Design and Synthesis of Potent C_2-Symmetric Diol-Based HIV-1 Protease Inhibitors: Effects of Fluoro Substitution

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Implementation of derivatized carbohydrates as C_2-symmetric HIV-1 protease inhibitors has previously been reported. With the objective of improving the anti-HIV activity of such compounds, we synthesized a series of fluoro substituted P1/P1′ analogues. These compounds were evaluated for antiviral activity toward both wild type and mutant virus. The potency of the analogues in blocking HIV-1 protease was moderate, with K_i values ranging from 1 to 7 nM. Nonetheless, compared to the parent nonfluorous inhibitors, a majority of the compounds exhibited improved antiviral activity, for example the 3-fluorobenzyl derivative **9b**, which had a K_i value of 7.13 nM and displayed one of the most powerful antiviral activities in the cellular assay of the series. Our results strongly suggest that fluoro substitution can substantially improve antiviral activity. The X-ray crystal structures of two of the fluoro substituted inhibitors (**9a** and **9f**) cocrystallized with HIV-1 protease are discussed.

Introduction

The human immunodeficiency virus (HIV) is the causative agent of acquired immunodeficiency syndrome (AIDS).[1−3] The RNA genome of HIV encodes a dimeric aspartyl protease that processes the viral gag and gag-pol polyproteins into structural and functional units. The HIV-1 protease (HIV-1 PR) has been shown to be essential for formation of mature and infectious virions;[4,5] hence inhibition of this enzyme has become an attractive target in the quest for effective antiviral agents, and numerous reports have been published describing potent inhibitors of HIV-1 PR.[6−11] Despite the success of the FDA-approved HIV-1 PR inhibitors saquinavir,[12] ritonavir,[13] indinavir,[14] nelfinavir,[15] amprenavir,[16] and lopinavir,[17] there is an urgent need for new and improved drugs against HIV-1 PR due to increasing viral resistance, a matter that is now of great concern.[6,7,18−21]

Our research group has focused on utilization of carbohydrates as building blocks in the design and synthesis of C_2-symmetric HIV-1 PR inhibitors.[22−26] The N- and C-termini of a substrate or inhibitor bind to identical subsites of the C_2-symmetric dimeric protease. A symmetric core unit can be produced by deleting either the N- or C-terminus and then duplicating the remaining portion.[27,28] We applied this methodology, placing the C_2-symmetry axis in the center of an asymmetric inhibitor (Figure 1) and deleting the N-terminus and duplicating the C-terminus, which gave

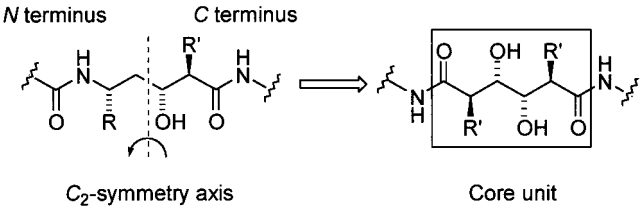

Figure 1. Design of C_2-symmetric inhibitor core unit.

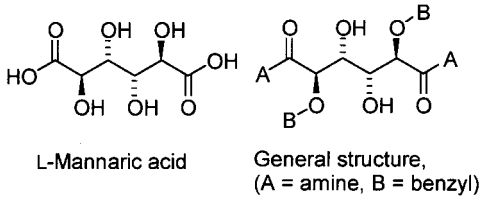

Figure 2.

us a core unit with stereochemical demands that were met by L-mannaric acid (Figure 2). Benzylation of the hydroxy groups at C-2 and C-5 and subsequent coupling with amino acids or amines gave a series of C_2-symmetric diol-based inhibitors with the general structure shown in Figure 2. Optimization of the P2/P2′ substituents provided the inhibitors **1** and **2** (Figure 3), which show good inhibitory profiles.[25]

Having succeeded in developing highly active protease inhibitors, we focused on modifying the P1/P1′ benzyloxy groups by fluoro substitution in an effort to further improve the anti-HIV activity of HIV wild type and of resistant mutant strains. The substitution of hydrogen by fluorine would introduce a minor increase in molecular weight and minimal steric changes, accompanied by a slight increase in lipophilicity.[29−32] Here we describe the efficient synthesis and biological evaluation of a series of fluoro inhibitors that, despite moderate

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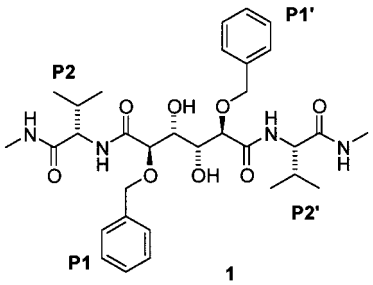

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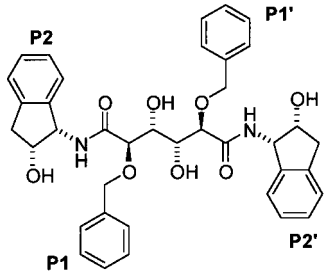

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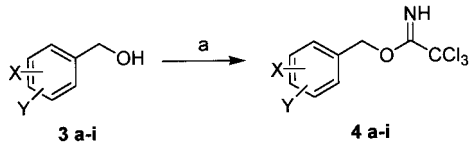
Figure 3. Parent inhibitors **1** and **2**.

Scheme 1. Preparation of Benzyl Trichloroacetimidates[a]



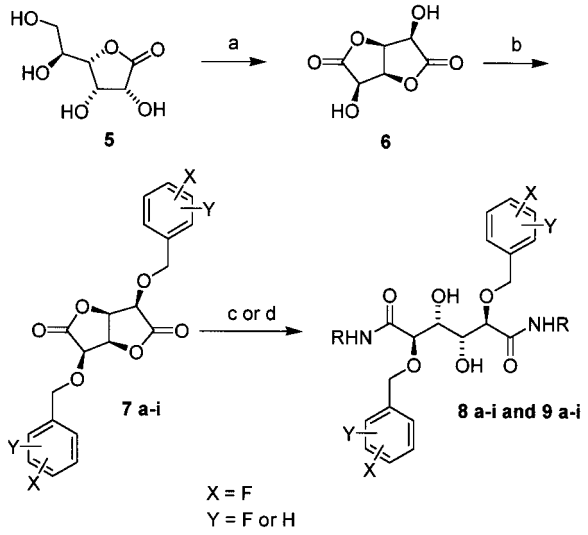
[a] Reagents: (a) CCl_3CN, 50% KOH, *n*-Bu_4NHSO_4, CH_2Cl_2.

inhibitory potencies as HIV-PR inhibitors, exhibit substantial antiviral activities.

Results and Discussion

Chemistry. Using the commercially available fluorobenzyl alcohols **3a**−**i**, various mono- and difluoro substituted benzyl trichloroacetimidates **4a**−**i** were prepared in excellent yields by reaction with trichloroacetonitrile under basic conditions (Scheme 1).[33] L-Mannaro-1,4:3,6-di-γ-lactone (**6**) was synthesized from L-mannonic-γ-lactone (**5**) via an aqueous nitric acid oxidation (Scheme 2), as previously described.[25] The dilactone **6** was benzylated with the crude fluorobenzyl trichloroacetimidates **4a**−**i** using a catalytic amount of trifluoromethanesulfonic acid in dry dioxane to give the dibenzylated lactones **7a**−**i**.[34−37] Subsequent opening of these dilactones with l-valine methylamide[38] in the presence of 2-hydroxypyridine[39] in 1,2-dichloroethane afforded the diamide derivatives **8a**−**i** in 30−92% yield. Similarly, opening with (1*S*,2*R*)-(−)-*cis*-1-amino-2-indanol and 2-hydroxypyridine in 1,2-dichloroethane generated the corresponding diamide derivatives **9a**−**i** in 47−72% yield. An undesired β-elimination attributed to the basicity of the amines constituted the major side reaction. The competing elimination process was countered to some extent by addition of the bifunctional catalyst 2-hydroxypyridine, which has previously been shown to improve yields in formation of amides from esters.[39]

Scheme 2[a]



[a] Reagents: (a) HNO_3; (b) **4a**−**i**, trifluoromethanesulfonic acid, dioxane; (c) for **8a**−**i**: l-valine methylamide, 2-hydroxypyridine, $C_2H_4Cl_2$; (d) for **9a**−**i**: (1*S*,2*R*)-(−)-*cis*-1-amino-2-indanol, 2-hydroxypyridine, $C_2H_4Cl_2$.

Biological Results. In Tables 1 and 2 the HIV-1 PR inhibitor values and the anti-HIV-1 activity toward wild type and mutant virus of the synthesized compounds are shown. HIV-1 PR was cloned and heterologously expressed in *Escherichia coli* as described elsewhere.[40] A fluorometric assay was used to determine inhibition of HIV-1 PR (K_i values).[41] Anti-HIV activity (ED_{50} values) was analyzed in vitro in MT4 cells according to a previously reported procedure that uses the colorimetric XTT assay to monitor cytopathogenic effects.[41]

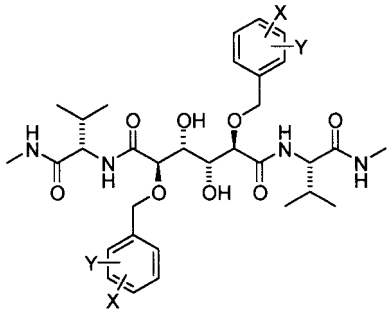
Selection of drug-resistant virus in vitro was done as follows: MT4 cells seeded in 96-well microplates were treated with sub-ED_{50} concentrations of respective drugs and infected with 20−50 times the 50% tissue culture infectious doses of HIV-1 (IIIb).

Virus replication was monitored by determining levels of p24 antigen in MT4 cell supernatants. Cell-free virus was further passaged in 5-fold serially increased concentrations of the drug. When virus was growing in concentrations of the drug that exceeded the ED_{50} concentration for wild-type virus more than 50-fold, the supernatant was divided into aliquots, which were used as virus stock in cross-resistance studies. Proviral DNA from infected cells in the final passage was analyzed with respect to nucleotide sequence in the protease coding region.

Structure−Activity Relationships. The present series of fluoro substituted compounds shows moderate to good protease inhibition (K_i values in the low nanomolar range), albeit poorer than the parent unsubstituted benzyl compounds **1** and **2**. Notably, in some cases, however, the cellular ED_{50} values were markedly improved compared to the parent inhibitors and even compared to the reference drugs ritonavir, saquinavir, and nelfinavir. This tendency can in part be rationalized by an improvement in cellular permeability attributed to the higher lipophilicity of the fluoro substituted compounds.[29,31]

Examination of the ED_{50} values for the monosubstituted derivatives reveals that the 2-fluoro substituted derivatives were the most potent over all. Thus, in the

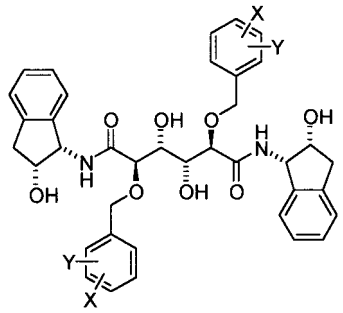
Table 1. HIV-1 Protease Inhibitory Activities of l-Valine Methylamide Compounds



					ED$_{50}$ MT4/mutant HIV-1 (μM)			
compd	X-	Y-	K_i[a] (nM)	ED$_{50}$ WT (μM)	V32I, M46I, A71V, V82A[b]	M46I, V82F, I84V[c]	A71V, I84V, L90M[d]	D30N, S37N, K45I, M46I, A71V, L90M[e]
1	H	H	0.80	1.32	8.13	>15	6.1	>15
8a	2-F	H	1.92	0.28	9.34	7.45	0.63	1.15
8b	3-F	H	1.83	0.68	1.84	1.69	1.04	1.10
8c	4-F	H	1.79	1.17	7.82	0.97	3.65	1.32
8d	2-F	3-F	1.28	0.66	1.54	2.26	1.11	0.34
8e	2-F	4-F	1.12	0.72	3.35	1.89	1.17	0.48
8f	2-F	5-F	1.98	0.65	10.73	10.92	1.38	1.38
8g	2-F	6-F	1.73	1.35	>15	>15	8.14	7.14
8h	3-F	4-F	1.98	0.67	2.84	1.22	0.81	0.85
8i	3-F	5-F	1.98	0.42	1.32	1.40	1.64	0.34
ritonavir			0.82	0.06	0.98	2.47	0.41	0.15
saquinavir			0.23	0.01	0.01	0.01	0.08	0.03
nelfinavir			0.23	0.02	0.07	0.11	0.12	2.44

[a] Standard error 20%. [b] Mutation selected with compound **1**. [c] Mutation selected with ritonavir. [d] Mutation selected with saquinavir. [e] Mutation selected with nelfinavir.

Table 2. HIV-1 Protease Inhibitory Activity of (1*S*,2*R*)-(−)-*cis*-1-Amino-2-indanol Compounds



					ED$_{50}$ MT4/mutant HIV-1 (μM)			
compd	X-	Y-	K_i[a] (nM)	ED$_{50}$ WT (μM)	V32I, M46I, A71V, V82A[b]	M46I, V82F, I84V[c]	A71V, I84V, L90M[d]	D30N, S37N, K45I, M46I, A71V, L90M[e]
2	H	H	1.22	0.10	0.46	1.28	0.07	0.10
9a	2-F	H	3.26	0.05	0.27	0.51	0.08	0.21
9b	3-F	H	7.13	0.06	0.18	0.53	0.95	0.21
9c	4-F	H	5.39	0.25	1.13	1.13	nd[f]	0.56
9d	2-F	3-F	4.00	0.03	0.24	0.88	0.05	0.06
9e	2-F	4-F	1.65	0.11	0.67	1.73	0.37	0.25
9f	2-F	5-F	3.29	0.02	0.16	0.71	0.08	0.10
9g	2-F	6-F	1.64	0.06	0.31	1.39	0.13	0.25
9h	3-F	4-F	3.90	0.13	1.05	1.30	0.16	0.30
9i	3-F	5-F	5.00	0.05	0.23	1.06	0.09	0.24
ritonavir			0.82	0.06	0.98	2.47	0.41	0.15
saquinavir			0.23	0.01	0.01	0.01	0.08	0.03
nelfinavir			0.23	0.02	0.07	0.11	0.12	2.44

[a] Standard error 20%. [b] Mutation selected with compound **1**. [c] Mutation selected with ritonavir. [d] Mutation selected with saquinavir. [e] Mutation selected with nelfinavir. [f] nd, not determined.

valine series the 2-, 3-, and 4-fluoro derivatives (**8a**−**c**, respectively) were equipotent in the enzyme essay, whereas the 2-fluoro compound exhibited the most pronounced activity in the cell system. This tendency can also be discerned in the indanolamine series (**9a**−**c**), but in that case the analysis is complicated by

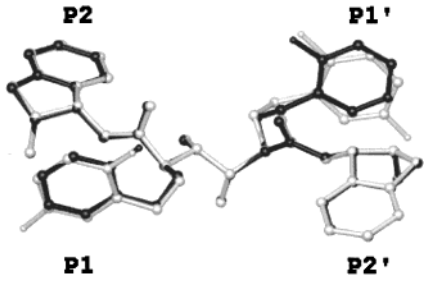


Figure 4. Superimposition of compound **9a** (black) and **9f** (gray) bound to the active site of HIV-1 PR. The mono- and disubstituted fluoro compounds have the same overall binding conformation. However, there is a small conformational difference in the P1′ orientation between compounds **9a** and **9f**. This difference has only a minor effect on the positioning of the fluorine substituents in the S1′ subsite, and it is related to the asymmetric positioning of the central diols. The image was compiled using the protein modeling software O[42] and the Web-based imaging program MOLRAY.[43]

variations in the K_i values. It is notable that in the indanolamine series, but not the valine series (cf. **8b** and **9b**), the 3-fluoro benzyl group was apparently less well accommodated in the enzyme. Considering the disubstituted derivatives, a 2-fluoro substitution was again favorable, and the most potent of all were the indanolamine **9d** (2,3-difluoro) and especially **9f** (2,5-difluoro). The latter compound had an ED_{50} value of 0.02 μM, despite its moderate K_i value of 3.29 nM (cf. nelfinavir in the same assays, which had an ED_{50} of 0.02 μM and a K_i of 0.23 nM). However, the most convincing results regarding the ability of fluorine substitution to improve antiviral activity in cell assays was observed for **9b**, which had an ED_{50} value of 0.06 μM and a K_i value as high as 7.13 nM.

X-ray Crystallography. The monofluoro substituted compound **9a** and the difluoro substituted analogue **9f** were cocrystallized with HIV-1 PR, and their structures were determined. When associated to the active site, **9a** and **9f** adopt a similar overall binding conformation (Figure 4). The hydroxy group of the indanolamine in P2/P2′ forms a hydrogen bond to the backbone nitrogen of D29 (3.0 Å). Furthermore, the structures reveal that one of the hydroxyls of the central diol points toward the D25/D125 residues in the active site and is hydrogen bonded to both carboxyl oxygens. The other hydroxyl group points away from the active site and is hydrogen bonded to one of the carbonyls. This interaction pattern of the diol results in asymmetric binding of this class of compounds.[25]

In compounds **9a** and **9f**, the 2-fluoro substituent is positioned in range for hydrophobic contacts with P81, V82, and I50. As deduced from the 3D structure, it is possible that the 5-fluoro substituent of **9f** participates in a hydrogen bond interaction with the R8 side chain (2.9 Å) at the water interface of the S1/S1′ subsites (Figure 5). However, the K_i values do not indicate that such a favorable interaction is established (cf. **9a** and **9f**, with K_i values of 3.26 and 3.29 nM, respectively). Compounds **9a** and **9f** exhibit a minor conformational difference in the P1′ orientation, but this slight dissimilarity seems to have only a minor effect on the positioning of the fluorine substituents in the S1′ subsite and is related to the asymmetric positioning of the central diols. As a consequence of close packing interactions to the P2/P2′ arms and S1/S1′ subsites, the phenyl rings are held coplanar in both the mono- and disubstituted compounds.

Conclusion

In summary, we discovered two P1/P1′ fluoro substituted benzyl analogues (**9d** and **9f**) with very potent anti-HIV activity on wild type and a wide range of mutant HIV-1 strains. Closer examination of the substitution pattern and antiviral activity shows that the 2-position in combination with substitution at the 3- or 5-position is most favorable for fluoro substitution. Our results strongly suggest that fluoro substitution might provide an efficient tool for improvement of antiviral activity.

Experimental Section

Chemistry. General Information. ^1H and ^{13}C NMR spectra were recorded on a Bruker AF-250 instrument, using DMSO-d_6 or $CDCl_3$ with Me_4Si as an internal standard, as solvents. Chemical shifts are given in ppm (δ scale). Thin-layer chromatography was performed on Merck precoated 60 F-254 plates, and spots were visualized with UV light and by charring with EtOH/H_2SO_4/HOAc/*p*-anisaldehyde 90:3:1:2. Column chromatography was performed using silica gel 60 (0.040−0.063 mm, Merck). Melting points were recorded on an electrothermal melting point apparatus and are uncor-

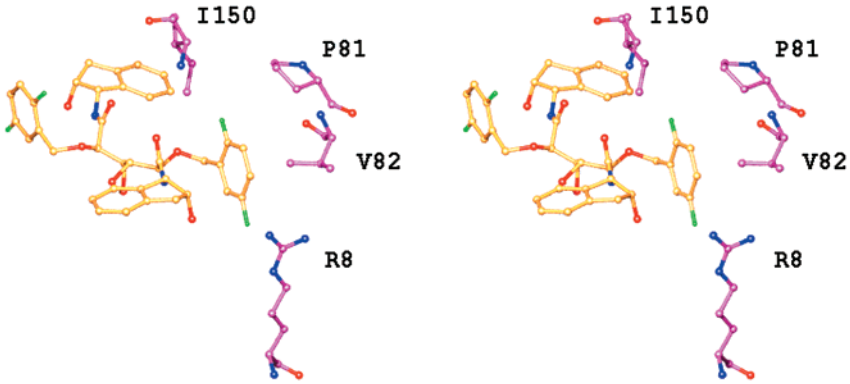


Figure 5. Stereoview of compound **9f** bound to the active site of HIV-1 PR. This orientation visualizes the interactions between the disubstituted phenyl ring of the P1 arm and the S1 subsite. The residues P81, V84, and I50 are within 4.0 Å of the 2-fluoro substituent, suggesting the presence of hydrophobic interactions. The 5-fluoro substituent might form a hydrogen bond to the guanidine group of R8 at the water interface of S1 (2.9 Å). The P1/P1′ arms are positioned for optimal hydrophobic interactions with the P2/P2′ arms and the S2/S2′ subsites. The image was compiled using the protein modeling software O[42] and the Web-based imaging program MOLRAY.[43]

rected. Optical rotations were obtained on a Perkin-Elmer 141 polarimeter. Specific rotations ($[\alpha]_D$) are reported in deg/dm, the concentration (c) values are given in g/100 mL of the specified solvent and were recorded at 21 ± 2 °C. Samples were lyophilized from p.a. dioxane prior to elemental analysis and biological testing. Elemental analyses were performed by Analytische Laboratorien, Lindlar, Germany, and the results are within ±0.4% of calculated values.Samples sent for elemental analysis were lyophilized from p.a. dioxane or water. Standard workup: organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo.

(2-Fluorobenzyl)-2,2,2-trichloroacetimidate (4a). Tetrabutylammonium hydrogen sulfate (10 mg) was added to a stirred and cooled (0 °C) mixture of 2-fluorobenzyl alcohol **3a** (0.510 g, 4.04 mmol) in CH_2Cl_2 and 50% aqueous KOH (20 mL, 1:1). After 5 min, trichloroacetonitrile (0.49 mL, 4.85 mmol) was added. The mixture was stirred for 30 min at 0 °C and 2 h at room temperature. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried and concentrated to give **4a** (0.973 g, 89%), as a yellow oil. The formed trichloroacetimidate was used without further purification. ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.41 (s, 2H), 7.05−7.19 (m, 2H), 7.28−7.42 (m, 2H), 7.46−7.57 (m, 2H), 8.44 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 64.7, 64.8, 91.2, 115.4 (d, J_{CF} = 20.3), 122.6 (d, J_{CF} = 14.8), 124.1 (d, J_{CF} = 3.7), 130.1 (m, 2C), 160.7 (d, J_{CF} = 247.9), 162.4.

(3-Fluorobenzyl)-2,2,2-trichloroacetimidate (4b). Compound **4b** was prepared from 3-fluorobenzyl alcohol **3b** in 95% yield by the same procedure as described for **4a**. ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.29 (s, 2H), 7.00−7.13 (m, 3H), 7.31−7.44 (m, 1H), 8.4 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 69.6, 91.2, 114.3 (d, J_{CF} = 21.3), 114.9 (d, J_{CF} = 22.2), 123.0 (m), 130.0 (d, J_{CF} = 7.4), 138.1 (d, J_{CF} = 7.4), 162.0 (d, J_{CF} = 243.0), 162.2.

(4-Fluorobenzyl)-2,2,2-trichloroacetimidate (4c). Compound **4c** was prepared from 4-fluorobenzyl alcohol **3c** in 94% yield by the same procedure as described for **4a**. ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.31 (s, 2H), 6.94−7.16 (m, 2H), 7.41−7.49 (m, 2H), 8.4 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 70.0, 90.4, 115.4 (d, 2C, J_{CF} = 22.2), 129.7 (d, 2C, J_{CF} = 7.4), 131.2 (m), 162.6 (d, J_{CF} = 247.8), 162.4.

(2,3-Difluorobenzyl)-2,2,2-trichloroacetimidate (4d). Compound **4d** was prepared from 2,3-difluorobenzyl alcohol **3d** in 96% yield by the same procedure as described for **4a**. ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.42 (s, 2H), 7.05−7.18 (m, 2H), 7.21−7.30 (m, 1H), 8.45 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 64.2, 91.1, 117.3 (d, J_{CF} = 16.6), 124.1 (m), 124.6 (d, J_{CF} = 3.7), 125.1 (d, J_{CF} = 11.1), 149.6 (m, 2C), 162.3.

(2,4-Difluorobenzyl)-2,2,2-trichloroacetimidate (4e). Compound **4e** was prepared from 2,4-difluorobenzyl alcohol **3e** in 98% yield by the same procedure as described for **4a**. ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.33 (s, 2H), 6.74−6.89 (m, 2H), 7.41−7.56 (m, 1H), 8.5 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 64.1, 91.1, 104.0 (t, J_{CF} = 24.9), 111.2 (dd, J_{CF} = 3.7, 20.3), 118.7 (dd, J_{CF} = 3.7, 18.5), 131.5 (m), 161.9 (dd, 2C, J_{CF} = 112.7, 246.0), 162.3.

(2,5-Difluorobenzyl)-2,2,2-trichloroacetimidate (4f). Compound **4f** was prepared from 2,5-difluorobenzyl alcohol **3f** in 97% yield by the same procedure as described for **4a**. ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.40 (s, 2H), 6.94−7.11 (m, 2H), 7.20−7.32 (m, 1H), 8.5 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 64.0, 91.0, 116.2 (m, 3C), 124.5 (m), 157.4 (dd, 2C, J_{CF} = 242.3, 138.7), 162.2.

(2,6-Difluorobenzyl)-2,2,2-trichloroacetimidate (4g). Compound **4g** was prepared from 2,6-difluorobenzyl alcohol **3g** in 93% yield by the same procedure as described for **4a**. ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.41 (s, 2H), 6.83−7.02 (m, 2H), 7.28−7.40 (m, 1H), 8.45 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 58.8, 91.1, 111.4 (m, 3C), 131.0 (m), 161.6 (m, 2C), 162.5.

(3,4-Difluorobenzyl)-2,2,2-trichloroacetimidate (4h). Compound **4h** was prepared from 3,4-difluorobenzyl alcohol **3h** in 98% yield by the same procedure as described for **4a**. ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.29 (s, 2H), 7.10−7.22 (m, 2H), 7.27−7.36 (m, 1H), 8.45 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 58.9, 91.1, 117.0 (m, 3C), 124.0 (m), 132.5 (m), 150.1 (m, 2C), 162.3.

(3,5-Difluorobenzyl)-2,2,2-trichloroacetimidate (4i). Compound **4i** was prepared from 3,5-difluorobenzyl alcohol **3i** in 99% yield by the same procedure as described for **4a**. ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.3 (s, 2H), 6.7−6.8 (m, 1H), 6.9−7.05 (m, 2H), 8.45 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 69.0, 91.0, 103.6 (t, J_{CF} = 25.9), 110.1 (d, 2C, J_{CF} = 25.9), 139.4 (m), 162.2, 162.6 (m, 2C).

L-Mannaro-1,4:3,6-dilactone (6). 6 was prepared from L-mannonic-γ-lactone **5** by the procedure described by Alterman.[25] The title compound was obtained as a white solid in 40% yield. ^{1}H NMR (250 MHz, DMSO-d_6) δ 4.77 (d, 2H, J = 4.02), 5.05 (d, 2H, J = 4.02), 6.43 (brs); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 69.0, 75.7, 174.1.

2,5-*O*-Bis-(2-fluorobenzyl)-L-mannaro-1,4:3,6-dilactone (7a). Compound **6** (0.200 g, 1.15 mmol) and 2-fluorobenzyl trichloroacetimidate **4a** (0.930 g, 3.44 mmol) were dissolved in dry dioxane (20 mL) with vigorous stirring in an N_2 atmosphere. Trifluoromethanesulfonic acid (107 μL) was slowly added. Within 1−2 h the color changed to a reddish-brown. After 6 h the reaction mixture was filtered through a plug of SiO_2/$NaHCO_3$/SiO_2, eluated with dioxane (20 mL), and then concentrated and dried under vacuum overnight. The resulting solid was suspended in hot Et_2O, and the Et_2O was decanted. This procedure was repeated twice, filtering the final time to obtain the bisbenzylated dilactone. The resulting solid was crystallized from $CHCl_3$ to give 0.303 g (68%) of the title compound as a white solid: mp 172−173 °C; $[\alpha]_D$ = −128.32 (c = 1.01, DMSO); ^{1}H NMR (250 MHz, DMSO-d_6) δ 4.80 and 4.85 (q, 4H, J_{AB} = 19.9), 4.97 (d, 2H, J = 3.7), 5.30 (d, 2H, J = 3.8), 7.13−7.24 (m, 4H), 7.36−7.55 (m, 4H); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 65.7, 65.8, 74.2, 75.0, 115.2 (d, J_{CF} = 20.3), 123.7 (d, J_{CF} = 14.8), 124.4 (d, J_{CF} = 3.7), 130.4 (m, 2C), 160.2 (d, J_{CF} = 246.0), 171.4. Anal. ($C_{20}H_{16}F_2O_6$) C, H.

2,5-*O*-Bis-(3-fluorobenzyl)-L-mannaro-1,4:3,6-dilactone (7b). Compound **7b** was obtained as a white solid (57% yield) from **4b** by the same procedure as reported for **7a**: mp 174−175 °C; $[\alpha]_D$ = −137.96 (c = 0.98, DMSO); ^{1}H NMR (250 MHz, DMSO-d_6) 4.76 and 4.81 (q, 4H, J_{AB} = 18.3), 4.92 (d, 2H, J = 3.7), 5.24 (d, 2H, J = 4.0), 7.10−7.25 (m, 6H), 7.39−7.50 (m, 2H); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 71.1, 74.3, 74.7, 114.0 (d, J_{CF} = 20.3), 114.1 (d, J_{CF} = 22.3), 123.3 (m), 130.0 (d, J_{CF} = 7.4), 140.1 (d, J_{CF} = 7.4), 162.0 (d, J_{CF} = 243.0), 171.6. Anal. ($C_{20}H_{16}F_2O_6$) C, H.

2,5-*O*-Bis-(4-fluorobenzyl)-L-mannaro-1,4:3,6-dilactone (7c). Compound **7c** was obtained as a white solid (54% yield) from **4c** by the same procedure as reported for **7a**: mp 157−158 °C; $[\alpha]_D$ = −77.17 (c = 0.92, DMSO); ^{1}H NMR (250 MHz, DMSO-d_6) δ 4.72 and 4.77 (q, 4H, J_{AB} = 18.9), 4.91 (d, 2H, J = 4.0), 5.26 (d, 2H, J = 4.0), 7.13−7.22 (m, 4H), 7.38−7.49 (m, 4H); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 71.2, 74.3, 74.7, 115.1 (m, 2C), 129.7 (m, 2C), 133.3 (m), 161.8 (d, J_{CF} = 247.8), 171.6. Anal. ($C_{20}H_{16}F_2O_6$) C, H.

2,5-*O*-Bis-(2,3-difluorobenzyl)-L-mannaro-1,4:3,6-dilactone (7d). Compound **7d** was obtained as a white solid (86% yield) from **4d** by the same procedure as reported for **7a**: mp 213−214 °C; $[\alpha]_D$ = −132.95 (c = 1.05, DMSO); ^{1}H NMR (250 MHz, DMSO-d_6) δ 4.89 (m, 4H), 5.00 (d, 2H, J = 4.0), 5.35 (s, 2H, J = 4.0), 7.21−7.52 (m, 6H); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 65.5, 74.2, 75.0, 117.4 (d, J_{CF} = 16.6), 124.9 (d, J_{CF} = 7.4), 125.6 (d, J_{CF} = 3.7), 126.3 (d, J_{CF} = 11.1), 148.6 (m, 2C), 171.3. Anal. ($C_{20}H_{14}F_4O_6$) C, H.

2,5-*O*-Bis-(2,4-difluorobenzyl)-L-mannaro-1,4:3,6-dilactone (7e). Compound **7e** was obtained as a white solid (71% yield) from **4e** by the same procedure as reported for **7a**. For **7e**−**i**, the product precipitates from the reaction mixture and was filtered off to give a white solid prior to filtration through $NaHCO_3$/SiO_2. The filtrate was treated in the same manner as for **7a**: mp 203−204 °C; $[\alpha]_D$ = −138.24 (c = 1.02, DMSO); ^{1}H NMR (250 MHz, DMSO-d_6) δ 4.77 and 4.83 (q, 4H, J_{AB} = 20.1), 4.92 (d, 2H, J = 2.2), 5.29 (d, 2H, J = 4.0), 7.04−7.16 (m, 2H), 7.20−7.35 (m, 2H), 7.51−7.59 (m, 2H); ^{13}C NMR (62.9

MHz, DMSO-d_6) δ 65.4, 74.2, 74.9, 103.9 (t, J_{CF} = 24.9), 111.4 (dd, J_{CF} = 3.7, 20.3), 120.3 (dd, J_{CF} = 3.7, 18.5), 132.1 (m), 161.2 (dd, 2C, J_{CF} = 112.8, 246.0) 171.3. Anal. ($C_{20}H_{14}F_4O_6$) C, H.

2,5-*O*-Bis-(2,5-difluorobenzyl)-L-mannaro-1,4:3,6-dilactone (7f). Compound **7f** was obtained as a white solid (59% yield) from **4f** by the same procedure as reported for **7e**: mp 195−196 °C; $[\alpha]_D$ = −109.25 (c = 1.06, DMSO); ^{1}H NMR (250 MHz, DMSO-d_6) δ 4.80 and 4.86 (q, 4H, J_{AB} = 19.7), 5.01 (d, 2H, J = 4.0), 5.34 (d, 2H, J = 4.0), 7.20−7.42 (m, 6H); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 65.5, 74.2, 75.1, 116.6, (m, 3C), 125.6 (m), 157.8 (m, 2C), 171.3. Anal. ($C_{20}H_{14}F_4O_6$) C, H.

2,5-*O*-Bis-(2,6-difluorobenzyl)-L-mannaro-1,4:3,6-dilactone (7g). Compound **7g** was obtained as a white solid (93% yield) from **4g** by the same procedure as reported for **7e**: mp 220−221 °C; $[\alpha]_D$ = −140.41 (c = 0.98, DMSO); ^{1}H NMR (250 MHz, DMSO-d_6) δ 4.81 (m, 4H), 4.90 (d, 2H, J = 3.7), 5.28 (d, 2H, J = 3.7), 7.09−7.22 (m, 4H), 7.43−7.57 (m, 2H); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 59.6, 74.2, 75.0, 111.6, (m, 3C), 131.0 (m), 160.1 (m, 2C), 171.2. Anal. ($C_{20}H_{14}F_4O_6$) C, H.

2,5-*O*-Bis-(3,4-difluorobenzyl)-L-mannaro-1,4:3,6-dilactone (7h). Compound **7h** was obtained as a white solid (71% yield) from **4h** by the same procedure as reported for **7e**: mp 192−193 °C; $[\alpha]_D$ = −136.17 (c = 0.94, DMSO); ^{1}H NMR (250 MHz, DMSO-d_6) 4.72 and 4.76 (q, 4H, J_{AB} = 18.7), 4.92 (d, 2H, J = 3.7), 5.24 (d, 2H, J = 3.7), 7.20−7.31 (m, 2H), 7.39−7.54 (m, 4H); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 70.6, 74.3, 74.8, 116.9 (m, 2C), 124.6 (m), 134.6 (m), 149.9 (m, 2C), 171.5. Anal. ($C_{20}H_{14}F_4O_6$) C, H.

2,5-*O*-Bis-(3,5-difluorobenzyl)-L-mannaro-1,4:3,6-dilactone (7i). Compound **7i** was obtained as a white solid (59% yield) from **4i** by the same procedure as reported for **7e**: mp 221−222 °C; $[\alpha]_D$ = −127.63 (c = 0.80, DMSO); ^{1}H NMR (250 MHz, DMSO-d_6) δ 4.78 (m, 4H), 4.95 (d, 2H, J = 3.3), 5.32 (d, 2H, J = 3.7), 7.12−7.24 (m, 6H); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 70.6, 74.3, 75.0, 103.2 (t, J_{CF} = 26.0), 110.3 (d, 2C, J_{CF} = 25.9), 141.6 (m), 162.0 (m, 2C), 171.4. Anal. ($C_{20}H_{14}F_4O_6$) C, H.

***N*1,*N*6-Bis-[(1*S*)-2-methyl-1-(methylcarbamoyl)propyl]-(2*R*,3*R*,4*R*,5*R*)-2,5-bis-(2-fluorobenzyloxy)-3,4-dihydroxyhexanediamide (8a).** l-Valine methylamide[38] (38 mg, 0.29 mmol) in dry 1,2-dichloroethane (3 mL) was added to a solution of **7a** (47 mg, 0.12 mmol) and 2-hydroxypyridine (10 mg, 0.12 mmol) in dry 1,2-dichloroethane (2 mL). The resulting mixture was stirred at 70 °C overnight and concentrated. The residue was dissolved in CH_2Cl_2 (9 mL) and MeOH (1 mL), and the organic phase was washed with 1 M HCl (5 mL), followed by saturated aqueous $NaHCO_3$ (5 mL), and then dried, filtered, and concentrated. Column chromatography (CH_2Cl_2−MeOH 24:1 → 14:1) gave 34 mg (44%) of the title compound as a white solid: mp 220−221 °C; $[\alpha]_D$ = +10.91 (c = 0.55, DMSO); ^{1}H NMR (250 MHz, DMSO-d_6) δ 0.93 (dd, 12H, J = 6.0), 2.16 (m, 2H), 2.68 (d, 6H, J = 4.4), 3.81 (dd, 2H, J = 6.9), 4.03 (d, 2H, J = 7.3), 4.17 (q, 2H, J = 2.1, 6.7), 4.60 (m, 4H), 4.89 (d, 2H, J = 7.1), 7.13−7.47 (m, 8H), 7.67 (d, 2H, J = 9.0), 7.92 (d, 2H, J = 4.6); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 18.2, 19.7, 26.2, 31.7, 59.8, 67.4, 72.4, 81.6, 116.2 (d, J_{CF} = 22.2), 125.4 (d, J_{CF} = 3.7), 125.7 (d, J_{CF} = 22.2), 131.5 (d, J_{CF} = 48.1), 131.6 (d, J_{CF} = 44.4), 159.8 (d, J_{CF} = 246.0), 173.3, 173.8. Anal. ($C_{32}H_{44}F_2N_4O_8$) C, H, N.

***N*1,*N*6-Bis-[(1*S*)-2-methyl-1-(methylcarbamoyl)propyl]-(2*R*,3*R*,4*R*,5*R*)-2,5-bis-(3-fluorobenzyloxy)-3,4-dihydroxyhexanediamide (8b).** The title compound was prepared in 30% yield from **7b** by the same procedure as described for **8a**: mp 230−231 °C; $[\alpha]_D$ = +11.17 (c = 0.94, DMSO); ^{1}H NMR (250 MHz, DMSO-d_6) δ 0.85 (q, 12H, J = 3.3), 2.02 (m, 2H), 2.6 (d, 6H, J = 4.4), 3.86 (dd, 2H, J = 7.5), 4.04 (d, 2H, J = 8.0), 4.21 (dd, 2H, J = 6.9, 8.7), 4.48 (m, 4H), 4.86 (d, 2H, J = 7.7), 7.07−7.24 (m, 6H), 7.29−7.43 (m, 2H), 7.76 (d, 2H, J = 8.8), 7.95 (d, 2H, J = 4.8); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 17.9, 19.1, 25.3, 30.4, 57.6, 69.5, 70.1, 79.3, 113.9 (d, J_{CF} = 22.2), 114.0 (d, J_{CF} = 20.3), 123.1 (m), 130.0 (d, J_{CF} = 7.4), 140.9 (d, J_{CF} = 7.4), 162.0 (d, J_{CF} = 242.2), 170.2, 171.0. Anal. ($C_{32}H_{44}F_2N_4O_8$) C, H, N.

***N*1,*N*6-Bis-[(1*S*)-2-methyl-1-(methylcarbamoyl)propyl]-(2*R*,3*R*,4*R*,5*R*)-2,5-bis-(4-fluorobenzyloxy)-3,4-dihydroxyhexanediamide (8c).** The title compound was prepared in 43% yield from **7c** by the same procedure as described for **8a**: mp 237−238 °C; $[\alpha]_D$ = +9.26 (c = 0.68, DMSO). ^{1}H NMR (250 MHz, DMSO-d_6) δ 0.79 (dd, 12H, J = 4.6, 6.5), 1.96 (m, 2H), 2.59 (d, 6H, J = 4.1), 3.83 (dd, 2H, J = 6.9), 4.01 (d, 2H, J = 7.3), 4.17 (q, 2H, J = 2.0, 6.7), 4.52 (m, 4H), 4.91 (d, 2H, J = 7.1), 7.09−7.44 (m, 8H), 7.71 (d, 2H, J = 9.0), 7.89 (d, 2H, J = 4.6). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 18.0, 19.1, 25.3, 30.4, 57.5, 69.6, 70.3, 79.2, 114.8 (d, 2C, J_{CF} = 20.3), 129.6 (d, 2C, J_{CF} = 7.4), 134.2 (m), 161.6 (d, J_{CF} = 242.3), 170.3, 171.0. Anal. ($C_{32}H_{44}F_2N_4O_8$) C, H, N.

***N*1,*N*6-Bis-[(1*S*)-2-methyl-1-(methylcarbamoyl)propyl]-(2*R*,3*R*,4*R*,5*R*)-2,5-bis-(2,3-difluorobenzyloxy)-3,4-dihydroxyhexanediamide (8d).** The title compound was prepared in 31% yield from **7d** by the same procedure as described for **8a**: mp 204−205 °C; $[\alpha]_D$ = +7.5 (c = 0.40, DMSO); ^{1}H NMR (250 MHz, DMSO-d_6) δ 0.80 (dd, 12H, J = 4.0, 6.6), 1.92 (m, 2H), 2.59 (d, 6H, J = 4.8), 3.78 (dd, 2H, J = 7.0), 4.00 (d, 2H, J = 7.7), 4.23 (dd, 2H, J = 7.0, 8.8), 4.61 (m, 4H), 4.83 (d, 2H, J = 7.0), 7.11−7.46 (m, 6H), 7.74 (d, 2H, J = 9.1), 7.91 (d, 2H, J = 4.8); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 18.0, 19.1, 25.3, 30.4, 57.6, 64.3, 69.5, 79.2, 116.7 (d, J_{CF} = 16.6), 124.6 (d, J_{CF} = 7.4), 125.2 (d, J_{CF} = 3.7), 127.4 (d, J_{CF} = 11.1), 148.3 (dd, J_{CF} = 116.5, 247.9), 148.5 (dd, J_{CF} = 117.4, 246.9), 170.0, 171.0. Anal. ($C_{32}H_{42}F_4N_4O_8$) C, H, N.

***N*1,*N*6-Bis-[(1*S*)-2-methyl-1-(methylcarbamoyl)propyl]-(2*R*,3*R*,4*R*,5*R*)-2,5-bis-(2,4-difluorobenzyloxy)-3,4-dihydroxyhexanediamide (8e).** The title compound was prepared in 58% yield from **7e** by the same procedure as decribed for **8a**: mp 223−224 °C; $[\alpha]_D$ = +8.26 (c = 0.69, DMSO); ^{1}H NMR (250 MHz, DMSO-d_6) δ 0.89 (dd, 12H, J = 4.8, 6.2), 2.03 (m, 2H), 2.61 (d, 6H, J = 4.4), 3.79 (t, 2H, J = 7.3), 3.99 (d, 2H, J = 7.7), 4.20 (dd, 2H, J = 6.6, 8.4), 4.61 (m, 4H), 4.84 (d, 2H, J = 7.3), 7.04−7.23 (m, 4H), 7.48 (m, 2H), 7.77 (d, 2H, J = 8.8), 7.92 (d, 2H, J = 4.8); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 17.9, 19.1, 25.3, 30.4, 57.5, 64.4, 69.6, 79.2, 103.6 (t, J_{CF} = 24.9), 111.2 (q, J_{CF} = 3.7, 20.3), 121.1 (d, J_{CF} = 18.5), 131.5 (m), 160.9 (dd, J_{CF} = 112.8, 246.0), 161.0 (dd, J_{CF} = 112.8, 246.0), 170.1, 171.0. Anal. ($C_{32}H_{42}F_4N_4O_8$) C, H, N.

***N*1,*N*6-Bis-[(1*S*)-2-methyl-1-(methylcarbamoyl)propyl]-(2*R*,3*R*,4*R*,5*R*)-2,5-bis-(2,5-difluorobenzyloxy)-3,4-dihydroxyhexanediamide (8f).** The title compound was prepared in 36% yield from **7f** by the same procedure as described for **8a**: mp 249−250 °C; $[\alpha]_D$ = +5.88 (c = 0.68, DMSO); ^{1}H NMR (250 MHz, DMSO-d_6) δ 0.82 (q, 12H, J = 3.3), 1.93 (m, 2H), 2.61 (d, 6H, J = 4.4), 3.84 (dd, 2H, J = 7.0), 4.07 (d, 2H, J = 7.7), 4.16 (dd, 2H, J = 7.0, 8.8), 4.48 (m, 4H), 4.91 (d, 2H, J = 7.0), 7.09−7.36 (m, 6H), 7.81 (d, 2H, J = 8.8), 7.88 (d, 2H, J = 4.8); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 17.9, 19.1, 25.3, 30.4, 57.6, 64.1, 64.2, 69.5, 79.4, 116.0, (m, 3C), 127.0 (m), 156.8 (dd, 2C, J_{CF} = 242.3, 147.9), 170.0, 171.0. Anal. ($C_{32}H_{42}F_4N_4O_8$) C, H, N.

***N*1,*N*6-Bis-[(1*S*)-2-methyl-1-(methylcarbamoyl)propyl]-(2*R*,3*R*,4*R*,5*R*)-2,5-bis-(2,6-difluorobenzyloxy)-3,4-dihydroxyhexanediamide (8g).** The title compound was prepared in 42% yield from **7g** by the same procedure as described for **8a**: mp 211−212 °C; $[\alpha]_D$ = +19.90 (c = 1.00, DMSO); ^{1}H NMR (250 MHz, DMSO-d_6) δ 0.82 (dd, 12H, J = 7.0), 1.93 (m, 2H), 2.58 (d, 6H, J = 4.4), 3.67 (dd, 2H, J = 5.9), 4.01(d, 2H, J = 6.6), 4.13 (dd, 2H, J = 6.6, 8.8), 4.54 (m, 4H), 4.85 (d, 2H, J = 5.9), 7.11 (m, 4H), 7.42 (m, 2H), 7.63 (d, 2H, J = 9.1), 7.87 (d, 2H, J = 4.8); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 17.8, 19.1, 25.3, 30.5, 57.3, 59.1, 70.1, 79.6, 111.5, (m, 2C), 112.8 (m), 131.0 (m), 161.5 (m, 2C), 169.9, 170.7. Anal. ($C_{32}H_{42}F_4N_4O_8$) C, H, N.

***N*1,*N*6-Bis-[(1*S*)-2-methyl-1-(methylcarbamoyl)propyl]-(2*R*,3*R*,4*R*,5*R*)-2,5-bis-(3,4-difluorobenzyloxy)-3,4-dihydroxyhexanediamide (8h).** The title compound was prepared in 92% yield from **7h** by the same procedure as for **8a**: mp 227−228 °C; $[\alpha]_D$ = +9.22 (c = 0.64, DMSO); ^{1}H NMR (250 MHz, DMSO-d_6) δ 0.77 (dd, 12H, J = 2.9, 6.6), 1.94 (m, 2H), 2.61 (d, 6H, J = 4.4), 3.80 (dd, 2H, J = 7.7), 4.02 (d, 2H, J =

8.0), 4.13 (dd, 2H, J = 6.9, 8.8), 4.39 (m, 4H), 4.79 (d, 2H, J = 7.7), 7.12−7.23 (m, 2H), 7.29−7.46 (m, 4H), 7.73 (d, 2H, J = 9.1), 7.87 (d, 2H, J = 4.8); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 18.0, 19.1, 25.3, 30.4, 57.6, 69.5, 79.1, 116.7 (m, 2C), 124.0 (m), 135.7 (m), 148.9 (m, 2C), 170.2, 171.0. Anal. ($C_{32}H_{42}F_4N_4O_8$) C, H, N.

***N*1,*N*6-Bis-[(1*S*)-2-methyl-1-(methylcarbamoyl)propyl]-(2*R*,3*R*,4*R*,5*R*)-2,5-bis-(3,5-difluorobenzyloxy)-3,4-dihydroxyhexanediamide (8i).** The title compound was prepared in 31% yield from **7i** by the same procedure as described for **8a**: mp 234−235 °C; $[\alpha]_D$ = +10.20 (c = 0.50, DMSO); ^{1}H NMR (250 MHz, DMSO-d_6) δ 0.86 (dd, 12H, J = 2.2, 6.6), 1.94 (m, 2H), 2.62 (d, 6H, J = 4.4), 3.84 (dd, 2H, J = 7.3), 3.98 (d, 2H, J = 8.1), 4.18 (dd, 2H, J = 7.0, 8.8), 4.5 (m, 4H), 4.83 (d, 2H, J = 6.9), 7.02−7.14 (m, 6H), 7.82 (d, 2H, J = 8.8), 7.94 (d, 2H, J = 4.8); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 18.0, 19.1, 25.3, 30.4, 57.6, 69.4, 79.2, 102.6 (m, J_{CF} = 25.9), 110.0 (m, 2C), 142.8 (m), 162.0 (m, 2C), 170.1, 171.0. Anal. ($C_{32}H_{42}F_4N_4O_8$) C, H, N.

***N*1,*N*6-Bis-[(2*R*)-hydroxy-1(*S*)-indanyl]-(2*R*,3*R*,4*R*,5*R*)-2,5-bis-(2-fluorobenzyloxy)-3,4-dihydroxyhexanediamide (9a).** (1*S*,2*R*)-(−)-*cis*-1-Amino-2-indanol (40 mg, 0.26 mmol) in dry 1,2-dichloroethane (3 mL) was added to a solution of **7a** (48 mg, 0.12 mmol) and 2-hydroxypyridine (12 mg, 0.13 mmol) in dry 1,2-dichloroethane (2 mL). The reaction mixture was stirred overnight at 70 °C and then concentrated. The residue was dissolved in EtOAc (10 mL) and washed with 1 M HCl (5 mL), followed by saturated aqueous $NaHCO_3$ (5 mL), and thereafter dried, filtered, and concentrated. Column chromatography (CH_2Cl_2−MeOH 24:1) gave 50 mg (61%) of the title compound as a white solid: mp 76−77 °C; $[\alpha]_D$ = +23.19 (c = 0.94, DMSO); ^{1}H NMR (250M Hz, DMSO-d_6) δ 2.74−3.15 (m, 4H), 3.95 (t, 2H, J = 7.3), 4.17 (d, 2H, J = 7.7), 4.43 (q, 2H, J = 3.8, 4.4), 4.61 and 4.65 (q, 4H, J_{AB} = 15.4), 4.89 (d, 2H, J = 7.2), 5.11 (d, 2H, J = 4.1), 5.31 (q, 2H, J = 3.6, 5.5), 7.13−7.49 (m, 16H), 7.78 (d, 2H, J = 8.7); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 40.3 (hidden in DMSO), 56.6, 64.9, 69.8, 72.0, 79.5, 114.9 (d, J_{CF} = 22.2), 124.4 (d, J_{CF} = 33.3), 124.7 (d, J_{CF} = 4.0), 126.1, 127.2, 129.8 (d, J_{CF} = 33.3), 129.9 (d, J_{CF} = 31.4), 140.6, 141.9, 159.8 (d, J_{CF} = 246.0), 170.6. Anal. ($C_{38}H_{38}F_2N_2O_8$) C, H, N.

***N*1,*N*6-Bis-[(2*R*)-hydroxy-1(*S*)-indanyl]-(2*R*,3*R*,4*R*,5*R*)-2,5-bis-(3-fluorobenzyloxy)-3,4-dihydroxyhexanediamide (9b).** The title compound was prepared in 67% yield from **7b** by the same procedure as reported for **9a**: mp 77−78 °C; $[\alpha]_D$ = +35.16 (c = 0.95, DMSO); ^{1}H NMR (250 MHz, DMSO-d_6) δ 2.87 (d, 2H, J = 16.2), 3.16 (dd, 2H, J = 4.6, 16.2), 3.97 (t, 2H, J = 7.6), 4.20 (d, 2H, J = 7.8), 4.42 (d, 2H, J = 4.0), 4.55 and 4.59 (q, 4H, J_{AB} = 17.9), 4.89 (d, 2H, J = 7.2), 5.13 (d, 2H, J = 2.5), 5.31 (m, 2H), 7.02−7.37 (m, 16H), 7.93 (d, 2H, J = 8.7); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 40.3 (hidden in DMSO), 56.6, 69.7, 70.2, 72.0, 79.5, 114.0 (d, J_{CF} = 20.3), 114.1 (d, J_{CF} = 22.2), 123.2 (m), 124.2, 124.7, 126.1, 127.2, 130.0 (d, J_{CF} = 7.4), 140.6, 141.0 (d, J_{CF} = 7.4), 141.9, 162.0 (d, J_{CF} = 242.2), 170.7. Anal. ($C_{38}H_{38}F_2N_2O_8$) C, H, N.

***N*1,*N*6-Bis-[(2*R*)-hydroxy-1(*S*)-indanyl]-(2*R*,3*R*,4*R*,5*R*)-2,5-bis-(4-fluorobenzyloxy)-3,4-dihydroxyhexanediamide (9c).** The title compound was prepared in 47% yield from **7c** by the same procedure as reported for **9a**: mp 79−80 °C; $[\alpha]_D$ = +26.40 (c = 0.75, DMSO); ^{1}H NMR (250 MHz, DMSO-d_6) δ 2.8−3.1 (m, 4H), 3.93 (t, 2H, J = 7.6), 4.09 (d, 2H, J = 8.0), 4.44 (m, 2H), 4.49 (m, 4H), 4.90 (d, 2H, J = 7.45), 5.12 (d, 2H, J = 4.2), 5.29 (2d, 2H, J = 3.6, 5.0), 7.14−7.78 (m, 16H), 8.27 (d, 2H, J = 8.8); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 40.3 (hidden in DMSO), 56.5, 69.7, 70.4, 72.0, 79.4, 114.8 (d, 2C, J_{CF} = 20.3), 124.2, 124.7, 126.1, 127.2, 129.6 (d, 2C, J_{CF} = 7.4), 134.1, 140.6, 141.9, 161.6 (d, J_{CF} = 242.3), 170.8. Anal. ($C_{38}H_{38}F_2N_2O_8$) C, H, N.

***N*1,*N*6-Bis-[(2*R*)-hydroxy-1(*S*)-indanyl]-(2*R*,3*R*,4*R*,5*R*)-2,5-bis-(2,3-difluorobenzyloxy)-3,4-dihydroxyhexanediamide (9d).** The title compound was prepared in 49% yield from **7d** by the same procedure as reported for **9a**: mp 84−85 °C; $[\alpha]_D$ = +27.53 (c = 0.81, DMSO); ^{1}H NMR (250 MHz, DMSO-d_6) δ 2.8−3.1 (m, 4H), 3.98 (t, 2H, J = 7.6), 4.14 (d, 2H, J = 6.0), 4.42 (m, 2H), 4.63 and 4.68 (q, 4H, J_{AB} = 15.0), 4.91 (d, 2H, J = 7.3), 5.13 (d, 2H, J = 4.0), 5.28 (2d, 2H, J = 4.8, 8.4), 7.10−7.34 (m, 14H), 7.87 (d, 2H, J = 8.8); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 40.2 (hidden in DMSO), 56.6, 64.5, 69.7, 70.4, 72.0, 79.4, 116.7 (d, J_{CF} = 16.6), 124.2, 124.6 (d, J_{CF} = 7.4), 124.7, 125.2 (d, J_{CF} = 3.7), 126.1, 127.2, 127.4 (d, J_{CF} = 11.1), 140.6, 141.9, 148.3, (dd, J_{CF} = 116.5, 247.9), 148.5 (q, J_{CF} = 117.4, 246.9), 170.5. Anal. ($C_{38}H_{36}F_4N_2O_8$) C, H, N.

***N*1,*N*6-Bis-[(2*R*)-hydroxy-1(*S*)-indanyl]-(2*R*,3*R*,4*R*,5*R*)-2,5-bis-(2,4-difluorobenzyloxy)-3,4-dihydroxyhexanediamide (9e).** The title compound was prepared in 59% yield from **7e** by the same procedure as reported for **9a**: mp 87−88 °C; $[\alpha]_D$ = +23.82 (c = 1.10, DMSO); ^{1}H NMR (250 MHz, DMSO-d_6) δ 2.88 (d, 2H, J = 16.5), 3.17 (2d, 2H, J = 16.4, 5.2), 3.96 (t, 2H, J = 7.7), 4.16 (d, 2H, J = 7.7), 4.45 (m, 2H), 4.55 and 4.60 (q, 4H, J_{AB} = 15.0), 4.85 (d, 2H, J = 7.3), 5.15 (d, 2H, J = 4.4), 5.23 (m, 2H), 7.01−7.21 (m, 12H), 7.48−7.55 (m, 2H), 7.82 (d, 2H, J = 8.8); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 40.3 (hidden in DMSO), 56.6, 64.5, 69.7, 70.4, 72.0, 79.4, 103.6 (t, J_{CF} = 25.8), 111.2 (dd, J_{CF} = 3.7, 20.3), 121.2 (m) 124.2, 124.7, 126.1, 127.2, 131.6 (m), 140.6, 141.9, 160.9 (dd, J_{CF} = 112.8, 246.0), 161.0 (dd, J_{CF} = 112.8, 246.0), 170.8. Anal. ($C_{38}H_{36}F_4N_2O_8$) C, H, N.

***N*1,*N*6-Bis-[(2*R*)-hydroxy-1(*S*)-indanyl]-(2*R*,3*R*,4*R*,5*R*)-2,5-bis-(2,5-difluorobenzyloxy)-3,4-dihydroxyhexanediamide (9f).** The title compound was prepared in 70% yield from **7f** by the same procedure as reported for **9a**: mp 86−87 °C; $[\alpha]_D$ = +25.16 (c = 0.64, DMSO); ^{1}H NMR (250 MHz, DMSO-d_6) δ 2.80 (d, 2H, J = 16.5), 3.11 (2d, 2H, J = 16.4, 5.2), 3.95 (m, 2H), 4.21 (d, 2H, J = 7.7), 4.42 (m, 2H), 4.59 and 4.64 (q, 4H, J_{AB} = 8.4), 4.92 (d, 2H, J = 7.3), 5.07 (d, 2H, J = 4.0), 5.27 (m, 2H), 7.04−7.34 (m, 14H), 7.88 (d, 2H, J = 8.8); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 40.2 (hidden in DMSO), 56.6, 64.2, 69.7, 72.0, 79.5, 115.4, (m, 3C), 124.2, 124.7, 126.1, 126.6 (m), 127.2, 140.6, 141.9, 156.8 (dd, 2C, J_{CF} = 242.3, 147.9), 170.4. Anal. ($C_{38}H_{36}F_4N_2O_8$) C, H, N.

***N*1,*N*6-Bis-[(2*R*)-hydroxy-1(*S*)-indanyl]-(2*R*,3*R*,4*R*,5*R*)-2,5-bis-(2,6-difluorobenzyloxy)-3,4-dihydroxyhexanediamide (9g).** The title compound was prepared in 72% yield from **7g** by the same procedure as reported for **9a**: mp 91−92 °C; $[\alpha]_D$ = +28.82 (c = 0.93, DMSO); ^{1}H NMR (250 MHz, DMSO-d_6) δ 2.80 (d, 2H, J = 16.5), 3.06 (2d, 2H, J = 16.3, 4.8), 3.85 (m, 2H), 4.11 (d, 2H, J = 7.7), 4.41 (m, 2H), 4.59 and 4.64 (q, 4H, J_{AB} = 18.6), 4.82 (d, 2H, J = 7.3), 5.08 (d, 2H, J = 4.0), 5.25 (m, 2H), 7.03−7.25 (m, 12H), 7.48 (m, 2H), 7.70 (d, 2H, J = 8.8); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 40.3 (hidden in DMSO), 56.4, 59.0, 69.9, 71.9, 79.6, 111.4, (m, 2C), 112.8 (m), 124.2, 124.7, 126.1, 127.2, 131.0 (m), 140.4, 141.9, 161.1 (m, 2C), 170.4. Anal. ($C_{38}H_{36}F_4N_2O_8$) C, H, N.

***N*1,*N*6-Bis-[(2*R*)-hydroxy-1(*S*)-indanyl]-(2*R*,3*R*,4*R*,5*R*)-2,5-bis-(3,4-difluorobenzyloxy)-3,4-dihydroxyhexanediamide (9h).** The title compound was prepared in 50% yield from **7h** by the same procedure as reported for **9a**: mp 72−73 °C; $[\alpha]_D$ = +29.48 (c = 0.96, DMSO); ^{1}H NMR (250 MHz, DMSO-d_6) δ 2.79 (d, 2H, J = 16.2), 3.08 (dd, 2H, J = 16.7, 4.8), 3.87 (m, 2H), 4.21 (m, 2H), 4.49 (m, 6H), 4.91 (m, 2H), 5.12 (d, 2H, J = 4.4), 5.28 (m, 2H), 7.09−7.45 (m, 14H), 7.78 (d, 2H, J = 8.7); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 40.2 (hidden in DMSO), 58.5, 59.9, 73.0, 74.0, 118.0 (m, 2C), 124.2, 124.7, 125.4 (m), 126.1, 127.2, 135.7 (m), 148.9 (m, 2C), 173.8. Anal. ($C_{38}H_{36}F_4N_2O_8$) C, H, N.

***N*1,*N*6-Bis-[(2*R*)-hydroxy-1(*S*)-indanyl]-(2*R*,3*R*,4*R*,5*R*)-2,5-bis-(3,5-difluorobenzyloxy)-3,4-dihydroxyhexanediamide (9i).** The title compound was prepared in 60% yield from **7i** by the same procedure as reported for **9a**: mp 74−75 °C; $[\alpha]_D$ = +38.46 (c = 0.78, DMSO); ^{1}H NMR (250 MHz, DMSO-d_6) δ 2.84 (d, 2H, J = 16.1), 3.07 (dd, 2H, J = 4.6, 16.6), 4.02 (m, 2H), 4.13 (d, 2H, J = 8.0), 4.42 (m, 2H), 4.55 and 4.61 (q, 4H, J_{AB} = 18.2), 4.93 (d, 2H, J = 7.7), 5.05 (d, 2H, J = 4.0), 5.25 (m, 2H), 7.06−7.21 (m, 14H), 7.85 (d, 2H, J = 8.8); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 40.3 (hidden in DMSO), 56.6, 66.2, 69.5, 72.0, 79.4, 102.6 (t, J_{CF} = 25.9), 110.0 (d, 2C, J_{CF} = 25.9), 124.2, 124.6, 126.0, 127.2, 140.5, 141.8, 142.8 (m), 162.1 (m, 2C), 170.5. Anal. ($C_{38}H_{36}F_4N_2O_8$) C, H, N.

Crystallography. The details of the crystallization and structure determinations will be published elsewhere. Briefly, the complexes of HIV-1 PR, **9a**, and **9f** were crystallized in space group $P2_12_12$ and determined to 1.8 and 1.9 Å resolutions, respectively.

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References

(1) Gallo, R. C.; Salahuddin, S. Z.; Popovic, M.; Shearer, G. M.; Kaplan, M.; Haynes, B. F.; Palker, T. J.; Redfield, R.; Oleske, J.; Safai, B.; White, G.; Foster, P.; Markham, P. D. Frequent Detection and Isolation of Cytopathic Retroviruses (HTLV-III) from Patients with AIDS and at Risk for AIDS. *Science* **1984**, *224*, 500−503.

(2) Gallo, R. C.; Sarin, P. S.; Gelmann, E. P.; Robert-Guroff, M.; Richardson, E.; Kalyanaraman, V. S.; Mann, D.; Sidhu, G. D.; Stahl, R. E.; Zolla-Pazner, S.; Leibowitch, J.; Popovic, M. Isolation of Human T-Cell Leukemia Virus in Acquired Immune Deficiency Syndrome (AIDS). *Science* **1983**, *220*, 865−867.

(3) Barré-Sinoussi, F.; C., C. J.; Rey, F.; Nugeyre, M. T.; Chamaret, S.; Gruest, J.; Dauguet, C.; Axler-Blin, C.; Vézinet-Brun, F.; Rouzioux, C.; Rozenbaum, W.; Montagnier, L. Isolation of a T-lymphocytic Retrovirus from a Patient at Risk for Acquired Immune Deficiency Syndrome (AIDS). *Science* **1983**, *220*, 868−871.

(4) Peng, C.; Ho, B. K.; Chang, T. W.; Chang, N. T. Role of Human Immunodeficiency Virus Type 1-Specific Protease in Core Protein Maturation and Viral Infectivity. *J. Virol.* **1989**, *63*, 2550−2556.

(5) 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.

(6) Flexner, C. J. HIV Protease Inhibitors. *N. Engl. J. Med.* **1998**, *338*, 1281−1292.

(7) Molla, A.; Granneman, G. R.; Sun, E.; Kempf, D. J. Recent developments in HIV protease inhibitor therapy. *Antiviral Res.* **1998**, 1−23.

(8) Kempf, D. J.; Sham, H. L. HIV Protease Inhibitors. *Curr. Pharm. Des.* **1996**, *2*, 225−246.

(9) De Clercq, E. Toward Improved Anti-HIV Chemotherapy: Therapeutic Strategies for Intervention with HIV Infections. *J. Med. Chem.* **1995**, *38*, 2491−2517.

(10) Wlodawer, A.; Erickson, J. W. Structure-Based Inhibitors of HIV-1 Protease. *Annu. Rev. Biochem.* **1993**, *62*, 543−585.

(11) Huff, J. R. HIV Protease: A Novel Chemotherapeutic Target for AIDS. *J. Med. Chem.* **1991**, *34*, 2305−2314.

(12) 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.; Kröhn, 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.

(13) Kempf, D. J.; Marsh, K. C.; Denissen, J. F.; McDonald, E.; Vasavanonda, S.; Flentge, C. A.; Green, B. E.; Fino, L.; Park, C. H.; Kong, X.-P.; Wideburg, N. E.; Saldivar, A.; Ruiz, L.; Kati, W. M.; Sham, H. L.; Robins, T.; Stewart, K. D.; Hsu, A.; Plattner, J. J.; Leonard, J. M.; Norbeck, D. W. ABT-538 is a Potent Inhibitor of Human Immunodeficiency Virus Protease and has High Oral Bioavailability in Humans. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 2484−2488.

(14) Vacca, J. P.; Dorsey, B. D.; Schleif, W. A.; Levin, R. B.; McDaniel, S. L.; Darke, P. L.; Zugay, J.; Quintero, J. C.; Blahy, O. M.; Roth, E.; Sardana, V. V.; Schlabach, A. J.; Graham, P. I.; Condra, J. H.; Gotlib, L.; Holloway, M. K.; Lin, J.; Chen, I.-W.; Vastag, K.; Ostovic, D.; Anderson, P. S.; Emini, E. A.; Huff, J. R. L-735,-524: An Orally Bioavailable Human Immunodeficiency Virus Type 1 Protease Inhibitor. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 4096−4100.

(15) Kalish, V.; Kaldor, S.; Shetty, B.; Tatlock, J.; Davies, J.; Hammond, M.; Dressman, B.; Fritz, J.; Appelt, K.; Reich, S.; Musick, L.; Wu, B.-W.; Su, K. Iterative Protein Structure-Based Drug Design and Synthesis of HIV Protease Inhibitors. *Eur. J. Med. Chem.* **1995**, *30* (Suppl), S201−S214.

(16) Navia, M. A.; Sato, V. L.; Tung, R. D. Design of VX-478, a Potent Inhibitor of HIV Protease. *Int. Antiviral News* **1995**, *3*, 143−145.

(17) Sham, H. L.; Kempf, D. J.; Molla, A.; Marsh, K. C.; Kumar, G. N.; Chen, C.-M.; Kati, W.; Stewart, K.; Lal, R.; Hsu, A.; Betebenner, D.; Korneyeva, M.; Vasavanonda, S.; McDonald, E.; Saldivar, A.; Japour, A. J.; Leonard, J. M.; Plattner, J.; Norbeck, D. ABT-378, a Highly Potent Inhibitor of the Human Immunodeficiency Virus Protease. *Antimicrob. Agents Chemother.* **1998**, *42*, 3218−3224.

(18) Schinzai, R. F.; Larder, B. A.; Mellors, J. W. Mutations in retroviral genes associated with drug resistance. *Int. Antiviral News* **1996**, *4*, 95−107.

(19) Molla, A.; Korneyeva, M.; Gao, Q.; Vasavanonda, S.; Schipper, P. J.; Mo, H.-M.; Markowitz, M.; Chernyavskiy, T.; Niu, P.; Lyons, N.; Hsu, A.; Granneman, G. R.; Ho, D. D.; Boucher, A. B. B.; Leonard, J. M.; Norbeck, D. W.; Kempf, D. J. Ordered accumulation of mutations in HIV protease confers resistance to ritonavir. *Nature Med.* **1996**, *2*, 760−766.

(20) Condra, J. H.; Schleif, W. A.; Blahy, O. M.; Gabryelski, L. J.; Graham, D. J.; Quintero, J. C.; Rhodes, A.; Robbins, H. L.; Roth, E.; Shivaprakash, M.; Tius, D.; Yang, T.; Teppler, H.; Squires, K. E.; Deutsch, P. J.; Emini, E. A. In vivo emergence of HIV-1 variants resistant to multiple protease inhibitors. *Nature* **1995**, *374*, 569−571.

(21) Coffin, J. M. HIV population dynamics in vivo: Implications for genetic variation, pathogenesis, and therapy. *Science* **1995**, *267*, 483−489.

(22) Wachtmeister, J.; Mühlman, A.; Classon, B.; Kvarnström, I.; Hallberg, A.; Samuelsson, B. Impact of the Central Hydroxyl Groups on the activity of Symmetrical HIV-1 Protease Inhibitors Derived From L-Mannaric Acid. *Tetrahedron* **2000**, *56*, 3219−3225.

(23) Oscarsson, K.; Classon, B.; Kvarnström, I.; Hallberg, A.; Samuelsson, B. Solid phase assisted synthesis of HIV-1 protease inhibitors. Expedient entry to unsymmetrical substitution of a C_2 symmetric template. *Can. J. Chem.* **2000**, *78*, 829−837.

(24) Alterman, M.; Andersson, H. O.; Garg, N.; Ahlsén, G.; Lövgren, S.; Classon, B.; Danielsson, H.; Kvarnström, I.; Vrang, L.; Unge, T.; Samuelsson, B.; Hallberg, A. Design and Fast Synthesis of *C*-Terminal Duplicated Potent C_2-Symmetric P1/P1′-Modified HIV-1 Protease Inhibitors. *J. Med. Chem.* **1999**, *42*, 3835−3844.

(25) Alterman, M.; Björsne, M.; Mühlman, A.; Classon, B.; Kvarnström, I.; Danielsson, H.; Markgren, P.-O.; Nillroth, U.; Unge, T.; Hallberg, A.; Samuelsson, B. Design and Synthesis of New Potent C_2-Symmetric HIV-1 Protease Inhibitors. Use of L-Mannaric Acid as a Peptidomimetic Scaffold. *J. Med. Chem.* **1998**, *41*, 3782−3792.

(26) Zucarello, G.; Bouzide, A.; Kvarnström, I.; Niklasson, G.; Svensson, S. C. T.; Brisander, M.; Danielsson, H.; Nillroth, U.; Karlén, A.; Hallberg, A.; Classon, B.; Samuelsson, B. HIV-1 Protease Inhibitors Based on Acyclic Carbohydrates. *J. Org. Chem.* **1998**, *63*, 4898−4906.

(27) Erickson, J.; Kempf, D. Structure-based design of symmetric inhibitors of HIV-1 protease. *Arch. Virol.* **1994**, *9*, 19−29.

(28) Kempf, D. J. Design of Symmetry-Based, Peptidomimetic Inhibitors of Human Immunodeficiency Virus Protease. *Methods Enzymol.* **1994**, 334−354.

(29) Patani, G. A.; LaVoie, E. J. Biosterism: A Rational Approach in Drug Design. *Chem. Rev.* **1996**, *96*, 3147−3176.

(30) Ojima, I.; Welch, J. T.; McCarthy, J. R. *Biomedical frontiers of fluorine chemistry*; American Chemical Society: Washington, DC, 1996.

(31) Filler, R.; Kobayashi, Y.; Yagupolski, L. M. *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*; Elsevier Science Publishers B. V.: Amsterdam, 1993.

(32) Filler, R.; Kobayashi, Y. *Biomedicinal aspects of fluorine chemistry*; Elsevier Biomedical Press: Amsterdam, 1982.

(33) Patil, V. J. A Simple Access to Trichloroacetimidates. *Tetrahedron Lett.* **1996**, *37*, 1481−1484.

(34) Jensen, H. S.; Limberg, G.; Pedersen, C. Benzylation of Aldonolactones with benzyl trichloroacetimidate. *Carbohydr. Res.* **1997**, 109−112.

(35) Eckenberg, P.; Groth, U.; Huhn, T.; Richter, N.; Schmeck, C. A Useful Application of Benzyl Trichloroacetimidate for the Benzylation of Alcohols. *Tetrahedron* **1993**, *49*, 1619−1624.

(36) Wessel, H.-P.; Iversen, T.; Bundle, D. R. Acid-catalysed Benzylation and Allylation by Alkyl Trichloroacetimidates. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2247−2250.

(37) Iversen, T.; Bundle, D. R. Benzyl Trichloroacetimidate, a Versatile Reagent for Acid-catalysed Benzylation of Hydroxy-groups. *J. Chem. Soc., Chem. Commun.* **1981**, 1240−1241.

(38) Poirier, V.; Calleman, C. J. The Nucleophilic Reactivity of Valine Methylamide. A Model of the N-Terminal valine Residues of Hemoglobin. *Acta Chem. Scand. Ser. B* **1983**, *37*, 817−822.

(39) Oppenshaw, H. T.; Whittaker, N. The Synthesis of Emetine and Related Compounds. Part VII. The Utility of Bifunctional catalysts in Amine-Ester Interactions. *J. Chem. Soc.* **1969**, 89−91.
(40) Danielsson, U. H.; Lindgren, M. T.; Markgren, P. O.; Nillroth, U. Investigation of an Allosteric Site of HIV-1 Proteinase Involved in Inhibition by Cu^{2+}. *Adv. Exp. Med. Biol.* **1998**, *436*, 99−103.
(41) Nillroth, U.; Vrang, L.; Markgren, P.-O.; Hultén, J.; Hallberg, A.; Danielsson, U. H. Human Immunodeficiency Virus Type 1 Proteinase Resistance to Symmetric Cyclic Urea Inhibitor Analogs. *Antimicrob. Agents Chemother.* **1997**, *41*, 2383−2388.
(42) Jones, T. A.; Zou, J.-Y.; Cowan, S. W.; Kjeldgaard, M. Improved Methods for Building Protein Models in Electron Density Maps and the Location of Errors in These Models. *Acta Crystallogr.* **1991**, *A47*, 110−119.
(43) Harris, M.; Jones, T. A. Molray: A Web-based Interface to POV-Ray for Production of High-quality Molecular-graphics Images from O Plot Files and Other Sources, 2000.

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