

Scheme III[a]



[a] (a) 1 M LiOH, DME, RT, 3 h. (b) *tert*-Butyldimethylsilyl chloride, imidazole, DMF, RT, 18 h; and then MeOH, RT, 5 h. (c) EDC·HCl, HOBt, 2(*S*)-amino-3(*R*)-hydroxyindan, Et_3N, DMF, RT, 24 h. (d) 1 M tetrabutylammonium fluoride in THF, 24 h. (e) MEMCl, $(i\text{-Pr})_2NEt$, CH_2Cl_2, RT, 24 h.

Our initial modification of the P_1' side chain was conducted with the pseudo pentapeptide inhibitor **1**. Replacement of the phenyl ring with the more sterically demanding naphthyl group, compound **9**, led to a 3-fold decrease in potency. Biphenyl **12** is equipotent with **1**, suggesting that the enzymatic cleft is tolerant of linearly extended side chains. This idea was explored further by preparing the *trans*-cinnamyl inhibitor **7** and its saturated

(11) Thompson, W. J.; Fitzgerald, P. M. D.; Holloway, M. K.; Emini, E. A.; Darke, P. L.; Tucker, T. J.; Schwering, J. E.; Schleif, W. A.; Quintero, J. C.; Nunberg, J.; Zugay, J. A.; Homnick, C. F.; Springer, J. P.; Huff, J. R. Synthesis and Antiviral Activity of a Series of HIV-1 Protease Inhibitors With Functionality Tethered to The P1 or P1′ Binding Pockets: X-ray Crystal Structure Assisted Design. *J. Med. Chem.*, preceding paper in this issue.

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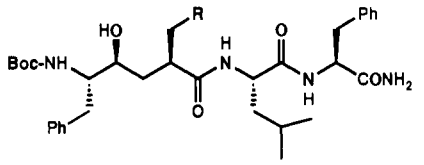
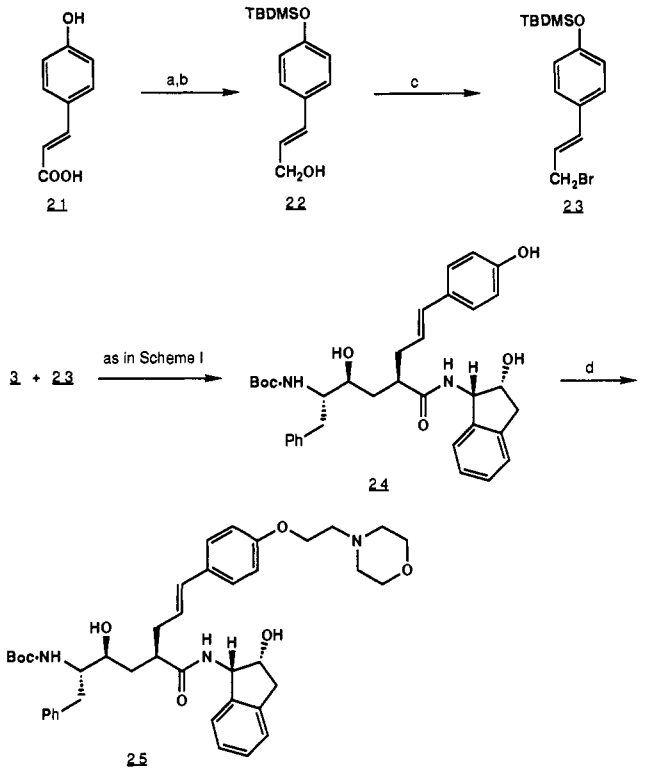
Table I. P_1' Modifications to Pseudo Pentapeptide 1



no.	R	IC_{50}, nM	MIC_{100}, nM	mp, °C	formula[a]
1 (L-682,679)	Ph	0.42	3000	218–219	$C_{39}H_{52}N_4O_6$
7	CHCHPh (*trans*)	0.23	6000	208–211	$C_{41}H_{54}N_4O_6$
9	1-naphthyl	1.20	not tested	215–217	$C_{43}H_{54}N_4O_6$
10	H	6.00	not tested	223–225	$C_{33}H_{48}N_4O_6$
11	CH_2CH_2Ph	0.36	not tested	206–208	$C_{41}H_{56}N_4O_6$
12	4-biphenyl	0.43	not tested	239–240	$C_{45}H_{56}N_4O_6$

[a] Satisfactory analyses (C, H, and N; ±0.4% of theoretical value) were obtained for all compounds.

Scheme IV[a]



[a] (a) *tert*-Butyldimethylsilyl chloride, imidazole, DMF, RT. (b) Dibal-H, Et_2O, 0 °C, 1 h. (c) PBr_3, Et_2O, 0 °C, 20 min. (d) $O(CH_2CH_2)_2NCH_2CH_2Cl$, Cs_2CO_3, dioxane, 95 °C, 18 h.

counterpart **11**. The olefin **7** is 2-fold more potent than the parent benzyl compound **1**. The saturated analogue **11** is slightly less potent, perhaps a result of the greater number of rotational degrees of freedom in the aliphatic methylene chain. A single compound in this series with an attenuated side chain, methyl analogue **10**, shows a substantial loss in potency. The reduced activity of **10** is indicative of the importance of a larger hydrophobic interaction in the P_1' cleft.

Further exploration in the pseudo pentapeptide series was limited due to the poor potency in cells coupled with the general problems of oral absorption of small peptides.[6b,13] The incorporation of the P_2' amino acid residue surrogate 2(*S*)-amino-3(*R*)-hydroxyindan in lieu of the P_2' and P_3' amino acids gives inhibitors of lower molecular weight and similar intrinsic in vitro potency.[6c] Continued development of P_1'-modified inhibitors focused on compounds incorporating this indane. Entries **8**, **24**, and **25** in Table II show conservation of the trend observed with the analogues of **1**: extending the aromatic ring by two additional carbons gives compounds with equivalent inhibitory potency. Substitution of the P_1' phenyl ring with halogen reduces the potency, more markedly so with the bulkier iodine atom (**26** and **27**). Nitro and amino substitution as well as addition of simple aliphatic groups change the potency little (**28–32**). Perfluorination of the P_1' phenyl does reduce potency by a factor of 2–3, but the compound still retains subnanomolar activity. Methylthio derivatives **34–36** were similar in activity to the parent **2**. A trend begins to appear with hydroxylated compounds **37–40** and **19**. Hydroxyl and hydroxyalkyl groups in the four position of the ring result in an increase in inhibitory activity. Hydroxypropyl compound **19** has an IC_{50} = 0.1 nM and is among the most potent inhibitors of HIV-1 protease prepared in the hydroxyethylene isostere series. A possible explanation for this boost in inhibitory activity can be found by looking at the orientation of hydroxyethylene transition state mimic based inhibitors bound in the crystalline enzyme.[11,14] The P_1' side chain lies along a cleft formed by the two monomeric halves. The distal end of the side chain lies close to the solvent-accessible surface of the enzyme. An appropriate functional group linked to the hydrophobic P_1' phenyl ring can provide a favorable hydrophilic interaction with the solvent water molecules at the surface of the enzyme. Inhibitors with nonpolar lipophilic groups in this position do not lend such a stabilization to the enzyme–inhibitor complex. Functionalization of the hydroxyl as a MEM ether leads to compounds **20** and **41**, which retain the high potency of the parent. Modification of the hydroxyl into an amine (compound **16**) results in a loss of potency. This loss extends to compound **17**, even though the quaternary salt should interact well with the solvent. Finally, heterocyclic substitution for the benzene ring is acceptable to the enzyme, e.g., quinoxaline **51**, however, simple aliphatic replacement (compounds **48–50**) is not well tolerated.

Antiviral Activity. Selected compounds in Tables I and II were tested in a viral spread assay which has been described earlier in detail.[6a] Essentially this assay determines the minimum concentration of an inhibitor required

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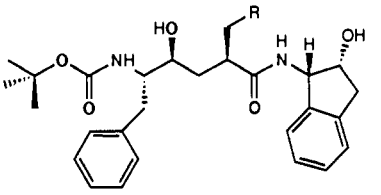
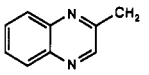
Table II. P_1' Modifications to Pseudo Tetrapeptide 2



no.	R	IC_{50}, nM	MIC_{100}, nM	mp, °C	formula[a]
2 (L-685,434)	Ph	0.23	400	210–212	$C_{33}H_{40}N_2O_5$
8	*trans*-PhCH=CH	0.23	400	205–207	$C_{35}H_{42}N_2O_6$
24	*trans*-4-HOC_6H_4CH=CH	0.17	200	233–234	$C_{35}H_{42}N_2O_6$
25	4-$(O(CH_2CH_2)_2NCH_2CH_2)C_6H_4CH$=CH	0.29	50	178–179	$C_{41}H_{53}N_3O_7$
26	4-FC_6H_4	0.44	not tested	188–191	$C_{33}H_{39}N_2O_5F$
27	4-IC_6H_4	0.72	not tested	233–234	$C_{33}H_{39}N_2O_5I$
28	4-$NO_2C_6H_4$	0.27	not tested	246–248	$C_{33}H_{39}N_3O_7$
29	4-$NH_2C_6H_4$	0.31	200	207–208	$C_{33}H_{41}N_3O_5$
30	4-$CH_3C_6H_4$	0.29	200	198–200	$C_{34}H_{42}N_2O_5$
31	4-*t*-BuC_6H_4	0.27	200	187–189	$C_{37}H_{48}N_2O_5$
32	4-$CF_3C_6H_4$	0.26	not tested	243–245	$C_{34}H_{39}N_2O_5F_3$
33	2,3,4,5,6-F_5C_6Ph	0.60	not tested	228–230	$C_{33}H_{35}N_2O_5F_5$
34	4-$(CH_3S)C_6H_4$	0.22	not tested	222–224	$C_{34}H_{42}N_2O_5S$
35	4-$CH_3S(O)C_6H_4$	0.51	not tested	219–221	$C_{34}H_{42}N_2O_6S$
36	4-$CH_3S(O)_2C_6H_4$	0.17	not tested	236–237	$C_{34}H_{42}N_2O_7S$
37	3-HOC_6H_4	0.21	not tested	208–210	$C_{33}H_{40}N_2O_6$
38	4-HOC_6H_4	0.16	25–50	218–219	$C_{33}H_{40}N_2O_6$
39	4-$(HOCH_2)C_6H_4$	0.17	not tested	217–218	$C_{34}H_{42}N_2O_6$
40	4-(HO-$CH_2CH_2C_6H_4$)	0.16	50	221–222	$C_{35}H_{44}N_2O_6$
19 (L-693,549)	4-(HO-$CH_2CH_2CH_2)C_6H_4$	0.10	25–50	190–192	$C_{36}H_{46}N_2O_6$
41	4-$(CH_3OCH_2CH_2OCH_2OCH_2CH_2)C_6H_4$	0.13	100	172–173	$C_{39}H_{52}N_2O_8$
20	4-$(CH_3OCH_2CH_2OCH_2O(CH_2)_3)C_6H_4$	0.07	50	176–177	$C_{40}H_{54}N_2O_8$
42	4-$(CH_3O)_2CH_2CH_2CH_2C_6H_4$	0.08	not tested	213–214	$C_{38}H_{50}N_2O_7$
43	4-$(O(CH_2CH_2)_2NCH_2CH_2CH_2)C_6H_4$	0.43	200	171–173	$C_{40}H_{53}N_3O_6$
44	4-$((CH_3OCH_2CH_2)_2N(CH_2)_3)C_6H_4$	0.59	200	157–159	$C_{42}H_{59}N_3O_7$
45	4-$(S(CH_2CH_2)_2NCH_2CH_2CH_2)C_6H_4$	1.00	not tested	169–171	$C_{40}H_{53}N_3O_5S$
16	4-$((CH_3)_2NCH_2CH_2CH_2)C_6H_4$	0.60	not tested	204–206	$C_{38}H_{51}N_3O_5$
46	4-$((CH_3)_2NCH_2)C_6H_4$	1.40	not tested	155–159[b]	$C_{36}H_{47}N_3O_5$
47	4-$(O(CH_2CH_2)_2NCH_2)C_6H_4$	1.15	100	104–106[b]	$C_{38}H_{49}N_3O_6$
17	4-$(I^-(CH_3)_3N^+CH_2CH_2CH_2)C_6H_4$	0.91	100	amorphous	$C_{39}H_{54}N_3O_5I$
48	$CH_3(CH_2)_{13}$	>3000	not tested	176–177	$C_{42}H_{66}N_2O_5$
49	CH_3	34.7	not tested	198–200	$C_{28}H_{38}N_2O_5$
50	H	62.7	not tested	198–199	$C_{27}H_{36}N_2O_5$
51		0.17	not tested	233–234	$C_{35}H_{40}N_4O_5$

[a] Satisfactory analyses (C, H, and N; ±0.4% of theoretical value) were obtained for all compounds. [b] Maleate salt.

to completely prevent the spread of infection of virus through a culture of T-cells. The value is reported as a MIC_{100}, in nM. Human H9 T-lymphoid cells are acutely infected with the HIV-1_{iiib} isolate at a multiplicity of infection of 0.01. Compounds are added at the time of infection as a DMSO solution. Fresh compound is added at 2–3-day intervals at which time the culture is sampled. Fifty percent of the culture medium is replaced at each sampling. The spread of infection is monitored by indirect immunofluorescence at 14 days, using anti-HIV-1 human serum as the primary antibody.

It is apparent from Table I that inhibitors containing the two amino acid residues Leu-Phe-NH_2 are not very potent as antiviral agents. In all cases tested, the smaller pseudo tetrapeptide inhibitors from Table II were substantially more potent than the lead compound 1. It is generally true that the more potent enzyme inhibitors like compound **19** were the more effective antiviral agents. However, addition of a basic amine to the side chain, as in compound **47**, results in antiviral activity somewhat better than would be predicted from an IC_{50} of 1.15 nM. This result is a trend for HIV protease inhibitors of this series which contain basic substituents.[6b,11] Freely water-soluble quaternary salt **17** was also effective as an inhibitor of virus spread, indicating that this obligate positively charged inhibitor is transported through the cell membrane. These compounds do not appear to be cytotoxic to H9 cells at the limit of their aqueous solubility. No gross morphological changes in the cells were observed with doses of these compounds effective in inhibiting virus spread.

Conclusions

Modifications to the P_1' side chain of hydroxyethylene isostere HIVP inhibitors based on natural amino acid residues leads to a new series of compounds that have increased intrinsic inhibitory potency. More significantly, several of these compounds have greatly improved antiviral activity as determined by a virus spread assay. Substitution of the P_1' phenyl ring with a 4-(3-hydroxypropyl) group led to L-693,549 (**19**) which is 60–120 times more potent than the lead compound 1 and 8–16 times more potent than the parent, indan-based inhibitor **2** as an antiviral agent in an ex vivo cell culture.

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. All reactions were conducted under an argon atmosphere. Melting

points (Pyrex capillary) were measured on a Thomas-Hoover apparatus and are uncorrected. NMR spectra were determined on a Varian XL-300 spectrometer. Chemical shifts are expressed in parts per million downfield of internal tetramethylsilane. Significant ^{1}H NMR data for representative compounds are tabulated in the following order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant(s) in hertz, number of protons. FAB mass spectra were obtained on a VG Model 7070E mass spectrometer and relevant data are tabulated as m/z. Elemental analyses were performed by the analytical Department, Merck Sharp and Dohme Research Laboratories, West Point, PA and were within ±0.4% of the theoretical values. The general method used to prepare compound 8 was used to prepare all compounds in Table I. The compounds in Table II not specifically mentioned were prepared by the general method given for compound 8. Representative examples of compounds with elaborated P_1' side chains are also given below.

***N*-[2(*R*)-Hydroxy-1(*S*)-indanyl]-5(*S*)-[[(1,1-dimethylethoxy)carbonyl]amino]-4(*S*)-hydroxy-6-phenyl-2(*R*)-(3-phenylprop-2-en-1-yl)hexanamide (8).** (5*S*,1′*S*)-Carbethoxy-5-[1-[[(1′,1-dimethylethoxy)carbonyl]amino]-2-phenylmethyl]-dihydrofuran-2(3*H*)-one[8] (4.15 g, 11.0 mmol) was dissolved in absolute EtOH (41 mL) containing NaOEt (0.75 g, 11.0 mmol). Cinnamyl bromide (2.17 g, 11.0 mmol) was added, and the mixture was stirred at ambient temperature for 18 h. LiOH (1.50 g, 62.6 mmol) and water (10.0 mL) were added, and the mixture was stirred for 5 h. The EtOH was removed in vacuo and the aqueous phase was partitioned between 10% aqueous citric acid and EtOAc. The layers were separated and the organic phase was washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was dissolved in toluene (250 mL), and this solution was heated at reflux for 24 h. The toluene was removed in vacuo and the crude diastereomeric lactones were chromatographed on silica gel (300 g) with 15% EtOAc in hexanes used as eluant. The faster eluting diastereomer (**5a**, 2.5 g) [^{1}H NMR ($CDCl_3$) δ 1.35 (s, 9 H), 2.10 (m, 1 H), 2.31 (m, 1 H), 2.42 (m, 1 H), 2.65 (m, 1 H), 2.81 (m, 1 H), 2.89 (d, J = 9.0, 1 H), 4.00 (br q, J = 8.3, 1 H), 4.45 (dt, J = 1.6, 6.0, 1 H), 4.53 (br d, J = 10.0, 1 H), 6.10 (m, H), 6.45 (d, J = 15.7, 1 H), 7.10–7.35 (m, 10 H)] was dissolved in DME (35 mL) and an aqueous solution of LiOH (35 mL, 1 N) was added, with stirring. This solution was stirred at ambient temperature for 3 h. The mixture was partitioned between 10% aqueous citric acid and EtOAc. The layers were separated and the organic phase was washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. This material was dissolved in dry DMF (35 mL) and *tert*-butyldimethylsilyl chloride (5.33 g, 35.35 mmol) and imidazole (4.81 g, 70.70 mmol) were added. This solution was stirred 24 h at ambient temperature. MeOH (100 mL) was added to this solution, and the mixture was stirred for 4 h. The solvents were removed in vacuo, and the residue was dissolved in EtOAc. This solution was washed with 10% aqueous citric acid and brine. Drying ($MgSO_4$), filtration, removal of the solvent, and chromatography on silica gel (250 g) using 15% EtOAc in $CHCl_3$ as eluant gave 2.14 g of *N*-[(1,1-dimethylethoxy)carbonyl]-5(*S*)-amino-4(*S*)-[[(1′,1′-dimethylethyl)dimethylsilyl]oxy]-6-phenyl-2(*R*)-(3-phenylprop-2-en-1-yl)hexanoic acid (**6**) [^{1}H NMR ($CDCl_3$) δ 0.10 (s, 3 H), 0.15 (s, 3 H), 0.92 (s, 9 H), 1.35 (s, 9 H), 1.62 (m, 1 H), 2.36 (m, 1 H), 2.61 (m, 2 H), 2.80 (m, 1 H), 3.79 (m, 1 H), 3.99 (br q, J = 7.3, 1 H), 4.79 (br d, J = 10.0, 1 H), 6.21 (m, 1 H), 6.27 (d, J = 15.1, 1 H), 7.10–7.40 (m, 10 H)]. To a stirred solution of **6** (200 mg, 0.36 mmol) in DMF (2.0 mL) was added 2(*S*)-amino-3-(*R*)-hydroxyindan[6b] (53 mg, 0.36 mmol), EDC·HCl (86 mg, 0.45 mmol), HOBt (61 mg, 0.45 mmol), and Et_3N (0.14 mL, 1.00 mmol). This solution was stirred for 20 h at ambient temperature. The mixture was diluted with EtOAc and washed with 10% aqueous citric acid and brine. Drying ($MgSO_4$), filtration, and removal of the solvent in vacuo gave a residue that was treated with tetrabutylammonium fluoride (5.0 mL, of a 1 M solution in THF) at ambient temperature for 24 h. The solution was diluted with aqueous citric acid and the solid product was collected by filtration. The crude product was chromatographed on silica gel (20 g) with 5% MeOH in $CHCl_3$ used as eluant to give 190 mg (92%) of **8** as a white solid: mp 205–207 °C; ^{1}H NMR ($CDCl_3$) δ 1.37 (s, 9 H), 1.73–1.95 (m, 2 H), 1.98 (d, J = 6, 1 H), 2.30–2.42 (m, 1 H), 2.51–2.63 (m, 1 H), 2.63–2.78 (m, 1 H), 2.85 (dd, J = 1.8, 16, 1 H), 2.92 (br d, J = 7.2, 2 H), 3.09 (dd, J = 6,16, 1 H), 3.62–3.72 (m, 1 H), 3.72–3.82 (m, 1 H), 3.87 (br s, 1 H), 4.40–4.46 (m, 1 H), 4.92 (br d, J = 10, 1 H), 5.32 (dd, J = 5.1, 8.4, 1 H), 6.15 (dt, J = 7.2, 16.5, 1 H), 6.38 (d, J = 16.5, 1 H), 6.39 (br d, J = 9, 1 H), 7.13–7.35 (m, 14 H). Anal. ($C_{35}H_{42}N_2O_5$) C, H, N.

***N*-[2(*R*)-Hydroxy-1(*S*)-indanyl]-5-(*S*)-[[(1,1-dimethylethoxy)carbonyl]amino]-4(*S*)-hydroxy-6-phenyl-2(*R*)-[[4-(3,3-dimethoxypropyl)phenyl]methyl]hexanamide (42). Step 1: 4-(3-Hydroxypropyl)benzyl Bromide.** A solution of 4-(3-hydroxypropyl)benzyl alcohol (26.1 g, 159 mmol) in dry Et_2O (1 L) was saturated with anhydrous HBr and aged 1 h at ambient temperature. The solution was resaturated with HBr and allowed to stand overnight. The Et_2O and excess HBr were removed in vacuo and the residue was dissolved in $CHCl_3$. The solution was washed with H_2O, saturated aqueous $NaHCO_3$, and brine. Drying ($MgSO_4$), filtration, and removal of the solvent in vacuo gave a light brown solid that was recrystallized from hexanes to give 30 g (83%) of 4-(3-hydroxypropyl)benzyl bromide as white crystals: mp 66–69 °C; ^{1}H NMR ($CDCl_3$) δ 1.40 (br s, 1 H), 1.91 (m, 2 H), 2.65 (t, J = 7.1, 2 H), 3.61 (t, J = 7.1, 2 H), 4.39 (s, 2 H), 7.05–7.36 (m, 4 H).

Step 2: *N*-[(1,1-Dimethylethoxy)carbonyl]-5(*S*)-amino-4(*S*)-[[(1′,1′-dimethylethyl)dimethylsilyl]oxy]-6-phenyl-2-(*R*)-[[4-(3,3-dimethoxypropyl)phenyl]methyl]hexanoic Acid. (5*S*,1′*S*)-3-Carbethoxy-5-[1-[[(1′,1-dimethylethoxy)carbonyl]-amino]-2-phenylethyl]dihydrofuran-2(3*H*)-one (4.00 g, 10.6 mmol) was dissolved in absolute EtOH (40 mL) containing NaOEt (0.72 g, 10.6 mmol). 4-(3-Hydroxypropyl)benzyl bromide (2.67 g, 11.7 mmol) was added, and the mixture was stirred at ambient temperature for 18 h. LiOH (1.27 g, 53 mmol) and water (20.0 mL) were added and the mixture was stirred for 5 h. The EtOH was removed in vacuo, and the aqueous phase was partitioned between 10% aqueous citric acid and EtOAc. The layers were separated, and the organic phase was washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was dissolved in toluene (300 mL), and this solution was heated at reflux for 24 h. The toluene was removed in vacuo, and the crude diastereomeric lactones were chromatographed on silica gel (300 g) with 15% EtOAc in hexanes used as eluant. The faster eluting diastereomer (14, 1.71 g, 35%) was dissolved in CH_2Cl_2 (60 mL) and cooled to 0 °C. To this well-stirred solution was added SO_3·Pyr (5.97 g, 37.48 mmol) in DMSO (18 mL) and Et_3N (7.84 mL, 56.22 mmol). This solution was allowed to warm to ambient temperature and was stirred for 18 h. The mixture was diluted with $CHCl_3$ and washed with 10% aqueous citric acid, saturated aqueous $NaHCO_3$ solution, and brine. Drying ($MgSO_4$), filtration, and removal of the solvent in vacuo gave the crude aldehyde which was dissolved in MeOH (100 mL) containing pyridinium *p*-toluenesulfonate (100 mg, 0.39 mmol). This solution was stirred at ambient temperature for 24 h. The solution was made basic with $NaHCO_3$, and the MeOH was removed in vacuo. The residue was chromatographed on 200 g of silica gel with 30% EtOAc in hexane used as eluant. There was obtained 1.66 g (98%) of (5*S*,3*R*,1′*S*)-3-[[4-(3,3-dimethoxypropyl)phenyl]methyl]-5-[1-[[(1′,1-dimethylethoxy)carbonyl]amino]-2-phenylethyl]dihydrofuran-2(3*H*)-one as a colorless foam. This material (1.66 g, 3.34 mmol) was dissolved in DME (20 mL), and an aqueous solution of LiOH (20 mL, 1N) was added, with stirring. This solution was stirred at ambient temperature for 3 h. The mixture was partitioned between 10% aqueous citric acid and EtOAc. The layers were separated, and the organic phase was washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. This material was dissolved in dry DMF (30 mL), and *tert*-butyldimethylsilyl chloride (5.03 g, 33.4 mmol) and imidazole (4.55 g, 66.8 mmol) were added. This solution was stirred 24 h at ambient temperature. MeOH (100 mL) was added to this solution, and the mixture was stirred for 2 h. The solvents were removed in vacuo, and the residue was dissolved in EtOAc. This solution was washed with 10% aqueous citric acid and brine. Drying ($MgSO_4$), filtration, removal of the solvent, and chromatography on silica gel (250 g) using 2% MeOH in $CHCl_3$ as eluant gave 1.39 g (69%) of *N*-[(1,1-dimethylethoxy)carbonyl]-5(*S*)-amino-4(*S*)-[[(1′,1′-dimethylethyl)dimethylsilyl]oxy]-6-phenyl-2(*R*)-[[4-(3-,3-dimethoxypropyl)phenyl]methyl]hexanoic acid.

Step 3: *N*-[2(*R*)-hydroxy-1(*S*)-indanyl]-5(*S*)-[[(1,1-dimethylethoxy)carbonyl]amino]-4(*S*)-hydroxy-6-phenyl-2-

(*R*)-[[4-(3,3-dimethoxypropyl)phenyl]methyl]hexanamide. To a stirred solution of the hexanoic acid (1.39 g, 2.31 mmol) in DMF (15.0 mL) was added 2(*S*)-amino-3-(*R*)-hydroxyindan (379 mg, 2.54 mmol), EDC·HCl (487 mg, 2.54 mmol), HOBt (343 mg, 2.54 mmol), and Et_3N (0.696 mL, 5.00 mmol). This solution was stirred for 20 h at ambient temperature. The mixture was diluted with EtOAc and washed with 10% aqueous citric acid and brine. Drying ($MgSO_4$), filtration, and removal of the solvent in vacuo gave 1.9 g of a colorless foam. This material was chromatographed on 90 g of silica gel with 35% EtOAc in hexanes used as eluant to give *N*-[2(*R*)-Hydroxy-1(*S*)-indanyl]-5(*S*)-[[(1,1-dimethylethoxy)carbonyl]amino]-4(*S*)-[[(1,1′-dimethylethyl)dimethylsilyl]oxy]-6-phenyl-2(*R*)-[[4-(3,3-dimethoxypropyl)phenyl]methyl]hexanamide (**15**, 1.26 g, 72%) as a foam. This material (1.26 g, 1.66 mmol) was treated with tetrabutylammonium fluoride (8.28 mL, of a 1 M solution in THF) at ambient temperature for 24 h. The solution was diluted with aqueous citric acid, and the solid product (**42**) was collected by filtration (1.0 g, 93%). An analytical sample was prepared by recrystallization from EtOAc: mp 213–214 °C; ^1H NMR ($CDCl_3$/DMSO-d_6 1:1) δ 1.30 (s, 9 H), 1.42 (m, 1 H), 1.65–1.78 (m, 1 H), 1.79–1.90 (m, 2 H), 2.52 (d, J = 1.8, 1 H), 2.54–2.72 (m, 3 H), 2.75–3.06 (complex m, 6 H), 3.25 (s, 6 H), 3.34 (s, 1 H), 3.55–3.70 (br s, 2 H), 4.27 (q, J = 4.2, 1 H), 4.33 (t, J = 5.8, 1 H), 4.58 (d, J = 4.0, 1 H), 4.68 (d, J = 5.6, 1 H), 5.15 (dd, J = 1.8, 4.0, 1 H), 6.29 (d, J = 9.2, 1 H), 7.0–7.30 (m, 13 H), 7.62 (d, J = 9.1, 1 H). Anal. ($C_{38}H_{50}N_2O_7$) C, H, N.

***N*-[2(*R*)-Hydroxy-1(*S*)-indanyl]-5(*S*)-[[(1,1-dimethylethoxy)carbonyl]amino]-4(*S*)-hydroxy-6-phenyl-2(*R*)-[[4-[3-(dimethylamino)propyl]phenyl]methyl]hexanamide (16).** To a solution of **15** (1.00 g, 1.54 mmol) in acetone (250 mL) was added H_2O (50 mL) and pyridinium *p*-toluenesulfonate (100 mg, 0.39 mmol). This solution was heated at reflux for 4 h, cooled to room temperature and diluted with EtOAc. The layers were separated, and the organic phase was washed with saturated aqueous $NaHCO_3$ solution and brine. Drying ($MgSO_4$), filtration, and removal of the solvent in vacuo left the crude aldehyde. This aldehyde (167 mg, 0.28 mmol) was dissolved in MeOH (7.5 mL), and the solution was saturated with anhydrous methylamine gas. To this well-stirred mixture was added aluminum foil (269 mg, 10.0 mmol, small pieces) and $HgCl_2$ (15 mg, 0.06 mmol). The mixture was stirred 24 h and then filtered through a Celite pad. The MeOH was removed in vacuo, and the crude product was chromatographed on silica gel (20 g) with 10% MeOH in $CHCl_3$ used as eluant to give 140 mg (79%) of **16** as a white solid. An analytical sample was obtained by recrystallization from EtOAc: mp 204–206 °C; ^1H NMR ($CDCl_3$) δ 1.37 (s, 9 H), 1.71 (m, 1 H), 1.89 (m, 2 H), 2.22 (s, 6 H), 2.24–2.40 (m, 2 H), 2.51 (m, 1 H), 2.62 (m, 1 H), 2.68 (m, 3 H), 2.80–3.05 (m, 3 H), 3.50 (m, 1 H), 3.82 (br s, 1 H), 4.12 (m, 2 H), 4.95 (d, J = 8.8, 1 H), 5.21 (dd, J = 5.03, 9.8, 1 H), 5.93 (d, J = 8.0, 1 H), 7.00–7.40 (m, 13 H); aqueous solubility (pH 3) = 1.21 mg mL^{-1}. Anal. ($C_{38}H_{51}N_3O_5$) C, H, N.

***N*-[2(*R*)-Hydroxy-1(*S*)-indanyl]-5(*S*)-[[(1,1-dimethylethoxy)carbonyl]amino]-4(*S*)-hydroxy-6-phenyl-2(*R*)-[[4-[3-(trimethylammonio)propyl]phenyl]methyl]hexanamide Iodide (17).** To a solution of *N*-[2(*R*)-hydroxy-1(*S*)-indanyl]-5(*S*)-[[(1,1-dimethylethoxy)carbonyl]amino]-4(*S*)-hydroxy-6-phenyl-2(*R*)-[[4-[3-(dimethylamino)propyl]phenyl]methyl]hexanamide (50 mg, 0.079 mmol) in MeOH (5.0 mL) was added methyl iodide (0.10 mL, 1.61 mmol), and the mixture was aged at ambient temperature for 20 h. The solvents were removed in vacuo to give a pale yellow oil. This material was preparatively chromatographed on a Vydac C-18 reverse phase HPLC column with H_2O–CH_3CN used as eluant. There was obtained 13.3 mg (22%) of **17** as an amorphous solid: ^1H NMR ($CDCl_3$) δ 1.40 (s, 9 H), 1.80–2.00 (m, 4 H), 2.68 (m, 8 H), 2.90–3.10 (m, 4 H), 3.75 (br d, J = 9.0, 1 H), 4.40 (br s, 1 H), 5.10 (br s, 1 H), 7.00–7.35 (m, 13 H), 7.79 (br d, J = 8.0, 1 H). An acceptable analysis was not obtained for this compound.

***N*-[2(*R*)-Hydroxy-1(*S*)-indanyl]-5(*S*)-[[(1,1-dimethylethoxy)carbonyl]amino]-4(*S*)-hydroxy-6-phenyl-2(*R*)-[[4-(3-hydroxypropyl)phenyl]methyl]hexanamide (19).** Lactone **14** (1.43 g, 3.15 mmol) was dissolved in DME (15 mL), and an aqueous solution of LiOH (15 mL, 1 N) was added, with stirring. This solution was stirred at ambient temperature for 24 h. The mixture was partitioned between 10% aqueous citric acid and EtOAc. The layers were separated and the organic phase was washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. This material was dissolved in dry DMF (20 mL) and *tert*-butyldimethylsilyl chloride (2.37 g, 15.76 mmol) and imidazole (2.15 g, 31.52 mmol) were added. This solution was stirred 24 h at ambient temperature. MeOH (100 mL) was added to this solution, and the reaction mixture was stirred for 4 h. The solvents were removed in vacuo, and the residue was dissolved in EtOAc. This solution was washed with 10% aqueous citric acid and brine. Drying ($MgSO_4$), filtration, removal of the solvent, and chromatography on silica gel (250 g) using 2% MeOH in $CHCl_3$ as eluant gave 2.43 g of *N*-[(1,1-dimethylethoxy)carbonyl]-5(*S*)-amino-4(*S*)-[[(1′,1′-dimethylethyl)dimethylsilyl]oxy]-6-phenyl-2(*R*)-[[4-[3-[[(1′,1′-dimethylethyl)dimethylsilyl]oxy]propyl]phenyl]methyl]hexanoic acid (**18**). To a stirred solution of **18** (1.75 g, 2.50 mmol) in DMF (10.0 mL) cooled to 0 °C, was added 2(*S*)-amino-3-(*R*)-hydroxyindan (410 mg, 2.75 mmol), EDC·HCl (530 mg, 2.75 mmol), HOBt (370 mg, 2.75 mmol), and Et_3N (0.56 mL, 4.00 mmol). This solution was stirred for 18 h at ambient temperature. The mixture was diluted with EtOAc and washed with 10% aqueous citric acid and brine. Drying ($MgSO_4$), filtration, and removal of the solvent in vacuo gave 2.81 g of a residue that was chromatographed on 200 g of silica gel with 25% EtOAc in hexane used as eluant. This material was treated with tetrabutylammonium fluoride (27.6 mL, of a 1 M solution in THF) at ambient temperature for 24 h. The solution was diluted with aqueous citric acid and extracted with EtOAc (3X). The combine EtOAc extracts were washed with H_2O, saturated aqueous $NaHCO_3$ solution, and brine. Drying ($MgSO_4$), filtration, and removal of the solvent in vacuo gave 1.54 g of a white solid. Recrystallization from EtOAc gave 950 mg of **19** (86%) as white crystals: mp 190–192 °C; ^1H NMR ($CDCl_3$) δ 1.29 (s, 9 H), 1.39 (m, 1 H), 1.72 (m, 2 H), 2.50–2.64 (m, 3 H), 2.71–3.05 (complex m, 3 H), 3.33 (s, 1 H), 3.45 (q, J = 5.1, 2 H), 3.61 (br s, 1 H), 4.29 (br q, J = 4.9, 1 H), 4.42 (t, J = 5.1, 1 H), 4.68 (m, 2 H), 5.15 (dd, J = 4.9, 8.5, 1 H), 6.35 (d, J = 9.0, 1 H), 7.00–7.30 (m, 13 H), 7.62 (d, J = 8.5, 1 H); aqueous solubility (pH 3) < 0.001 mg mL^{-1}. Anal. ($C_{36}H_{46}N_2O_6$) C, H, N.

***N*-[2(*R*)-Hydroxy-1(*S*)-indanyl]-5(*S*)-[[(1,1-dimethylethoxy)carbonyl]amino]-4(*S*)-hydroxy-6-phenyl-2(*R*)-[[4-[3-[(2-methoxyethoxy)methoxy]propyl]phenyl]methyl]hexanamide (20).** To a solution of **19** (78 mg, 0.129 mmol) in CH_2Cl_2 (6.0 mL) was added MEM Cl (0.015 mL, 0.135 mmol) and diisopropylethylamine (0.035 mL, 0.20 mmol). This mixture was stirred at ambient temperature for 24 h. The CH_2Cl_2 was removed in vacuo, and the residue was dissolved in EtOAc. This solution was washed with 10% aqueous citric acid, saturated aqueous $NaHCO_3$, and brine. Drying ($MgSO_4$), filtration, and removal of the solvent in vacuo gave 89 mg (100%) of MEM ether **20**. An analytical sample was prepared by recrystallization from EtOAc–hexane (1:1): mp 176–177 °C; ^1H NMR ($CDCl_3$) δ 1.39 (s, 9 H), 1.90 (m, 4 H), 2.60–3.08 (complex, 10 H), 3.38 (s, 3 H), 3.57 (t, J = 6.2, 2 H), 3.68 (t, J = 6.2, 2 H), 3.81 (br s, 1 H), 3.89 (s, 1 H), 4.19 (br q, J = 4.9, 1 H), 4.72 (s, 2 H), 4.91 (br d, J = 8.9, 1 H), 5.25 (dd, J = 4.9, 8.5), 5.86 (br d, J = 8.5, 1 H), 7.00–7.33 (m, 13 H); aqueous solubility (pH 3) = 0.002 mg mL^{-1}. Anal. ($C_{40}H_{54}N_2O_8$) C, H, N.

***N*-[2(*R*)-Hydroxy-1(*S*)-indanyl]-5(*S*)-[[(1,1-dimethylethoxy)carbonyl]amino]-4(*S*)-hydroxy-6-phenyl-2(*R*)-(3-(4-hydroxyphenyl)prop-2-en-1-yl)hexanamide (24). Step 1: Preparation of 3-[4-[[(1′,1′-Dimethylethyl)dimethylsilyl]oxy]phenyl]prop-2-enyl Bromide (23).** To a solution of trans 4-hydroxycinnamic acid (16.42 g, 100 mmol) in DMF 200 mL) was added *tert*-butyldimethylsilyl chloride (31.65 g, 210 mmol) and imidazole (20.42 g, 300 mmol). This solution was stirred at ambient temperature for 48 h. The DMF was removed in vacuo at 55 °C. The residue was taken up in Et_2O (500 mL), and this solution was washed with 5% aqueous citric acid, H_2O, and brine. Drying ($MgSO_4$), filtration, and removal of the solvent in vacuo gave the silyl ether–silyl ester (39.1 g, 99%) as a colorless oil. This material (38.9 g, 99.1 mmol) was dissolved in Et_2O (300 mL) and cooled to 0 °C. To this solution was added Dibal-H (35.5 g, 250 mmol, 250 mL, of a 1 M solution in hexane) dropwise over 1 h. The mixture was maintained at or below 5 °C for an additional 1 h, and the reaction was quenched by careful addition of an saturated aqueous solution of sodium potassium tartrate (250 mL). This mixture was stirred for 18 h at ambient temperature and

then diluted with Et_2O (1 L). The layers were separated, and the organic phase was washed with brine. Drying ($MgSO_4$), filtration (Celite pad), removal of the solvent in vacuo, and chromatography on silica gel (1 kg) using 20% EtOAc in hexane as eluant gave 17.3 g (66%) of alcohol **22** as a colorless oil: ^1H NMR ($CDCl_3$) δ 0.07 (s, 6 H), 0.87 (s, 9 H), 1.65 (br s, 1 H), 4.15 (br d, J = 5.6, 2 H), 6.11 (dt, J = 5.6, 15.7, 1 H), 6.42 (d, J = 15.7 1 H), 6.68 (d, J = 8.5, 2 H), 7.10 (d, J = 8.5, 2 H). A solution of alcohol **22** (1.24 g, 4.69 mmol) in Et_2O (25 mL) was cooled to 0 °C, and PBr_3 (0.49 mL, 5.16 mmol) was added with a syringe. This mixture was stirred 20 min and then poured into saturated aqueous $NaHCO_3$ solution. The mixture was diluted with hexane, and the layers were separated. The organic phase was washed with brine, dried ($MgSO_4$), filtered through a pad of silica gel, and concentrated in vacuo to give 1.04 g of **21** (68%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 0.20 (s, 6 H), 0.99 (s, 9 H), 4.16 (d, J = 7.1, 2 H), 6.25 (m, 2 H), 6.59 (d, J = 15.5, 1 H), 6.80 (d, J = 8.4, 2 H), 7.26 (d, J = 8.4, 2 H). By following the procedure outlined for compound **8**, bromide **23** was carried on to the title compound, **24**: mp 233–234 °C; ^1H NMR ($CDCl_3$/DMSO-d_6 1:1) δ 1.33 (s, 9 H), 1.60 (m, 1 H), 1.75 (m, 1 H), 2.25 (m, 1 H), 2.50 (m, 1 H), 2.56 (s, 1 H), 2.26–2.91 (complex, 4 H), 3.05 (dd, J = 4.6, 16.1, 2 H), 3.29 (br s, 1 H), 3.67 (m, 2 H), 4.40 (br s, 1 H), 4.72 (br s, 2 H), 5.27 (dd, J = 4.8, 8.4, 1 H), 5.86 (d, J = 12.0, 1 H), 6.02 (m, 1 H), 6.29 (d, J = 15.8, 1 H), 6.70 (d, J = 8.5, 1 H), 7.00–7.30 (m, 13 H), 7.55 (d, J = 7.5, 1 H). Anal. ($C_{35}H_{42}N_2O_6$) C, H, N.

***N*-[2(*R*)-Hydroxy-1(*S*)-indanyl]-5(*S*)-[[(1,1-dimethylethoxy)carbonyl]amino]-4(*S*)-hydroxy-6-phenyl-2(*R*)-[3-[4-(morpholinoethoxy)phenyl]prop-2-en-1-yl]hexanamide (25).** To a solution of phenol **24** (105 mg, 0.187 mmol) in dioxane (35 mL) was added finely powdered Cs_2CO_3 (609 mg, 1.87 mmol) and (2-chloroethyl)morpholine (783 mg, 5.27 mmol). This well-stirred solution was heated at 90–95 °C for 1 h. The solids were removed by filtration, and the dioxane was removed in vacuo. The residue was chromatographed on silica gel (20 g) with 5% MeOH in EtOAc used as eluant to give 40 mg (32%) of **25** as a crystalline solid: mp 178–179 °C; FABMS (M + H) 700; ^1H NMR (DMSO-d_6) δ 1.28 (s, 9 H), 1.45 (m, 1 H), 1.79 (m, 1 H), 2.25 (m, 1 H), 2.45–2.86 (complex m, 10 H), 3.03, (dd, J = 4.4, 12.6, 1 H), 3.63 (m, 6 H), 4.12 (m, 2 H), 4.35 (br s, 1 H), 4.78 (d, J = 4.8, 1 H), 5.00 (br s, 1 H), 5.21 (dd, J = 5.3, 8.8, 1 H), 6.10 (m, 1 H), 6.35 (d, J = 15.7, 1 H), 6.51 (d, J = 8.8, 1 H), 6.90 (d, J = 8.5, 2 H), 7.25 (m, 10 H), 7.67 (d, J = 8.8, 1 H). Anal. ($C_{41}H_{53}N_3O_7$) C, H, N.

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