Flexible Cyclic Ethers/Polyethers as Novel P2-Ligands for HIV-1 Protease Inhibitors: Design, Synthesis, Biological Evaluation, and Protein−Ligand X-ray Studies[†]

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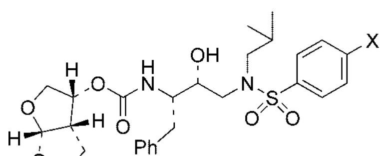
We report the design, synthesis, and biological evaluation of a series of novel HIV-1 protease inhibitors. The inhibitors incorporate stereochemically defined flexible cyclic ethers/polyethers as high affinity P2-ligands. Inhibitors containing small ring 1,3-dioxacycloalkanes have shown potent enzyme inhibitory and antiviral activity. Inhibitors **3d** and **3h** are the most active inhibitors. Inhibitor **3d** maintains excellent potency against a variety of multi-PI-resistant clinical strains. Our structure−activity studies indicate that the ring size, stereochemistry, and position of oxygens are important for the observed activity. Optically active synthesis of 1,3-dioxepan-5-ol along with the syntheses of various cyclic ether and polyether ligands have been described. A protein−ligand X-ray crystal structure of **3d**-bound HIV-1 protease was determined. The structure revealed that the P2-ligand makes extensive interactions including hydrogen bonding with the protease backbone in the S2-site. In addition, the P2-ligand in **3d** forms a unique water-mediated interaction with the NH of Gly-48.

Introduction

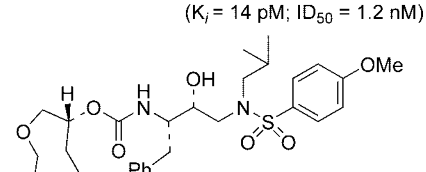
The introduction of protease inhibitors (PIs) into highly active antiretroviral therapy (HAART), a combination therapy based on coadministration of PIs with reverse-transcriptase inhibitors, marked the beginning of a new era in HIV/AIDS chemotherapy. HAART treatment regimens have led to a significant decline in the number of deaths due to HIV infection in the developed world.[1] Unfortunately, there are a number of factors that severely limit current HAART treatment regimens. High frequency of dosing, heavy pill burden, and issues of tolerability and toxicity can lead to poor adherence to treatment.[2] The need for more potent, less toxic drug regimens is quite apparent.

It is the rapid emergence of drug resistance, however, that is proving to be the most formidable problem. Mutations causing drug resistance are thought to occur spontaneously, through the recombination of mixed viral populations, and also due to drug pressure, particularly when administered at substandard doses.[3−6] A growing number of patients are developing multidrug-resistant HIV-1 variants.[7,8] There is ample evidence that these viral strains can be transmitted. Thus, the development of antiretroviral agents able to maintain potency against resistant HIV strains has become an urgent priority.

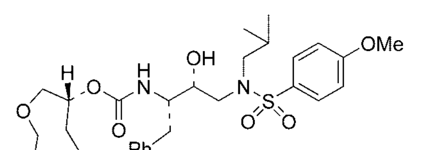
Darunavir (TMC-114, **1**, Figure 1) is a new nonpeptidic PI recently approved by the FDA for the treatment of antiretroviral therapy-experienced patients.[9] Inhibitor **1**, and its related analogue **2**, are exceedingly active against both wild-type and multidrug resistant HIV strains. Both PIs demonstrated potent in vitro activity against viral isolates resistant to currently licensed PIs.[10−12] Our structure-based design strategies for these PIs are based on the presumption that maximizing active site interactions with the inhibitor, particularly hydrogen bonding with the protein backbone, would give rise to potent inhibitors retaining activity against mutant strains.[13,14] Indeed, side chain amino acid mutations cannot easily disrupt inhibitor−backbone interactions because the active site backbone conformation of mutant proteases is only minimally distorted compared to the wild-type HIV-1 protease.[15−17] In this context, the fused bis-tetrahydrofuran (bis-THF) urethane of compounds **1** and **2** was demonstrated to be a privileged P2-ligand, being able to engage



1 (darunavir, X = NH_2)
(K_i = 16 pM; ID_{50} = 1.6 nM)
2 (TMC-126, X = OMe)
(K_i = 14 pM; ID_{50} = 1.2 nM)



3c (K_i = 0.16 nM)



3d (GRL-0255A)
(K_i = 26 pM; IC_{50} = 5 nM)

Figure 1. Structure of inhibitors **1**, **2**, and **3c**,**d**.

[†] The PDB accession code for **3d**-bound HIV-1 protease X-ray structure is 3DJK.

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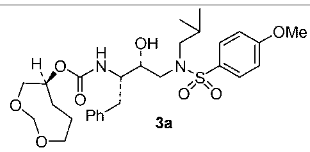
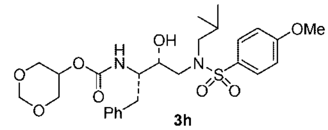
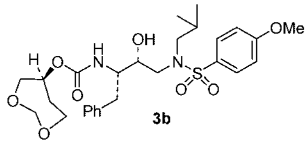
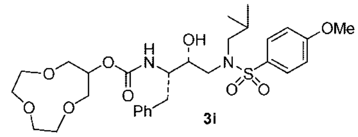
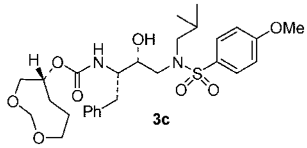
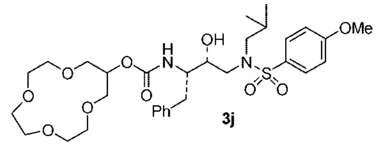
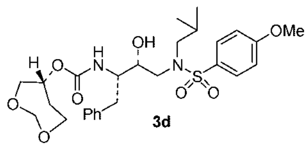
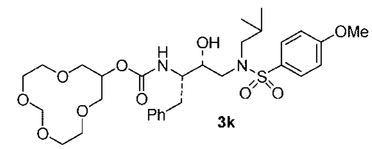
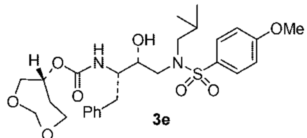
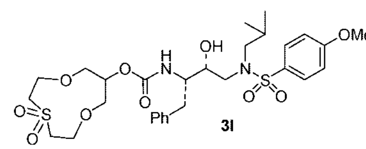
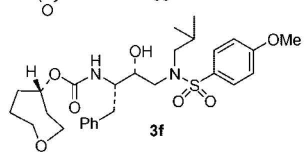
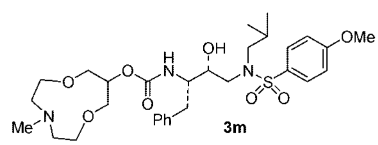
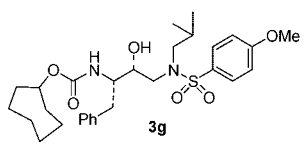
Table 1. Enzyme Inhibitory and Antiviral Activity of Inhibitors **3a−m**

entry	inhibitor	K_i (nM)	IC_{50} (nM)[a]	entry	inhibitor	K_i (nM)	IC_{50} (nM)[a]
1	 **3a**	0.15 ± 0.019	nd[b]	8	 **3h**	0.041 ± 0.002	3.4 ± 0.7
2	 **3b**	0.16 ± 0.04	30 ± 1	9	 **3i**	16 ± 2.2	nd
3	 **3c**	0.16 ± 0.011	nd	10	 **3j**	33 ± 1.9	nd
4	 **3d**	0.026 ± 0.012	4.9 ± 0.3	11	 **3k**	6.3 ± 0.57	>1000
5	 **3e**	0.81 ± 0.12	nd	12	 **3l**	1.9 ± 0.2	>1000
6	 **3f**	0.74 ± 0.15	nd	13	 **3m**	19 ± 0.76	>1000
7	 **3g**	27 ± 0.81	nd	SQV[c]	-	-	16 ± 3
				APV[d]	-	-	27 ± 6

[a] MT-2 human T-lymphoid cells exposed to HIV-1_{LAI}. [b] nd = not determined. [c] SQV = saquinavir. [d] APV = amprenavir.

in a number of hydrogen bonding interactions with the backbone atoms of amino acids at the protease S2-site.

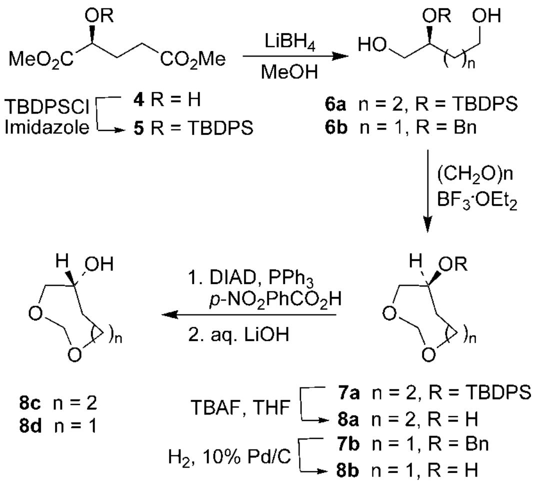
We are continuing our efforts toward the development of novel PIs characterized by a high activity against both wild-type HIV-1 and resistant strains. We further speculated that an inhibitor interacting strongly with the protein backbone, while being able to accommodate amino acid side chain variations by means of repacking with a flexible ring, would maintain significant affinity against both wild-type and mutant enzymes. With this goal in mind, we designed a series of PIs based on the (*R*)-(hydroxyethylamino)sulfonamide isostere and bearing flexible cyclic ethers and polyethers as P2-ligands (inhibitors **3a−m**, Table 1). Starting from compound **3c**, incorporating a (1*R*)-3,5-dioxacyclooctan-1-yl urethane, which can be considered as the flexible counterpart of the bis-THF moiety, we designed a series of structural variants of this inhibitor. These inhibitors contain polyether-based P2-ligands ranging from 6- to 13-membered rings coupled to a *p*-methoxyphenylsulfonamide as the P2′-ligand. Herein we report the structure-based design, synthesis, and preliminary biological evaluation of inhibitors **3a−m**. Among these inhibitors, **3d** (Figure 1) is the most potent, with an impressive enzyme inhibitory and antiviral activity (K_i = 26 pM, IC_{50} = 4.9 nM). Furthermore, a protein−ligand X-ray structure of **3d**-bound HIV-1 protease has revealed important molecular insight regarding ligand-binding site interactions.

Chemistry. The syntheses of seven- and eight-membered 1,3-dioxacycloalkanes **8a−d** for the corresponding inhibitors **3a−d** are shown in Scheme 1. Protected diol **6a** was prepared by a two-step procedure starting from (*S*)-hydroxyglutaric acid **4**, obtained by following a known protocol.[18] The hydroxyl group of **4** was protected as a *tert*-butyldiphenylsilylether **5** in quantitative yield. $LiBH_4$ reduction of both ester groups afforded **6a** in good yield.[19]

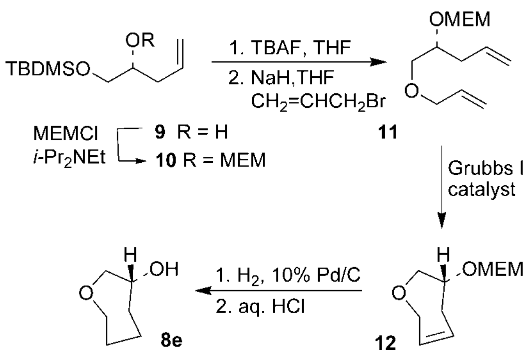
Compounds **6a** and **6b**[20] were converted to cyclic derivatives by exposure to paraformaldehyde and $BF_3 \cdot OEt_2$[21] to afford cyclic ethers **7a** and **7b** in 51% and 82% yield, respectively. Deprotection of compounds **7a** to **8a** was carried out by using n-$Bu_4N^+F^-$ in THF. Benzylether of **7b** was removed by a catalytic hydrogenation over 10% Pd−C to furnish **8b**. Mitsunobu inversion of the secondary hydroxyl groups of **8a**,**b** was accomplished by using *p*-nitrobenzoic acid, triphenylphosphine, and diisopropylazodicarboxylate in benzene at 23 °C. Saponification of the resulting esters provided **8c** and **8d**.

For the synthesis of compounds **8e** and **8f**, which represent the monoxygenated analogues of **8d**, a synthetic strategy based on a ring-closing metathesis reaction as the key step was planned (Schemes 2 and 3). Accordingly, secondary alcohol **9**[22] (Scheme

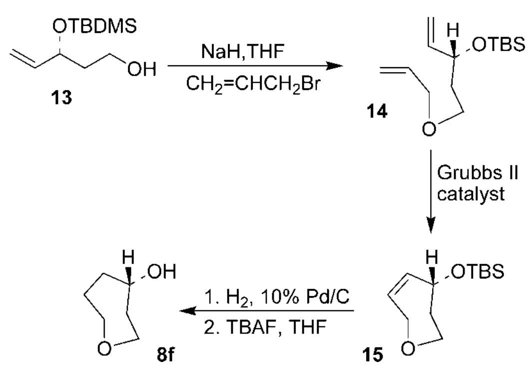
Scheme 1. Synthesis of Optically Active 1,3-Dioxacycloalkanes



Scheme 2. Synthesis of Cyclic Ether **8e**



Scheme 3. Synthesis of Cyclic Ether **8f**

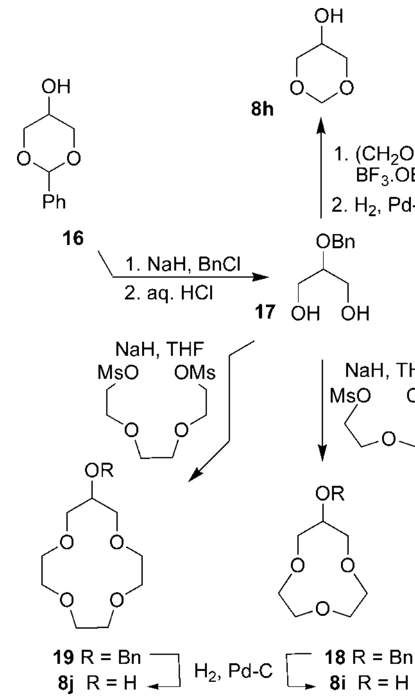


2) was protected as the corresponding methoxyethoxymethyl (MEM)-ether **10** in 90% yield using an excess of MEM-Cl in the presence of DIPEA in CH_2Cl_2.

Subsequent n-$Bu_4N^+F^-$-promoted deprotection of the TBDMS-group afforded the corresponding primary alcohol, which was treated with sodium hydride and alkylated with allyl bromide in the presence of a catalytic amount of n-$Bu_4N^+I^-$ to afford olefin **11** in 78% yield (2 steps). A 0.01 M solution of **11** in CH_2Cl_2 was then treated with a catalytic amount (5 mol%) of second generation Grubbs catalyst and heated to 45 °C to afford the cyclooxepane **12** in 94% yield. The double bond of **12** was finally reduced by catalytic hydrogenation using 10% Pd−C as the catalyst, and the MEM-ether was removed by acidic hydrolysis in a 1:1 THF/H_2O mixture to obtain the target alcohol **8e** in good overall yield.

For the synthesis of alcohol **8f** (Scheme 3), compound **13** was used as the starting material. It was in turn prepared following a described procedure starting from acrolein and *tert*-butylacetate.[23] Alkylation of the primary hydroxyl group of **13** with allyl bromide and n-$Bu_4N^+I^-$ using sodium hydride as the base furnished the ring closing metathesis precursor **14**. The cyclization reaction was performed by using second generation Grubbs catalyst (5 mol%) in CH_2Cl_2 and afforded olefin **15** in good yield. Subsequent hydrogenation of the double bond and n-$Bu_4N^+F^-$-mediated removal of TBDMS-ether finally afforded the target alcohol **8f**.

Scheme 4. Synthesis of Polyethers **8h**−**j**

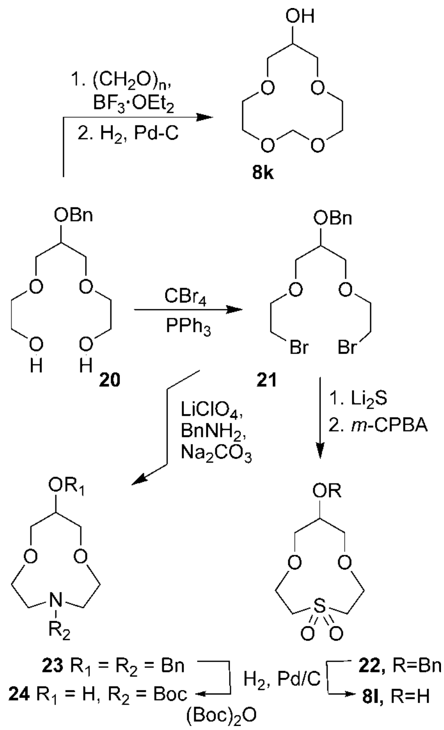


Alcohols **8h**−**j** required for the preparation of inhibitors **3h**−**j** were synthesized by starting from the common intermediate 2-benzyloxypropane-1,3-diol **17** as shown in Scheme 4. Compound **17** was prepared by alkylation of commercially available benzylidene acetal **16** with benzyl chloride in the presence of sodium hydride and a catalytic amount of n-$Bu_4N^+I^-$ in THF at 23 °C. The benzylidene group was subsequently removed by hydrolysis with 6 N HCl in a mixture (1:1) of THF and water to give 2-benzyloxy-1,3-propanediol **17** in quantitative yield. Treatment of **17** with paraformaldehyde and $BF_3 \cdot OEt_2$ as described above, followed by hydrogenolysis of the resulting *O*-benzylether afforded **8h** in 78% overall yield.

Treatment of diol **17** with an excess of sodium hydride in refluxing THF followed by addition of di(ethyleneglycol)dimesylate or tri(ethyleneglycol)dimesylate afforded macrocycles **18** and **19** in 19% and 29% yield, respectively. Dilution of the reaction mixture to assist the intramolecular cyclization reaction did not result in a significant improvement of the reaction yields. Given the poor enzymatic inhibitory activity observed for the corresponding final compounds **3i** and **3j**, no further attempts were made to improve the cyclization yield for the preparation of these 10- and 13-membered polyether rings. Compounds **18** and **19** were subsequently deprotected by hydrogenolysis to obtain alcohols **8i** and **8j**.

We planned to investigate the effect of heteroatom functionalities in the polyether rings. In this context, we prepared the compounds **8k**, **8l**, and **24** from known diols **20**[24] as shown in Scheme 5. Thus, exposure of **20** to paraformaldehyde in the presence of $BF_3 \cdot OEt_2$ furnished the corresponding cyclic

Scheme 5. Synthesis of Alcohols **8k**,**l** and **24**



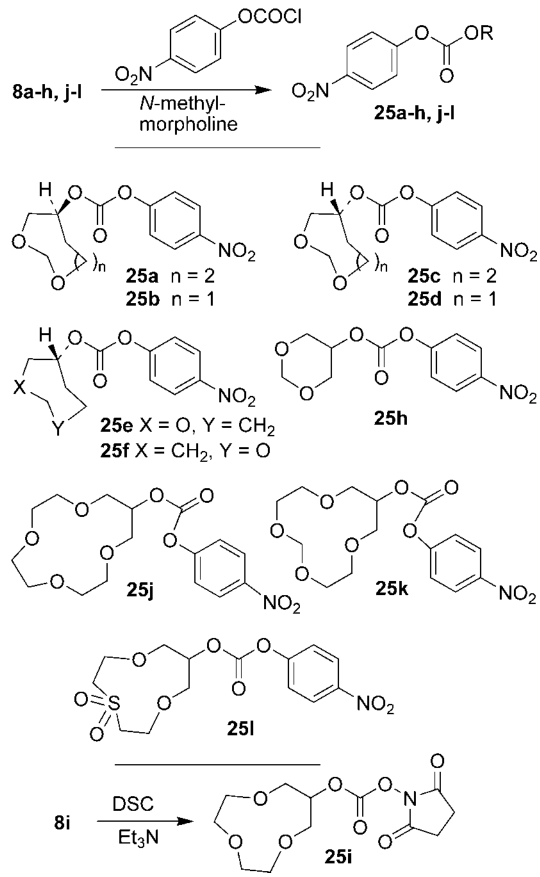
polyether product, which, upon hydrogenolysis, gave alcohol **8k**. Bromination of **20** using carbon tetrabromide and triphenylphosphine afforded dibromide **21**.[24] This dibromide was used for the synthesis of sulfone **8l** and protected amine **24**. Thus, compound **21** was reacted with one equivalent of benzylamine in refluxing MeCN in the presence of sodium carbonate, as reported by Calverley and Dale,[25] to provide **23** in 24% yield. Dimerization is the main side product in this reaction and one can reduce such dimerization by using an excess of $LiClO_4$.[26] Benzylamine **23** was hydrogenated over 10% Pd−C in the presence of di-*t*-butyl dicarbonate to provide *N*-Boc protected alcohol **24**. Sulfone **22** was obtained by cyclization of **21** with lithium sulfide, followed by oxidation of the corresponding sulfide with an excess of *m*-CPBA in CH_2Cl_2 at 23 °C. Benzyl derivative **22** was converted to **8l** by a catalytic hydrogenation over 10% Pd−C.

Scheme 6 depicts the conversion of various P2-ligands to the corresponding active carbonates for urethane formation. Accordingly, alcohols **8a−h**,**j−l** were reacted with *p*-nitrophenylchloroformate and *N*-methylmorpholine in THF at 23 °C to provide corresponding carbonates **25a−h**,**j−l** in 67−89% yields. Alcohol **8i** was converted to succinimidylcarbamate **25i** by treatment with *N*,*N*′-succinimidylcarbonate in the presence of Et_3N in MeCN in 37% isolated yield.

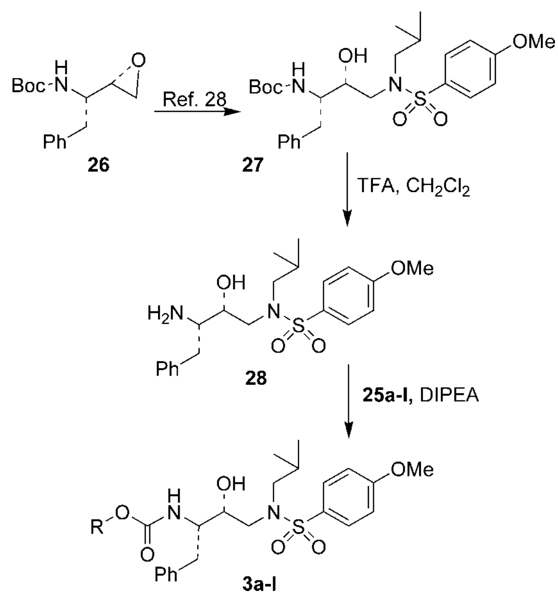
The synthesis of designed inhibitors **3a−l** is shown in Scheme 7. Methoxysulfonamide derivative **27** was prepared from commercially available epoxide **26** as described previously.[27] The Boc group in **27** was removed by exposure to a 30% solution of TFA in CH_2Cl_2 at 23 °C. The resulting amine **28** was reacted with the suitable mixed activated carbonates **25a−l** in THF at 23 °C for 2−4 days to furnish inhibitors **3a−l** in 36−89% yield.

The synthesis of inhibitor **3m** is shown in Scheme 8. Alcohol **24** was converted to active carbonate **29** as described above in Scheme 6. Reaction of **29** with amine **28** provided urethane **30** in good yield. Removal of Boc group of **30** by exposure to 30% TFA in CH_2Cl_2 furnished amine **31**. The resulting secondary

Scheme 6. Synthesis of Various Active Carbonates



Scheme 7. Synthesis of Inhibitors **3a−l**

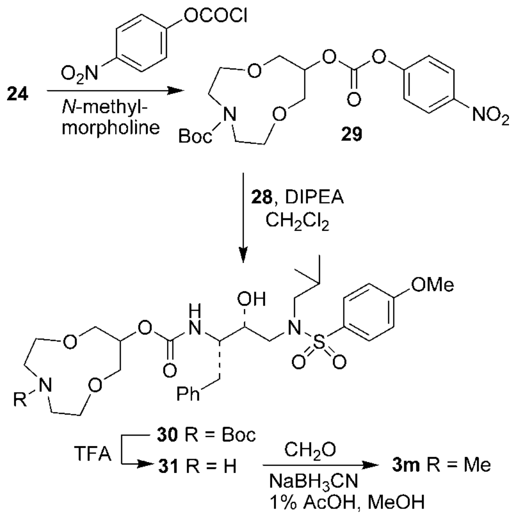


amine was subjected to a reductive amination reaction using 37% aqueous formaldehyde and sodium cyanoborohydride in 1% acetic acid in MeOH to furnish *N*-methyl derivative **3m** in 87% yield.

Results and Discussion

All inhibitors contain a (*R*)-hydroxyethylamine sulfonamide isostere with a *p*-methoxysulfonamide as the P2′-ligand and various designed cyclic ethers and polyethers as the P2-ligands.

Scheme 8. Synthesis of Inhibitor **3m**



These inhibitors were first evaluated in an enzyme inhibitory assay utilizing a protocol described by Toth and Marshall.[28] Compounds that showed potent enzymatic K_i values were then further evaluated in an antiviral assay. The results are shown in Table 1. The K_i-values denote the mean values of at least four determinations.

As it can be seen, introduction of the 8-membered (*S*)- or (*R*)-1,3-dioxacyclooctan-5-yl urethanes as P2-ligands (inhibitors **3a** and **3c**) resulted in subnanomolar inhibitors. However, these inhibitors are significantly less potent than inhibitor **2** that contains the bis-THF ligand. Interestingly, incorporation of a (5*R*)-1,3-dioxacycloheptan-5-yl urethane as the P2-ligand resulted in the most potent inhibitor **3d** in this series with a K_i value of 26 pM. We speculated that the 7-membered 1,3-dioxepanyl-ligand with *R*-configuration may bind to residues in the S2-site similar to bis-THF ligand of inhibitor **2**. Inhibitor **3d** exhibited more than 6-fold potency increase relative to epimeric (5*S*)-1,3-dioxacycloheptan-5-yl urethane **3b**, suggesting an important role for the ring stereochemistry. Inhibitors **3e–g** were prepared to assess the role played by both oxygen atoms of **3d** on the binding mode of this latter compound. As shown in Table 1, a dramatic drop in enzymatic inhibitory activity was observed when the cycloheptanol was introduced as the P2-ligand (**3g**). Moreover, nearly 30-fold reduction in enzymatic inhibitory potency of both **3e** and **3f** with respect to **3d** clearly demonstrated that both oxygen atoms are crucial for the interaction with the enzyme at the S2-subsite. It appears that both oxygen atoms engage in strong hydrogen bonding, which equally contribute to the binding affinity for the enzyme. This result was further confirmed by the determination of the X-ray crystal structure of **3d**-bound HIV-1 protease.

Further reduction of the ring size of the P2-ligand resulted in the design of inhibitor **3h**, bearing a 6-membered 1,3-dioxan-5-yl urethane. This inhibitor also showed an impressive enzymatic K_i value of 41 pM. This result suggested that the 1,3-dioxane ring could be nicely accommodated by the S2-site. Furthermore, both oxygens may be involved in specific interactions with the amino acid residues in this region.

Subsequently, we tested compounds **3i–m**, presenting larger polyether rings, but all compounds showed K_i values in the high nM range (K_is ranging from 6.3 to 33 nM), proving that large rings could not be easily accommodated at the S2-site.

However, subtle differences in the activity among these compounds suggested that not only the ring size, but also the position of the oxygen atoms within the polyether structure, could be important for inhibitory activity. In fact, compound **3k**, presenting a 12-membered ring bearing a methylenedioxy unit instead of the ethylenedioxy of **3j**, exhibited 5-fold potency enhancement compared to inhibitor **3j**. It is also more than 2-fold more potent compared to **3i**, which contains a smaller 10-membered ring. Substitution of a ring oxygen in **3i** by a *N*-Me group provided inhibitor **3m** with no change in inhibitory activity. However, replacement of ring oxygen with a SO_2 moiety provided inhibitor **3l** with a 9-fold improvement in potency. The sulfone oxygens may be involved in specific interactions with the amino acid residues at the S2 site.

In MT-2 human T-lymphoid cells exposed to HIV-1_{LAI}, inhibitors **3d** and **3h** have shown antiviral IC_{50} values of 4.9 nM and 3.4 nM, respectively (Table 1). Consistent with its enzymatic potency, compound **3b** showed an antiviral activity of 30 nM in the same assay system, while compounds **3k–m** did not exhibit appreciable antiviral properties at doses up to 1 μM. We have examined two selected compounds, **3d** and **3h**, for their activity against HIV-1 using a human CD4+ T-cell line (MT-2 cells) and human peripheral blood mononuclear cells (PBMCs) as target cells. We employed two end points for the activity against HIV-1: (i) the inhibition of the HIV-1-elicited cytopathic effect for MT-2 cells and (ii) the inhibition of HIV-1 p24 production for PBMCs.[14a] As examined in MT-2 cells as target cells, the two compounds **3d** and **3h** exerted extremely potent antiviral activity against an X4-HIV-1 isolate (HIV-1_{LAI}) with IC_{50} values of 4.9 and 3.4 nM, respectively (Table 1). Such anti-HIV-1 potency was generally parallel to the potency in enzymatic inhibition of the compounds. We further examined the two compounds in PBMCs against a clinical wild-type X4-HIV-1 isolate (HIV-$1_{ERS104pre}$) along with various multidrug-resistant clinical X4- and R5-HIV-1 isolates (Table 2).[14] The activity of **3d** and **3h** against HIV-$1_{ERS104pre}$ was more potent or at least comparable as compared to those of currently available protease inhibitors, APV, IDV, and RTV. It is interesting to note that the values of **3d** were greater than those with MT-2 cells by factors of about 4. With regard to this difference, considering that **3d** was highly potent as examined in human T cells (MT-2 cells) but its activity was slightly less in PBMCs, it is possible that relatively higher concentrations of **3d** are required to suppress HIV-1 production in chronically infected macrophages.[42] Two currently available protease inhibitors (IDV and RTV) were not capable of efficiently suppressing the replication of most of the multidrug-resistant clinical isolates examined (HIV-1_{MDR-B}, HIV-1_{MDR-G}, HIV-1_{MDR-TM}, HIV-$1_{MDR-JSL}$, and HIV-1_{MDR-MM}) with IC_{50} values of >1.0 μM. Although the two selected compounds were also less potent against the multidrug-resistant clinical isolates examined, their IC_{50} values were quite low with 0.22–0.54 μM (Table 2). During testing of the anti-HIV-1 activity of compounds **3b**, **3d**, **3h**, and **3k–m**, we examined four concentrations (1, 0.1, 0.01, and 0.001 μM) in the antiretroviral assay, conducted on three independent occasions (each assay was performed in duplicate). As noted, no cytotoxicity was observed for any of the compounds examined. Thus, it was deemed that the CC_{50} values were greater than the highest concentration, 1 μM.

X-ray Crystallography. The mode of binding of the inhibitor was determined by analyzing the atomic resolution crystal structure of HIV-1 protease with **3d**. The crystal structure was solved and refined to an R factor of 14.9% at 1.00 Å resolution. The inhibitor binds with extensive interactions from P2 to P2′ with the protease atoms and, most notably, the favorable polar

Table 2. Antiviral Activity (IC_{50}) of Inhibitors **3d** and **3h** against Clinical HIV-1 Isolates in PBMC Cells (nM)

virus	IC_{50} (nM) values[a]					
	3d	**3h**	DRV	RTV	APV	IDV
ERS104pre(wild-type)	20	6	3.5	34	33	26
MDR/TM	220 (11)	64 (10)	4 (1)	>1000 (>29)	290 (9)	>1000 (>38)
MDR/MM	250 (13)	110 (5)	17 (5)	>1000 (>29)	300 (9)	>1000 (>38)
MDR/JSL	500 (25)	330 (55)	26 (7)	>1000 (>29)	430 (13)	>1000 (>38)
MDR/B	340 (17)	230 (38)	26 (7)	>1000 (>29)	320 (10)	>1000 (>38)
MDR/C	210 (11)	160 (27)	7 (2)	>1000 (>29)	230 (7)	>1000 (>38)
MDR/G	360 (18)	300 (50)	7 (2)	>1000 (>29)	340 (10)	290 (11)
MDR/A	20 (1)	13 (2)	3 (1)	>1000 (>29)	100 (3)	>1000 (>38)

[a] Amino acid substitutions identified in the protease-encoding region compared to the consensus type B sequence cited from the Los Alamos database include L63P in HIV-$1_{ERS104pre}$; L10I, K14R, L33I, M36I, M46I, F53I, K55R, I62V, L63P, A71V, G73S, V82A, L90M, and I93L in HIV-$1_{MDR\text{-}B}$; L10I, V11I, T12E, I15V, L19I, R41K, M46L, L63P, A71T, V82A, and L90 M in HIV-$1_{MDR\text{-}G}$; L10I, K14R, R41K, M46L, I54V, L63P, A71V, V82A, L90M, I93L in HIV-$1_{MDR\text{-}TM}$; L10I, L24I, I33F, E35D, M36I, N37S, M46L, I54V, R57K, I62V, L63P, A71V, G73S, and V82A in HIV-$1_{MDR\text{-}JSL}$; and L10I, K43T, M46L, I54V, L63P, A71V, V82A, L90M, and Q92K in HIV-$1_{MDR\text{-}MM}$. HIV-$1_{ERS104pre}$ served as a source of wild-type HIV-1.The IC_{50} values were determined by employing PHA-PBMC (phytohemaglutinin-activated peripheral blood mononuclear cells) as target cells and the inhibition of p24Gag protein production as the end point. All values were determined in triplicate. DRV (Darunavir), SQV (Saquinavir), APV (Amprenavir), IDV (Indinavir).

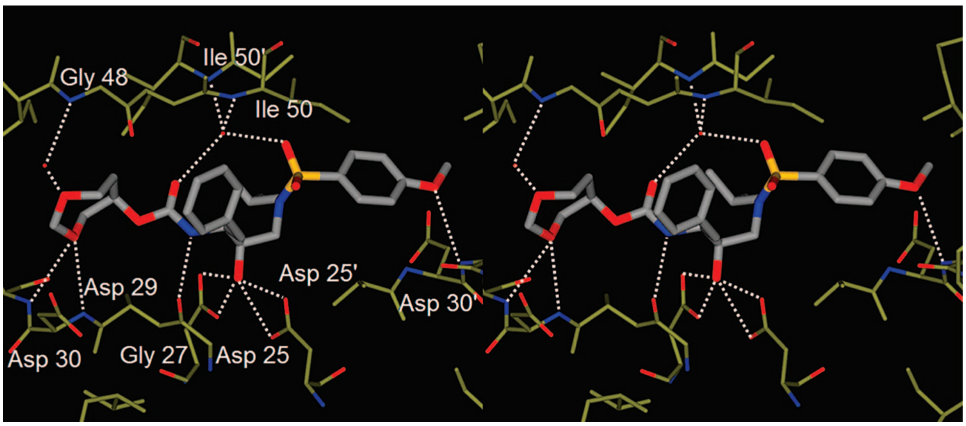


Figure 2. Stereoview of compound **3d** bound to the active site of wild-type HIV-1 protease.

interactions including hydrogen bonds, weaker C−H···O and C−H···π interactions, as shown in Figure 2. The central hydroxyl group forms hydrogen bonds to the side chain carboxylate oxygen atoms of the catalytic Asp25 and Asp25′ residues. The inhibitor hydrogen bonds with protease main chain atoms of the amides of Asp29 and Asp30, the carbonyl oxygen of Gly 27, and the water-mediated interactions with the amides of Ile50 and 50′, which is conserved in the majority of protease complexes with inhibitors[29] and substrate analogues.[30] Inhibitor **3d** has retained the water-mediated interaction with the π system of the P2′ aromatic ring, which was observed for darunavir (**1**) and GRL-98065.[31] The P2′ methoxy group forms a hydrogen bond with the amide of Asp30′. Interestingly, the P2 group forms a water-mediated interaction with the amide of Gly48, similar to the interactions described for several peptide substrate analogues.[30]

Conclusions. In summary, a series of novel and highly potent HIV-1 protease inhibitors were designed, synthesized, and evaluated. The inhibitors incorporate a variety of flexible cyclic ethers/polyethers as the P2-ligand. Inhibitors containing small size 1,3-dioxacycloakanes have shown potent inhibitory properties. In particular, inhibitors **3d** and **3h** have shown remarkable enzyme inhibitory and antiviral potency. Inhibitors incorporating medium-size cyclic polyethers or polyethers containing a sulfone or amine functionality were significantly less potent in antiviral assays. For inhibitor **3d**, we have carried out an optically active synthesis of (*R*)-1,3-dioxepan-5-ol using (*S*)-malic acid as the starting material. Syntheses of various cyclic ethers/polyethers were developed albeit in moderate yields. Inhibitor **3d** has shown excellent activity against multi-PI-resistant variants compared to other FDA approved inhibitors. A protein−ligand X-ray structure of **3d**-bound HIV-1 protease was determined at 1.0 Å resolution. One of the oxygens of the 1,3-dioxepane ligand is involved in hydrogen bonding with Asp29 and Asp30 NH's. The other oxygen is involved in a unique interaction with Gly-48 NH through a water molecule. One goal of our inhibitor design strategy is to combat drug-resistant HIV. The design of inhibitor using the concept of maximizing "backbone binding" has led to the development of PIs characterized by high potency against both wild-type and multidrug-resistant HIV-1 strains. Further design of inhibitors utilizing this molecular insight is in progress.

Experimental Section

General. All moisture sensitive reactions were carried out under nitrogen or argon atmosphere. Anhydrous solvents were obtained as follows: THF, diethyl ether and benzene, distilled from sodium and benzophenone; dichloromethane, pyridine, triethylamine, and diisopropylethylamine, distilled from CaH_2. All other solvents were HPLC grade. Column chromatography was performed with Whatman 240−400 mesh silica gel under low pressure of 5−10 psi. TLC was carried out with E. Merck silica gel 60-F-254 plates. ^{1}H and ^{13}C NMR spectra were recorded on Varian Mercury 300 and Bruker Avance 400 and 500 spectrometers. Optical rotations were measured using a Perkin-Elmer 341 polarimeter.

(*S*)-2-(*tert*-Butyldiphenylsilyloxy)pentadioic Acid Dimethyl Ester (5). A mixture of (2*S*)-hydroxypentadioic acid dimethyl ester **4**[18] (0.39 g, 2.2 mmol), imidazole (0.45 g, 6.6 mmol), and *tert*-butyldiphenylsilyl chloride (1.2 mL, 4.4 mmol) in dry DMF (4 mL) was stirred at 23 °C for 4 h. Subsequently, the reaction mixture was poured into water and the aqueous phase was extracted with Et_2O, the organic extracts were washed with 1 N HCl and brine, dried (Na_2SO_4), and the solvent was removed. The residue was purified by flash-chromatography (1:10 EtOAc/hex) to furnish 0.89 g (90%) of **5** as a colorless oil: $[\alpha]_D^{20}$ −21.1 (*c* 9.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.69−7.62 (m, 4H), 7.46−7.33 (m, 6H), 4.31 (t, *J* = 5.4 Hz, 1H), 3.64 (s, 3H), 3.45 (s, 3H), 2.57−2.34 (m, 2H), 2.14−2.04 (m, 2H), 1.11 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 173.4, 172.9, 135.9, 135.7, 133.0, 132.9, 129.9, 129.8, 127.7, 127.5, 71.4, 51.6, 51.5, 29.9, 28.9, 26.9, 19.4.

(*S*)-2-(*tert*-Butyldiphenylsilyloxy)pentan-1,5-diol (6a). Compound **5** (0.8 g, 1.8 mmol) was dissolved in dry Et_2O (8.5 mL) and the solution was cooled to 0 °C, afterward lithium borohydride (0.12 g, 5.4 mmol) and dry methanol (0.22 mL, 5.4 mmol) were sequentially added. The resulting suspension was stirred at 23 °C for 24 h, then a few drops of 6 N HCl were added and the salts were filtered off. The filtrate was concentrated under reduced pressure and the residue was purified by flash-chromatography (1:1 EtOAc/hex) to furnish 0.61 g (93%) of **6a** as a colorless oil: $[\alpha]_D^{20}$ −15.6 (*c* 3.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.70−7.65 (m, 4H), 7.44−7.32 (m, 6H), 3.82−3.77 (m, 1H), 3.53−3.48 (m, 2H), 3.45−3.41 (m, 2H), 1.65−1.47 (m, 4H), 1.05 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 135.9, 135.7, 133.8, 133.7, 130.1, 129.8, 127.7, 127.6, 73.6, 65.7, 62.7, 29.7, 28.0, 27.0, 19.3.

(*S*)-1-(*tert*-Butyldiphenylsilyloxy)-3,5-dioxacyclooctane (7a). To a mixture of **6a** (0.55 g, 1.5 mmol) and paraformaldehyde (46 mg, 1.5 mmol) in EtOAc (30 mL), boron trifluoride etherate (195 μL, 1.5 mmol) was added and the resulting mixture was stirred at 23 °C for 4 h. The organic phase was washed with a saturated solution of $NaHCO_3$, dried (Na_2SO_4), and the solvent was removed. The residue was purified by flash-chromatography (1:4 EtOAc/hex) to afford 0.29 g (51%) of **7a** as a colorless oil: $[\alpha]_D^{20}$ −8.7 (*c* 1.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.67−7.63 (m, 4H), 7.45−7.34 (m, 6H), 4.69 (d, *J* = 6.2 Hz, 1H), 4.45 (d, *J* = 6.2 Hz, 1H), 4.03−3.95 (m, 1H), 3.70−3.61 (m, 1H), 3.59−3.48 (m, 3H), 1.93−1.80 (m, 1H), 1.77−1.61 (m, 2H), 1.47−1.34 (m, 1H), 1.12 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 135.7, 134.2, 129.5, 127.5, 95.6, 72.2, 71.9, 69.0, 33.2, 27.0, 26.7, 19.2.

(*S*)-*O*-Benzyl-3,5-dioxacycloheptan-1-ol (7b). Compound **6b**[20] (50 mg, 0.26 mmol) was reacted as described for compound **6a** to afford 44 mg (82%) of **7b** after chromatographic purification (1:9 EtOAc/hex): $[\alpha]_D^{20}$ +64.6 (*c* 1.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.35−7.26 (m, 5H), 4.81−4.77 (m, 2H), 4.58 (s, 2H), 3.95−3.73 (m, 3H), 3.73−3.62 (m, 2H), 1.98−1.91 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 138.3, 128.3, 127.5, 126.2, 94.9, 75.8, 70.7, 68.8, 62.6, 35.0.

(*S*)-3,5-Dioxacyclooctan-1-ol (8a). Compound **7a** (0.27 g, 0.74 mmol) was dissolved in dry THF (5 mL) and TBAF (1.0 M solution in THF, 0.81 mL, 0.81 mmol) was added. The resulting mixture was stirred at 23 °C overnight, afterward a saturated solution of $NaHCO_3$ was added, the solvent was removed, and the aqueous phase was extracted with EtOAc. The organic extracts were dried and evaporated and the residue was purified by flash-chromatography (EtOAc) to afford 76 mg (77%) of **8a** as a colorless oil: $[\alpha]_D^{20}$ −12.6 (*c* 1.6, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 4.65 (d, *J* = 6.0 Hz, 1H), 4.57 (d, *J* = 6.0 Hz, 1H), 4.92−3.81 (m, 2H), 3.75−3.60 (m, 2H), 3.55 (dd, *J* = 3.4, 12.1 Hz, 1H), 2.96 (bs, 1H), 1.95−1.69 (m, 3H), 1.65−1.53 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 94.9, 73.7, 69.3, 68.2, 30.2, 24.7.

(*S*)-3,5-Dioxacycloheptan-1-ol (8b). To a solution of **7b** (38 mg, 0.18 mmol) in EtOAc (3 mL), 10% Pd/C was added and the resulting suspension was stirred at 23 °C under a hydrogen atmosphere. After 12 h, the catalyst was filtered off, the filtrate was evaporated in vacuo, and the residue (19 mg, 91%) was used in the next step without further purification: $[\alpha]_D^{20}$ +12.9 (*c* 0.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 4.78−4.74 (m 2H), 3.93−3.91 (m, 1H), 3.81−3.75 (m, 4H), 2.51 (bs, 1H), 1.93−1.83 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 94.4, 69.5, 68.4, 62.3, 37.8.

(*R*)-3,5-Dioxacyclooctan-1-ol (8c). To a mixture of (*S*)-**8a** (46 mg, 0.35 mmol), *p*-nitrobenzoic acid (86 mg, 0.52 mmol), and triphenylphosphine (181 mg, 0.69 mmol), diisopropylazodicarboxylate (135 μL, 0.69 mmol) was added dropwise and the resulting mixture was stirred at 23 °C overnight. The solvent was removed under reduced pressure, and the residue was purified by flash-chromatography (1:3 EtOAc/hex). The resulting ester was dissolved in a 3:2:1 mixture of THF, methanol, and water (4 mL) and $LiOH \cdot H_2O$ (72 mg, 1.7 mmol) was added. The yellow mixture was stirred at 23 °C overnight and then the solvent was removed in vacuo, the residue was diluted with water, and the aqueous phase was extracted with ether. The organic extracts were dried (Na_2SO_4) and the solvent evaporated. Purification of the residue by flash-chromatography (EtOAc) afforded 20 mg (44%) of (*R*)-**8c** as a colorless liquid. $[\alpha]_D^{20}$ +12.1 (*c* 1.4, $CHCl_3$). ^{1}H and ^{13}C NMR are consistent with those reported for the (*S*)-enantiomer **8a**.

(*R*)-3,5-Dioxacycloheptan-1-ol (8d). The title compound was obtained from **8b** as described for (*S*)-**8c** in 73% yield. Flash-chromatography was performed using a 1:1 mixture of EtOAc and $CHCl_3$ as the eluant: $[\alpha]_D^{20}$ −12.6 (*c* 1.3, $CHCl_3$). ^{1}H and ^{13}C NMR are consistent with those reported for the (*S*)-enantiomer **8b**.

(*R*)-1-(*tert*-Butyldimethylsilyloxy)-2-[(2-methoxyethoxy) methoxy]pent-4-ene (10). To a mixture of **9** (350 mg, 1.6 mmol) and diisopropylethylamine (1.2 mL, 7.2 mmol) in CH_2Cl_2 (8 mL), cooled to 0 °C, MEM-Cl (550 μL, 4.8 mmol) was added and the resulting mixture was stirred at 23 °C for 56 h. The organic phase was washed with 0.1 N HCl, brine and dried (Na_2SO_4). The solvent was removed and the residue was purified by flash-chromatography (1:10 EtOAc/hex) to afford 440 mg (90%) of **10** as a colorless oil: $[\alpha]_D^{20}$ +12.0 (*c* 1.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 5.88−5.74 (m, 1H), 5.11−5.01 (m, 2H), 4.82 (d, *J* = 6.9 Hz, 1H), 4.74 (d, *J* = 6.9 Hz, 1H), 3.76−3.63 (m, 3H), 3.60−3.51 (m, 4H), 3.37 (s, 3H), 2.38−2.19 (m, 2H), 0.86 (s, 9H), 0.02 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 134.6, 117.0, 94.8, 77.4, 71.6, 66.7, 65.0, 58.9, 36.0, 25.7, 18.2, −5.5.

(*R*)-1-Allyloxy-2-[(2-methoxyethoxy)methoxy]pent-4-ene (11). A mixture of **10** (440 mg, 1.4 mmol) and TBAF (1.0 M solution in THF, 4.7 mL, 4.7 mmol) in THF (3 mL) was stirred at 23 °C for 3 h, afterward a saturated solution of $NaHCO_3$ was added, the solvent was removed, and the aqueous phase was extracted with $CHCl_3$. The organic extracts were dried (Na_2SO_4), and the solvent was removed. The residue was purified by flash-chromatography to afford 237 mg (87%) of (*R*)-2-[(2-methoxyethoxy)methoxy]pent-4-en-1-ol as a colorless oil: $[\alpha]_D^{20}$ −55.0 (*c* 1.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 5.85−5.71 (m, 1H), 5.11−5.02 (m, 2H), 4.81 (d, *J* = 7.5 Hz, 1H), 4.75 (d, *J* = 7.5 Hz, 1H), 3.87−3.80 (m, 1H), 3.71−3.61 (m, 3H), 3.59−3.46 (m, 3H), 3.37 (s, 3H), 3.22 (bs, 1H), 2.36−2.19 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 134.1, 117.3, 95.4, 81.0, 71.5, 67.3, 64.8, 58.9, 36.2. To a mixture of the above compound (240 mg, 1.25 mmol), allyl bromide (225 μL, 1.9 mmol) and a catalytic amount of TBAI in THF (12 mL), at 0 °C, sodium hydride (60% dispersion in oil, 102 mg, 2.5 mmol) was added in small portions. After 30 min, the reaction mixture was allowed to warm to 23 °C and was stirred at the same temperature for 18 h. Subsequently, the reaction was quenched with a saturated solution of NH_4Cl, the organic solvent was removed, and the aqueous phase was extracted with $CHCl_3$. The organic extracts were dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by flash-chromatography (10:1 $CHCl_3$/EtOAc) to afford 229 mg (80%) of **11** as a colorless oil. $[\alpha]_D^{20}$ −5.2 (*c* 3.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 5.87−5.79 (m, 2H), 5.34 (dd, *J* = 1.3, 19.1 Hz, 1H), 5.16−5.03 (m, 3H), 4.81 (d, *J* = 7.0 Hz, 1H), 4.77 (d, *J* = 7.0 Hz, 1H), 3.98−3.97 (m, 2H), 3.84−3.81 (m, 1H), 3.72 (t, *J* = 5.0 Hz, 2H), 3.54 (t, *J* = 5.0 Hz, 2H), 3.46−3.44 (m, 2H), 3.38 (s, 3H), 2.35−2.31 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 134.6, 134.3, 117.3, 116.7, 94.6, 75.3, 72.1, 71.9, 71.6, 66.7, 58.9, 36.3.

(*R*,*Z*)-3-[(2-Methoxyethoxy)methoxy]-2,3,4,7-tetrahydrooxepine (12). A mixture of **11** (100 mg, 0.43 mmol) and second generation Grubbs catalyst (18 mg, 0.02 mmol) in CH_2Cl_2 (10 mL) was heated to 45 °C for 1 h. After this time, the solvent was removed and the residue was purified by flash-chromatography (5:1 $CHCl_3$/EtOAc) to afford 83 mg (94%) of **12** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 5.87−5.66 (m, 2H), 4.77−4.18 (m, 2H), 4.18−4.14 (m, 2H), 4.01−3.89 (m, 2H), 3.75−3.68 (m, 3H), 3.56−3.53 (m, 2H), 3.38 (s, 3H), 2.54−2.51 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 130.6, 125.9, 94.3, 75.6, 75.1, 71.6, 70.3, 66.8, 58.9, 31.8.

(*R*)-Oxepan-3-ol (8e). A mixture of **12** (90 mg, 0.44 mmol) and a catalytic amount of 10% Pd/C in EtOAc (3 mL) was stirred at 23 °C under a hydrogen atmosphere for 3 h. After this time, the catalyst was filtered off through a pad of celite and the filtrate was concentrated under reduced pressure to afford (*R*)-3-[(2-methoxyethoxy)methoxy]oxepane (83 mg, 92%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 4.70 (d, $J = 7.2$ Hz, 1H), 4.67 (d, $J = 7.2$ Hz, 1H), 3.83−3.58 (m, 7H), 3.50 (t, $J = 4.6$ Hz, 2H), 3.34 (s, 3H), 1.72−1.67 (m, 1H), 1.46−1.44 (m, 4H), 1.22−1.19 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 93.9, 76.5, 73.7, 71.8, 71.6, 66.7, 58.8, 32.6, 30.7, 20.9. A mixture of the above compound (50 mg, 0.24 mmol) and 6 N HCl (0.5 mL) in THF (2 mL) was stirred at 23 °C for 16 h. The solvent was removed, and the aqueous phase was extracted with $CHCl_3$. The organic extracts were washed with a saturated solution of $NaHCO_3$, dried (Na_2SO_4), and the solvent was removed. The residue was purified by flash-chromatography (1:4 EtOAc/$CHCl_3$) to afford **8e** (24 mg, 84%) as a colorless oil: $[\alpha]_D^{20}$ −4.2 (*c* 0.8, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 3.87−3.85 (m, 1H), 3.76−3.62 (m, 4H), 2.37 (bs, 1H), 1.78−1.65 (m, 5H), 1.54−1.52 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 73.2, 70.7, 70.4, 36.4, 30.0, 20.2.

(*R*)-3-(*tert*-Butyldimethylsilyloxy)-5-(allyloxy)pent-1-ene (14). A mixture of **13** (50 mg, 0.23 mmol), allyl bromide (30 μL, 0.35 mmol), and a catalytic amount of TBAI was cooled to 0 °C and sodium hydride (60% in mineral oil, 11 mg, 0.28 mmol) was added. The resulting mixture was allowed to warm to 23 °C and stirred for 18 h. The reaction was quenched by adding a saturated solution of NH_4Cl, the solvent was removed, and the aqueous phase was extracted with $CHCl_3$. The organic extracts were dried (Na_2SO_4), and the solvent was removed. The residue was purified by flash-chromatography (1:20 EtOAc/hex) to afford 57 mg (97%) of **14** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 5.96−5.87 (m, 1H), 5.85−5.78 (m, 1H), 5.29−5.24 (m, 1H), 5.19−5.13 (m, 2H), 5.04−5.00 (m, 1H), 4.31−4.26 (m, 1H), 3.96−3.94 (m, 2H), 3.55−3.42 (m, 2H), 1.84−1.67 (m, 2H), 0.90 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 141.5, 134.9, 116.6, 113.6, 71.8, 70.6, 66.5, 38.0, 25.8, 18.1, −4.5, −5.1.

(*R*,*Z*)-4-(*tert*-Butyldimethysilyloxy)-2,3,4,7-tetrahydrooxepine (15). The title compound was obtained from **14** as described for **12** in 80% yield. Flash-chromatography was performed using a 1:10 mixture of EtOAc and hex as the eluant. ^{1}H NMR ($CDCl_3$) δ 5.79−5.75 (m, 1H), 5.63−5.60 (m, 1H), 4.64−4.62 (m, 1H), 4.14−4.12 (m, 2H), 3.91−3.85 (m, 1H), 3.80−3.74 (m, 1H), 2.11−2.05 (m, 1H), 1.96−1.91 (m, 1H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 138.4, 127.8, 69.9, 68.2, 67.4, 38.8, 25.8, 18.3, −4.8.

(*S*)-Oxepan-4-ol (8f). Hydrogenolysis of **15** was carried out as described for **8e** to afford (*S*)-4-(*tert*-butyldimethylsilyloxy)oxepane in 95% yield as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 4.03−3.96 (m, 1H), 3.79−3.57 (m, 4H), 1.98−1.69 (m, 5H), 1.64−1.51 (m, 1H), 0.88 (s, 9H), 0.044 (s, 3H), 0.038 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 70.2, 69.4, 64.2, 40.1, 34.5, 25.7, 23.7, 18.0, −4.9. Deprotection of the above compound was performed as described for compound **11** and afforded the title compound in 75% yield as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 4.03−3.98 (m, 1H), 3.82−3.59 (m, 4H), 2.02−1.98 (m, 1H), 1.89−1.80 (m, 4H), 1.66−1.64 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 70.5, 69.6, 64.7, 38.9, 34.9, 24.3.

2-(Benzyloxy)propane-1,3-diol (17). To a solution of **16** (2.5 g, 13.8 mmol) in dry THF (20 mL), cooled to 0 °C, NaH (60% in mineral oil, 0.56 g, 14 mmol) was added portionwise. After 30 min, tetra-*n*-butylammonium iodide (51 mg, 0.14 mmol) and a solution of benzyl bromide (1.65 mL, 13.9 mmol) in THF (5 mL) were added. The reaction mixture was stirred at 23 °C for 3 h; afterward, it was poured into ice. The organic solvent was removed, and the aqueous phase was extracted with $CHCl_3$. The organic extracts were dried (Na_2SO_4), and the solvent was removed. The crude 5-(benzyloxy)-2-phenyl-1,3-dioxane thus obtained was dissolved in a 1:1 mixture of THF and H_2O (60 mL), and to the resulting solution, 6 N HCl was slowly added. After stirring at 23 °C, the reaction mixture was brought to pH 8 by addition of a saturated solution of $NaHCO_3$, the solvent was removed, and the aqueous phase was extracted with diethyl ether. The organic extracts were dried and evaporated, and the residue was purified by flash-column chromatography (2:1 EtOAc/hex) to afford the title compound as a colorless oil in quantitative yield. Physical and spectroscopic data are consistent with those reported in the literature.[32]

1,3-Dioxan-5-ol (8h). To a mixture of **17** (100 mg, 0.55 mmol) and paraformaldehyde (17 mg, 0.55 mmol) in EtOAc (10 mL), boron trifluoride etherate (70 μL, 0.55 mmol) was added and the reaction mixture was stirred at 23 °C for 4 h. The organic phase was washed with a saturated solution of $NaHCO_3$, dried, and the solvent was removed. The residue was purified by flash-chromatography eluting with a 1:4 mixture of EtOAc and hexanes to afford 84 mg (78%) of *O*-benzyl-1,3-dioxan-5-ol as a colorless oil. The above compound was dissolved in EtOAc (3 mL), Pd/C was added, and the resulting suspension was stirred at rt under a hydrogen atmosphere. After 12 h, the catalyst was filtered off, the filtrate was evaporated in vacuo, and the residue (39 mg, 100%) was used in the next step without further purification: ^{1}H NMR ($CDCl_3$) δ 4.93 (d, $J = 6.3$ Hz, 1H), 4.76 (d, $J = 6.3$ Hz, 1H), 3.94−3.84 (m, 4H), 3.64−3.61 (m, 1H), 2.78 (bs, 1H). ^{13}C NMR ($CDCl_3$) δ 94.0, 71.7, 64.1.

***O*-Benzyl-3,6,9-trioxacyclodecan-1-ol (18).** To a refluxing suspension of sodium hydride (60% in mineral oil, prewashed with hexane, 84 mg, 2.1 mmol) in dry THF (5 mL), a solution of **17** (182 mg, 1.0 mmol) and di(ethyleneglycol)dimethanesulfonate (260 mg, 1.0 mmol) in dry THF (5 mL) was added dropwise. The resulting mixture was heated under reflux for 20 h and afterward was cooled to 23 °C and H_2O (2 mL) was added. The solvent was removed, and the aqueous phase was extracted with $CHCl_3$. The organic extracts were washed several times with water, dried (Na_2SO_4), and evaporated. The residue was purified by flash-chromatography (2:3 CH_2Cl_2/EtOAc) to afford 49 mg (19%) of **18** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.36−7.26 (m, 5H), 4.66 (s, 2H), 3.75−3.57 (m, 13H). MS (ESI) *m/z* 275 $[M + Na]^+$.

***O*-Benzyl-3,6,9,12-tetraoxacyclotridecan-1-ol (19).** Compound **19** was obtained as described for **18** starting from **17** and tri(ethyleneglycol)dimethanesulfonate in 29% yield. ^{1}H NMR ($CDCl_3$) δ 7.39−7.26 (m, 5H), 4.72 (s, 2H), 3.83−3.58 (m, 17 H). MS (ESI) *m/z* 319 $[M + Na]^+$.

3,6,9-Trioxacyclodecan-1-ol (8i). A mixture of **18** (34 mg, 0.13 mmol) and a catalytic amount of 10% Pd/C in methanol (2 mL) was stirred at 23 °C under a hydrogen atmosphere. After 18 h, the catalyst was filtered off and the filtrate was evaporated to afford 22 mg (99%) of **8i** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 3.74−3.53 (m, 13H), 2.73 (bs, 1H).

3,6,9,12-Tetraoxacyclotridecan-1-ol (8j). Starting from **19**, compound **8j** was obtained as described for **8i** in quantitative yield: ^{1}H NMR ($CDCl_3$) δ 3.81−3.60 (m, 17 H), 2.95 (bs, 1H).

3,6,8,11-Tetraoxa-1-cyclododecanol (8k). To a mixture of **20**[24] (78 mg, 0.29 mmol) and paraformaldehyde (8.7 mg, 0.29 mmol) in EtOAc (4 mL), boron trifluoride etherate (37 μL, 0.29 mmol) was added and the resulting mixture was stirred at 23 °C for 2 h. Subsequently, a saturated solution of $NaHCO_3$ was added and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried (Na_2SO_4), and the solvent was removed in vacuo. The residue was purified by flash-chromatography to afford 31 mg (37%) of *O*-benzyl-3,6,8,11-tetraoxacyclododecan-1-ol as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.35−7.27 (m, 5H), 4.67 (s, 2H), 3.88 (s, 2H), 3.86−3.81 (m, 2H), 3.77−3.61 (m, 11H). ^{13}C NMR ($CDCl_3$) δ 133.6, 128.3, 127.7, 126.2, 94.6, 75.8, 71.5, 69.6, 65.3, 64.6. MS (ESI) *m/z* 305 $[M + Na]^+$. A mixture of the above compound and a catalytic amount of 10% Pd/C in EtOAc (2 mL) was stirred at 23 °C under a hydrogen atmosphere. After 18 h, the catalyst was filtered off and the filtrate was evaporated to afford 21 mg (99%) of **8k** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 4.67 (s, 2H), 3.85−3.63 (m, 11H), 3.54 (dd, $J = 6.4$, 8.2 Hz, 2H), 2.22 (d, $J = 8.7$ Hz, 1H).

***O*-Benzyl-3,9-dioxa-6-thiacyclodecan-1-ol 6,6-dioxide (22).** A solution of lithium sulfide (11 mg, 0.23 mmol) in water (0.3 mL) was added dropwise within 30 min to a solution of **21**[24] (60 mg, 0.15 mmol) in refluxing ethanol (15 mL). The resulting mixture was heated under reflux for 3 h and then was cooled to 23 °C. The solvent was removed and the aqueous phase was extracted with $CHCl_3$. The organic extracts were dried (Na_2SO_4), and the solvent was removed. Flash-chromatography of the residue (1:4 EtOAc/hexanes) afforded 16 mg (38%) of *O*-benzyl-3,9-dioxa-6-thiacyclodecan-1-ol as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.36−7.27 (m, 5H), 4.59 (s, 2H), 3.90−3.85 (m, 2H), 3.82−3.48 (m, 7H), 2.91−2.74 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 133.5, 128.3, 127.7, 126.0, 75.9, 71.9, 71.6, 68.0, 33.4. MS (ESI) *m/z* 291 $[M + Na]^+$, 286 $[M + H + NH_3]^+$, 269 $[M + H]^+$. To a solution of the above compound (11 mg, 0.040 mmol) in CH_2Cl_2 (2 mL), cooled to 0 °C, *m*-chloroperbenzoic acid (77%, 22 mg, 0.09 mmol) was added in small portions. After 18 h, a 1% solution of sodium bisulfite was added, the layers were separated, and the organic phase was washed with a saturated solution of $NaHCO_3$. The organic extracts were dried (Na_2SO_4) and evaporated. The residue was purified by flash-chromatography (1:4 EtOAc/$CHCl_3$) to afford 11 mg (93%) of **22** as a brown oil. ^{1}H NMR ($CDCl_3$) δ 7.37−7.29 (m, 5H), 4.57 (s, 2H), 4.01−3.96 (m, 4H), 3.77−3.72 (m, 1H), 3.66−3.60 (m, 4H), 3.40−3.38 (m, 2H), 3.34−3.23 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 133.4, 128.4, 127.9, 127.7, 74.7, 71.8, 66.4, 64.6, 52.4.

3,9-Dioxa-6-thiacyclodecan-1-ol-6,6-dioxide (8l). A mixture of **22** (25 mg, 0.083 mmol) and a catalytic amount of 10% Pd/C in EtOAc (3 mL) was stirred at 23 °C under a hydrogen atmosphere. After 48 h, the catalyst was filtered off and the filtrate was evaporated to afford 16 mg (92%) of **8l** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 4.08−3.95 (m, 4H), 3.67 (dd, $J = 4.2$, 9.9 Hz, 2H), 3.61−3.59 (m, 1H), 3.51 (dd, $J = 5.7$, 9.9 Hz, 2H), 3.38−3.23 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 69.0, 68.3, 64.5, 52.6.

***O*,6-Dibenzyl-3,9-dioxa-6-azocyclodecan-1-ol (23).** A mixture of **21**[24] (150 mg, 0.37 mmol), benzylamine (41 μL, 0.37 mmol), lithium perchlorate (340 mg, 3.7 mmol), and sodium carbonate (200 mg, 1.9 mmol) in acetonitrile (7.5 mL) was heated under reflux for 48 h. After cooling to 23 °C, the solvent was removed, the residue was suspended in $CHCl_3$, and the organic phase was washed with water and dried (Na_2SO_4). Flash-chromatography of the residue (2:1 EtOAc/$CHCl_3$) afforded 31 mg (24%) of **23** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.36−7.20 (m, 10H), 4.59 (s, 2H), 3.87−3.78 (m, 4H), 3.69 (s, 2H), 3.67−3.49 (m, 5H), 2.91−2.72 (m, 4H). MS (ESI) *m/z* 342 $[M + 1]^+$.

***N*-(*tert*-Butoxycarbonyl)-3,9-dioxa-6-azocyclodecan-1-ol (24).** A mixture of **23** (40 mg, 0.12 mmol), Boc_2O (26 mg, 0.12 mmol), and a catalytic amount of 10% Pd/C in EtOAc (3 mL) was stirred at 23 °C under a hydrogen atmosphere. After 18 h, the catalyst was filtered off and the filtrate was evaporated to afford 26 mg (95%) of **24** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 3.83−3.70 (m, 7H), 3.65−3.59 (m, 2H), 3.49−3.29 (m, 4H), 1.75 (bs, 1H), 1.46 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 155.7, 79.8, 71.4, 71.0, 70.3, 69.9, 50.5, 50.2, 28.5.

(*S*)-1-(4-Nitrophenoxycarbonyloxy)-3,5-dioxacyclooctane (25a). To a solution of **8a** (15 mg, 0.11 mmol) and *N*-methylmorpholine (38 μL, 0.34 mmol) in dry THF (3 mL), *p*-nitrophenylchloroformate (70 mg, 0.28 mmol) was added and the resulting mixture was stirred at 23 °C for 1 h. To the reaction mixture was added water, the solvent was removed under reduced pressure, and the aqueous phase was extracted with $CHCl_3$. The organic extracts were dried (Na_2SO_4), and the solvent was removed. The residue was purified by flash-chromatography (1:4 EtOAc $CHCl_3$) to afford 28 mg (81%) of **25a** as a pale-yellow solid. ^{1}H NMR ($CDCl_3$) δ 8.27 (d, $J = 9.3$ Hz, 2H), 7.38 (d, $J = 9.3$ Hz, 2H), 5.09−5.01 (m, 1H), 4.72−4.66 (m, 2H), 3.94−3.82 (m, 3H), 3.64−3.56 (m, 1H), 2.18−2.04 (m, 1H), 2.03−1.93 (m, 2H), 1.90−1.71 (m, 1H).

(*S*)-1-(4-Nitrophenoxycarbonyloxy)-3,5-dioxacycloheptane (25b). The title compound was obtained from (*S*)-**8b** as described for **25a** in 72% yield. Flash-chromatography was performed using a 1:5 mixture of EtOAc and $CHCl_3$ as the eluant. ^{1}H NMR ($CDCl_3$) δ 8.28 (d, $J = 9.3$ Hz, 2H), 7.40 (d, $J = 9.3$ Hz, 2H), 5.00−4.98 (m, 1H), 4.84 (d, $J = 4.5$ Hz, 1H), 4.79 (d, $J = 4.5$ Hz, 1H), 4.11 (dd, $J = 4.7$, 13.1 Hz, 1H), 3.99−3.90 (m, 2H), 3.85−3.78 (m, 1H), 2.19−2.04 (m, 2H).

(*R*)-1-(4-Nitrophenoxycarbonyloxy)-3,5-dioxacyclooctane (25c). The title compound was obtained from (*R*)-**8c** as described for **25a** in 87% yield after flash-chromatography (1:4 EtOAc/$CHCl_3$). ^{1}H NMR data are consistent with those reported for the (*S*)-enantiomer **25a**.

(*R*)-1-(4-Nitrophenoxycarbonyloxy)-3,5-dioxacycloheptane (25d). The title compound was obtained from (*R*)-**8d** as described for **25a** in 70% yield after flash-chromatography (1:5 EtOAc/$CHCl_3$). ^{1}H data are consistent with those reported for the (*S*)-enantiomer **25b**.

(*R*)-3-(4-Nitrophenoxycarbonyloxy)oxepane (25e). The title compound was obtained from **8e** as described for **25a** in 86% yield. Flash-chromatography was performed using a 1:20 mixture of EtOAc and $CHCl_3$ as the eluant. ^{1}H NMR ($CDCl_3$) δ 8.26 (d, $J =$ 9.3 Hz, 2H), 7.38 (d, $J = 9.3$ Hz, 2H), 5.02−4.95 (m, 1H), 3.98−3.83 (m, 3H), 3.71−3.63 (m, 1H), 2.15−1.74 (m, 5H), 1.65−1.53 (m, 1H).

(*S*)-4-(4-Nitrophenoxycarbonyloxy)oxepane (25f). The title compound was obtained from **8f** as described for **25a** in 77% yield. Flash-chromatography was performed using a 1:20 mixture of EtOAc and $CHCl_3$ as the eluant. ^{1}H NMR ($CDCl_3$) δ 8.27 (d, $J =$ 8.8 Hz, 2H), 7.36 (d, $J = 8.8$ Hz, 2H), 5.05−5.01 (m, 1H), 3.84−3.62 (m, 4H), 2.18−1.86 (m, 5H), 1.78−1.63 (m, 1H).

1-(4-Nitrophenoxycarbonyloxy)cycloheptane (25g). The title compound was obtained from commercially available cycloheptanol as described for **25a** in 89% yield. Flash-chromatography was performed using a 1:10 mixture of EtOAc and $CHCl_3$ as the eluant. ^{1}H NMR ($CDCl_3$) δ 8.26 (d, $J = 8.7$ Hz, 2H), 7.37 (d, $J = 8.7$ Hz, 2H), 4.96−4.89 (m, 1H), 2.08−2.02 (m, 2H), 1.86−1.78 (m, 2H), 1.71 (m, 2H), 1.59 (m, 4H), 1.40−1.36 (m, 2H).

5-(4-Nitrophenoxycarbonyloxy)-1,3-dioxane (25h). The title compound was obtained from **8h** as described for **25a** in 72% yield. Flash-chromatography was performed using a 1:4 mixture of EtOAc and $CHCl_3$ as the eluant. ^{1}H NMR ($CDCl_3$) δ 8.30 (d, $J = 8.7$ Hz, 2H), 7.42 (d, $J = 8.7$ Hz, 2H), 5.03 (d, $J = 6.3$ Hz, 1H), 4.87 (d, $J = 6.3$ Hz, 1H), 4.71 (t, $J = 2.8$ Hz, 1H), 4.19−4.06 (m, 4H).

3,6,9-Trioxa-1-cyclodecanol succinimidylcarbonate (25i). To a solution of **8i** (18 mg, 0.11 mmol) in dry acetonitrile (1 mL), *N*,*N*′-disuccimidyl carbonate (43 mg, 0.17 mmol) and triethylamine (32 μL, 0.23 mmol) were added and the resulting mixture was stirred at 23 °C. After 8 h, the solvent was removed, the residue was taken up in a saturated solution of $NaHCO_3$, and the aqueous phase was extracted with EtOAc. The organic extracts were dried (Na_2SO_4), and the solvent was removed in vacuo. Purification of the residue (10:1 EtOAc/MeOH) afforded **17b** (13 mg) in 37% yield. ^{1}H NMR ($CDCl_3$) δ 5.12−5.03 (m, 1H), 3.96−3.65 (m, 12H), 2.81 (s, 4H).

12-(4-Nitrophenoxycarbonyloxy)-1,4,7,10-tetraoxacyclotridecane (25j). The title compound was obtained from **8j** as described for **25a** in 70% yield after flash-chromatography (EtOAc). ^{1}H NMR ($CDCl_3$) δ 8.27 (d, $J = 9.3$ Hz, 2H), 7.39 (d, $J = 9.3$ Hz, 2H), 5.15−5.08 (m, 1H), 3.92 (dd, $J = 6.3$, 10.2 Hz, 2H), 3.82 (dd, $J =$ 4.5, 10.2 Hz, 2H), 3.74−3.60 (m, 12H).

9-(4-Nitrophenoxycarbonyloxy)-1,7-dioxa-4-thiacyclodecane 4,4-dioxide (25k). The title compound was obtained from **8k** as described for **25a** in 73% yield after flash-chromatography (1:4 EtOAc/$CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 8.28 (d, $J = 9.0$ Hz, 2H), 7.37 (d, $J = 9.0$ Hz, 2H), 5.10−5.03 (m, 1H), 4.13−4.06 (m, 4H), 3.83−3.73 (m, 4H), 3.43−3.22 (m, 4H).

11-(4-Nitrophenoxycarbonyloxy)-1,4,6,9-tetraoxacyclododecane (25l). The title compound was obtained from **8l** as described for **25a** in 67% yield after flash-chromatography (EtOAc). ^{1}H NMR ($CDCl_3$) δ 8.27 (d, $J = 8.7$ Hz, 2H), 7.38 (d, $J = 8.7$ Hz, 2H), 5.01−4.95 (m, 1H), 4.70 (s, 2H), 3.91−3.76 (m, 12H).

(1*S*,2*R*)-{1-Benzyl-2-hydroxy-3-[isobutyl(4-methoxybenzenesulfonyl)amino]propyl}carbamic Acid (1*S*)-3,5-Dioxacyclooctan-1-yl ester (3a). A solution of **27** (25 mg, 0.05 mmol) in a mixture of 30% trifluoracetic acid in CH_2Cl_2 (5 mL) was stirred at 23 °C for 40 min and then the solvent was removed under reduced pressure. Compound **28** thus obtained was dissolved in CH_2Cl_2 (4 mL) and a solution of **25a** (16 mg, 0.05 mmol) in THF (2 mL) were added followed by diisopropylethylamine. After 48 h, the organic phase was washed with water, dried (Na_2SO_4), and evaporated. The residue was purified by flash-chromatography eluting with a 1:4 mixture of EtOAc and hexane to afford **3a** in 63% yield after flash-chromatography (1:4 EtOAc/$CHCl_3$) as a foam: $[\alpha]_D^{20}$ +8.6 (*c* 1.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.70 (d, *J* = 9.0 Hz, 2H), 7.31−7.21 (m, 5H), 6.97 (d, *J* = 9.0 Hz, 2H), 4.83−4.78 (m, 2H), 4.65−4.59 (m, 2H), 3.87 (s, 3H), 3.83−3.81 (m, 3H), 3.68 (dd, *J* = 4.9, 12.1 Hz, 1H), 3.55−3.48 (m, 2H), 3.14−2.90 (m, 5H), 2.78 (dd, *J* = 6.8, 12.6 Hz, 1H), 1.85−1.80 (m, 5H), 0.90 (d, *J* = 6.3 Hz, 3H), 0.85 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 163.0, 153.4, 137.6, 129.8, 129.6, 129.5, 128.4, 126.5, 114.3, 95.7, 73.9, 72.6, 69.2, 68.6, 58.7, 55.6, 55.0, 53.7, 35.4, 29.2, 27.2, 26.1, 20.1, 29.8. HRMS-ESI (*m*/*z*): (M + Na)$^+$ calcd for $C_{28}H_{40}N_2NaO_8S$, 587.2403; found, 587.2380.

(1*S*,2*R*)-{1-Benzyl-2-hydroxy-3-[isobutyl(4-methoxybenzenesulfonyl)amino]propyl}carbamic Acid (1*S*)-3,5-Dioxacycloheptan-1-yl Ester (3b). The title compound was obtained from **27** and **25b** as described for **3a** in 69% yield after flash-chromatography (1:4 EtOAc/$CHCl_3$) as an amorphous solid: $[\alpha]_D^{20}$ +10.5 (*c* 1.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.70 (d, *J* = 8.7 Hz, 2H), 7.31−7.19 (m, 5H), 6.97 (d, *J* = 8.7 Hz, 2H), 4.93 (d, *J* = 8.4 Hz, 1H), 4.77−4.71 (m, 3H), 3.87 (s, 3H), 3.81−3.69 (m, 6H), 3.09−2.90 (m, 5H), 2.77 (dd, *J* = 6.9, 13.2 Hz, 1H), 1.98−1.95 (m, 1H), 1.85−1.76 (m, 2H), 0.90 (d, *J* = 6.9 Hz, 3H), 0.85 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 162.9, 155.5, 137.5, 129.7, 129.5, 129.4, 128.4, 126.5, 114.3, 94.9, 72.5, 71.9, 68.8, 62.3, 58.9, 55.6, 55.2, 53.7, 35.3, 27.3, 20.2, 19.9. HRMS-ESI (*m*/*z*): (M + Na)$^+$ calcd for $C_{27}H_{38}N_2NaO_8S$, 573.2247; found, 573.2260.

(1*S*,2*R*)-{1-Benzyl-2-hydroxy-3-[isobutyl(4-methoxybenzenesulfonyl)amino]propyl}carbamic Acid (1*R*)-3,5-Dioxacyclooctan-1-yl Ester (3c). The title compound was obtained from **27** and **25c** as described for **3a** in 50% yield after flash-chromatography (1:4 EtOAc/$CHCl_3$) as an amorphous solid $[\alpha]_D^{20}$ +9.8 (*c* 1.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.70 (d, *J* = 8.7 Hz, 2H), 7.31−7.21 (m, 5H), 6.97 (d, *J* = 8.7 Hz, 2H), 4.80−4.79 (m, 2H), 4.65−4.61 (m, 2H), 3.87 (s, 3H), 3.82−3.80 (m, 2H), 3.71−3.62 (m, 2H), 3.56−3.48 (m, 2H), 3.12−2.85 (m, 5H), 2.77 (dd, *J* = 6.3, 13.2 Hz, 1H), 1.83−1.74 (m, 4H), 1.71−1.66 (m, 1H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.86 (d, *J* = 6.6 Hz, 3H). HRMS-ESI (*m*/*z*): (M + Na)$^+$ calcd for $C_{28}H_{40}N_2NaO_8S$, 587.2403; found, 587.2405.

(1*S*,2*R*)-{1-Benzyl-2-hydroxy-3-[isobutyl(4-methoxybenzenesulfonyl)amino]propyl}carbamic Acid (1*R*)-3,5-Dioxacycloheptan-1-yl Ester (3d). The title compound was obtained from **27** and **25d** as described for **3a** in 59% yield after flash-chromatography (1:4 EtOAc/$CHCl_3$) as a foam: $[\alpha]_D^{20}$ +15.9 (*c* 0.6, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.71 (d, *J* = 9.0 Hz, 2H), 7.30−7.18 (m, 5H), 6.98 (d, *J* = 9.0 Hz, 2H), 4.88 (d, *J* = 8.7 Hz, 1H), 4.77−4.71 (m, 3H), 3.87 (s, 3H), 3.81−3.61 (m, 6H), 3.18−3.07 (m, 2H), 3.04−2.92 (m, 2H), 2.86−2.74 (m, 2H), 1.90−1.77 (m, 3H), 0.92 (d, *J* = 6.3 Hz, 3H), 0.86 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 162.8, 155.5, 137.6, 129.7, 129.5, 129.4, 128.4, 126.4, 114.3, 94.8, 72.6, 71.9, 68.6, 62.3, 58.8, 55.6, 55.1, 53.8, 35.8, 35.2, 27.3, 20.2, 19.9. HRMS-ESI (*m*/*z*): (M + Na)$^+$ calcd for $C_{27}H_{38}N_2NaO_8S$, 573.2247; found, 573.2254.

(1*S*,2*R*)-{1-Benzyl-2-hydroxy-3-[isobutyl(4-methoxybenzenesulfonyl)amino]propyl}carbamic Acid (*R*)-Oxepan-3-yl Ester (3e). The title compound was obtained from **27** and **25e** as described for **3a** in 72% yield after flash-chromatography (1:2 EtOAc/hex) as an amorphous solid. ^{1}H NMR ($CDCl_3$) δ 7.70 (d, 8.8 Hz, 2H), 7.30−7.19 (m, 5H), 6.97 (d, *J* = 8.8 Hz, 2H), 4.81 (d, *J* = 8.2 Hz, 1H), 4.77−4.74 (m, 1H), 3.87 (s, 3H), 3.81 (m, 3H), 3.70−3.69 (m, 2H), 3.61−3.57 (m, 1H), 3.12 (dd, *J* = 8.2, 14.7 Hz, 1H), 3.05−3.84 (m, 4H), 2.77 (dd, *J* = 6.6, 13.2 Hz, 1H), 1.86−1.60 (m, 6H), 1.49−1.41 (m, 1H), 0.91 (d, *J* = 6.7 Hz, 3H), 0.86 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 162.9, 155.8, 137.5, 129.6, 129.5, 129.4, 128.4, 126.4, 114.2, 74.5, 73.6, 72.5, 72.4, 58.7, 55.5, 54.8, 53.7, 35.6, 31.9, 30.9, 27.1, 21.0, 20.0, 19.8. HRMS-ESI (*m*/*z*): (M + Na)$^+$ calcd for $C_{28}H_{40}N_2NaO_7S$, 571.2454; found, 571.2458.

(1*S*,2*R*)-{1-Benzyl-2-hydroxy-3-[isobutyl(4-methoxybenzenesulfonyl)amino]propyl}carbamic acid (*S*)-oxepan-4-yl ester (3f). The title compound was obtained from **27** and **25f** as described for **3a** in 68% yield after flash-chromatography (1:2 EtOAc/hex) as an amorphous solid. ^{1}H NMR ($CDCl_3$) δ 7.71 (d, *J* = 8.8 Hz, 2H), 7.29−7.21 (m, 5H), 6.98 (d, *J* = 8.8 Hz, 2H), 4.78−4.76 (m, 2H), 3.94−3.81 (m, 5H), 3.71−3.60 (m, 3H), 3.56−3.50 (m, 1H), 3.12 (dd, *J* = 8.0, 15.2 Hz, 1H), 3.04−2.86 (m, 4H), 2.79 (dd, *J* = 6.4, 13.1 Hz, 1H), 1.94−1.64 (m, 7H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.86 (d, *J* = 6.5 Hz, 3H). HRMS-ESI (*m*/*z*): (M + Na)$^+$ calcd for $C_{28}H_{40}N_2NaO_7S$, 571.2454; found, 571.2452.

(1*S*,2*R*)-{1-Benzyl-2-hydroxy-3-[isobutyl(4-methoxybenzenesulfonyl)amino]propyl}carbamic Acid Cycloheptanyl Ester (3g). The title compound was obtained from **27** and **25g** as described for **3a** in 84% yield after flash-chromatography (1:6 EtOAc/$CHCl_3$) as an amorphous solid: $[\alpha]_D^{20}$ +16.0 (*c* 0.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.70 (d, *J* = 8.7 Hz, 2H), 7.31−7.22 (m, 5H), 6.97 (d, *J* = 8.7 Hz, 2H), 4.69−4.68 (m, 2H), 3.87 (s, 3H), 3.82−3.78 (m, 2H), 3.05−2.77 (m, 6H), 1.83−1.73 (m, 4H), 1.60−1.45 (m, 8H), 1.22−1.20 (m, 1H), 0.90 (d, *J* = 6.3 Hz, 3H), 0.86 (d, *J* = 6.3 Hz, 3H). HRMS-ESI (*m*/*z*): (M + Na)$^+$ calcd for $C_{29}H_{42}N_2NaO_6S$, 569.2661; found, 569.2663.

(1*S*,2*R*)-{1-Benzyl-2-hydroxy-3-[isobutyl(4-methoxybenzenesulfonyl)amino]propyl}carbamic Acid 1,3-Dioxan-5-yl Ester (3h). The title compound was obtained from **25h** and **27** as described for **3a** in 67% yield after flash-chromatography (1:6 EtOAc/$CHCl_3$): $[\alpha]_D^{20}$ +7.9 (12.3 mg/mL CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.71 (d, *J* = 9.3 Hz, 2H), 7.32−7.22 (m, 5H), 6.98 (d, *J* = 9.3 Hz, 2H), 5.06 (d, *J* = 8.4 Hz, 1H), 4.92 (d, *J* = 6.2 Hz, 1H), 4.75 (d, *J* = 6.2 Hz, 1H), 4.51−4.49 (m, 1H), 3.95−3.74 (m, 9H), 3.14 (dd, *J* = 8.1, 15.0 Hz, 1H), 3.06−2.84 (m, 4H), 2.77 (dd, *J* = 6.7, 13.3 Hz, 1H), 1.86−1.77 (m, 1H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 162.9, 155.4, 137.3, 129.7, 129.6, 129.5, 128.5, 126.5, 114.3, 93.6, 72.3, 68.7, 66.3, 58.8, 55.6, 55.2, 53.8, 35.7, 27.3, 20.2, 19.9. HRMS-ESI (*m*/*z*): (M + Na)$^+$ calcd for $C_{26}H_{36}N_2NaO_8S$, 559.2090; found, 559.2094.

(1*S*,2*R*)-(1-Benzyl-2-hydroxy-3-[isobutyl(4-methoxybenzenesulfonyl)amino]propyl}carbamic Acid 3,6,9-Trioxacyclodecan-1-yl Ester (3i). The title compound was obtained from **25i** and **27** as described for **3a** in 37% yield after flash-chromatography (1:1 EtOAc/$CHCl_3$) as a white solid: mp 60−62 °C; $[\alpha]_D^{20}$ + 6.2 (*c* 0.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.69 (d, *J* = 8.7 Hz, 2H), 7.33−7.18 (m, 5H), 6.96 (d, *J* = 8.7 Hz, 2H), 5.33 (d, *J* = 8.1 Hz, 1H), 4.84−4.82 (m, 1H), 3.86 (s, 3H), 3.79−3.75 (m, 2H), 3.68−3.55 (m, 12H), 3.07−2.78 (m, 6H), 1.84−1.81 (m, 1H), 0.89 (d, *J* = 7.2 Hz, 3H), 0.85 (d, *J* = 7.2 Hz, 3H). HRMS-ESI (*m*/*z*): (M + Na)$^+$ calcd for $C_{29}H_{42}N_2NaO_9S$, 617.2509; found, 617.2501.

(1*S*,2*R*)-{1-Benzyl-2-hydroxy-3-[isobutyl(4-methoxybenzenesulfonyl)amino]propyl}carbamic Acid 3,6,9,12-Tetraoxacyclotridecan-1-yl Ester (3j). The title compound was obtained from **27** and **25j** as described for **3a** in 30% yield after flash-chromatography (EtOAc) as a foam: $[\alpha]_D^{20}$ +17.0 (*c* 0.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.70 (d, *J* = 9.0 Hz, 2H), 7.29−7.19 (m, 5H), 6.97 (d, *J* = 9.0 Hz, 2H), 4.96 (d, *J* = 8.0 Hz, 1H), 4.85−4.83 (m, 1H), 3.87 (s, 3H), 3.83−3.81 (m, 2H), 3.80−3.60 (m, 15H), 3.52 (dd, *J* = 3.5, 9.5 Hz, 1H), 3.13 (dd, *J* = 9.0, 15.5 Hz, 1H), 3.02−2.86 (m, 4H), 2.77 (dd, *J* = 6.5, 13.5 Hz, 1H), 1.83−1.76 (m, 1H), 0.90 (d, *J* = 6.5 Hz, 3H), 0.85 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$) (500 MHz) δ 163.0, 155.4, 137.6, 129.7, 129.6, 129.5, 128.5, 126.5, 114.4, 72.4, 71.7, 70.2, 70.1, 69.9, 67.8, 58.7, 55.6, 55.1, 53.7, 35.5, 27.3, 20.2, 19.9. HRMS-ESI (*m*/*z*): (M + Na)$^+$ calcd for $C_{31}H_{46}N_2NaO_{10}S$, 661.2771; found, 661.2788.

(1*S*,2*R*)-{1-Benzyl-2-hydroxy-3-[isobutyl(4-methoxybenzenesulfonyl)amino]propyl}carbamic Acid 3,6,8,11-Tetraoxacyclododecan-1-yl Ester (3k). The title compound was obtained from **27** and **25k** as described for **3a** in 47% yield after flash-chromatography (EtOAc) as a foam: $[\alpha]_D^{20}$ +6.5 (*c* 0.5, $CHCl_3$). 1H NMR ($CDCl_3$) 7.70 (d, *J* = 8.7 Hz, 2H), 7.30−7.18 (m, 5H), 6.97 (d, *J* = 8.7 Hz, 2H), 4.92 (d, *J* = 8.1 Hz, 1H), 4.81−4.76 (m, 1H), 4.66 (s, 2H), 3.87 (s, 3H), 3.78−344 (m, 14H), 3.13 (dd, *J* =

8.4, 15.3 Hz, 1H), 3.06−2.82 (m, 4H), 2.75 (dd, *J* = 6.9, 13.5 Hz, 1H), 1.83−1.74 (m, 1H), 0.90 (d, *J* = 6.6 Hz, 3H), 0.85 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 163.0, 155.6, 137.5, 129.8, 129.6, 129.5, 128.5, 126.5, 114.4, 94.7, 72.4, 71.5, 69.7, 64.9, 64.5, 58.8, 55.7, 55.1, 53.8, 35.6, 27.3, 20.2, 19.9. HRMS-ESI (*m*/*z*): (M + Na)$^+$ calcd for $C_{30}H_{44}N_2NaO_{10}S$, 647.2615; found, 647.2590.

(1*S*,2*R*)-{1-Benzyl-2-hydroxy-3-[isobutyl(4-methoxybenzenesulfonyl)amino]propyl}carbamic Acid 3,9-Dioxa-6-thiacyclodecan-1-yl 6,6-Dioxide Ester (3l). The title compound was obtained from **27** and **25l** as described for **3a** in 36% yield after flash-chromatography (1:1 EtOAc/$CHCl_3$) as an amorphous solid: $[\alpha]_D^{20}$ +5.5 (*c* 0.7, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.70 (d, *J* = 9.0 Hz, 2H), 7.31−7.20 (m, 5H), 6.98 (d, *J* = 9.0 Hz, 2H), 4.97 (d, *J* = 8.4 Hz, 1H), 4.85 (t, *J* = 4.5 Hz, 1H), 4.01−3.96 (m, 4H), 3.88 (s, 3H), 3.85−3.83 (m, 2H), 3.71−3.69 (m, 1H), 3.61 (dd, *J* = 3.9, 9.3 Hz, 1H), 3.54−3.47 (m, 2H), 3.61−3.27 (m, 4H), 3.13 (dd, *J* = 8.4, 15.0 Hz, 1H), 3.00−2.82 (m, 4H), 2.75 (dd, *J* = 6.6, 13.5 Hz, 1H), 1.83−1.75 (m, 1H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.86 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 163.0, 155.1, 137.4, 131.1, 129.6, 129.4, 128.4, 126.5, 114.3, 72.4, 70.2, 66.0, 64.6, 58.8, 55.7, 55.1, 53.7, 52.2, 35.4, 27.3, 20.2, 19.9. HRMS-ESI (*m*/*z*): (M + Na)$^+$ calcd for $C_{29}H_{42}N_2NaO_{10}S_2$, 665.2179; found, 665.2191.

***N*-(*tert*-Butoxycarbonyl)-9-(4-nitrophenoxycarbonyloxy)-1,7-dioxa-4-azocyclodecane (29).** The title compound was obtained from **24** as described for **25a** in 73% yield after flash-chromatography (1:4 EtOAc/$CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 8.27 (d, *J* = 9.0 Hz, 2H), 7.37 (d, *J* = 9.0 Hz, 2H), 5.02−4.96 (m, 1H), 3.98−3.76 (m, 8H), 4.52−3.23 (m, 4H), 1.47 (s, 9H).

(1*S*,2*R*)-{1-Benzyl-2-hydroxy-3-[isobutyl(4-methoxybenzenesulfonyl)amino]propyl}carbamic Acid *N*-(*tert*-Butoxycarbonyl)-1,7-dioxa-4-azocyclodecan-9-yl Ester (30). The title compound was obtained from **27** and **29** as described for **3a** in 74% yield after flash-chromatography (1:1 EtOAc/$CHCl_3$) as a white solid: mp 71−73 °C; $[\alpha]_D^{20}$ +4.7 (*c* 1.7, $CHCl_3$). ^{1}H NMR ($CDCl_3$) 7.70 (d, *J* = 9.0 Hz, 2H), 7.30−7.20 (m, 5H), 7.0 (d, *J* = 9.0 Hz, 2H), 4.92−4.90 (m, 1H), 4.81 (t, *J* = 4.0 Hz, 1H), 3.86 (s, 3H), 3.79−3.66 (m, 6H), 3.62−3.57 (m, 2H), 3.49−3.42 (m, 2H), 3.40−3.28 (m, 4H), 3.12 (dd, *J* = 7.8, 15.3 Hz, 1H), 3.01−2.82 (m, 4H), 2.75 (dd, *J* = 6.3, 13.2 Hz, 1H), 1.83−1.74 (m, 1H), 1.44 (s, 9H), 0.90 (d, *J* = 6.6 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$) 163.0, 155.6, 155.4, 137.4, 129.7, 129.5, 129.4, 128.4, 126.5, 114.3, 79.9, 72.4, 71.9, 71.0, 68.6, 68.1, 58.7, 55.6, 55.0, 53.7, 50.3, 35.6, 28.5, 27.3, 20.2, 19.9.

(1*S*,2*R*)-{1-Benzyl-2-hydroxy-3-[isobutyl(4-methoxybenzenesulfonyl)amino]propyl}carbamic Acid 1,7-Dioxa-4-azocyclodecan-9-yl Ester (31). A solution of **30** (13 mg, 0.02 mmol) in a mixture of 30% trifluoracetic acid in CH_2Cl_2 (1 mL) was stirred at 23 °C for 30 min and then the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2, and the organic phase was washed with a saturated solution of $NaHCO_3$, dried (Na_2SO_4), and evaporated to afford 11 mg (100%) of **31** as a white solid: mp 65−66 °C; $[\alpha]_D^{20}$ +13.8 (*c* 0.7, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.70 (d, *J* = 8.7 Hz, 2H), 7.30−7.18 (m, 5H), 6.97 (d, *J* = 8.7 Hz, 2H), 5.20 (d, *J* = 8.4 Hz, 1H), 4.82−4.79 (m, 1H), 3.87 (s, 3H), 3.84−3.80 (m, 2H), 3.75−3.64 (m, 7H), 3.54 (dd, *J* = 5.4, 10.2 Hz, 1H), 3.13 (dd, *J* = 8.4, 15.3 Hz, 1H), 3.04−2.84 (m, 8H), 2.77 (dd, *J* = 6.9, 13.5 Hz, 1H), 2.38 (bs, 1H), 1.85−1.76 (m, 1H), 0.90 (d, *J* = 6.3 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 162.9, 155.3, 137.5, 129.8, 129.5, 129.4, 128.4, 126.4, 114.3, 72.4, 71.8, 68.6, 58.7, 55.6, 55.1, 53.6, 53.4, 48.2, 35.6, 27.2, 20.2, 19.9.

(1*S*,2*R*)-{1-Benzyl-2-hydroxy-3-[isobutyl(4-methoxybenzenesulfonyl)amino]propyl}carbamic Acid *N*-Methyl-1,7-dioxa-4-azocyclodecan-9-yl Ester (3m). To a solution of **31** (9.0 mg, 0.015 mmol) in a mixture of 1% acetic acid in methanol (0.5 mL), formaldehyde (37% solution in H_2O, 12 μL, 0.15 mmol), and sodium cyanoborohydride (2.0 mg, 0.03 mmol) were added. After 18 h, a saturated solution of $NaHCO_3$ was added, the solvent was removed and the aqueous phase was extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4), evaporated, and the residue was purified by flash-chromatography eluting with a 10:1 mixture of $CHCl_3$ and MeOH to afford 8.0 mg (87%) of **3m** as an amorphous solid: $[\alpha]_D^{20}$ +8.1 (*c* 0.6, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.70 (d, *J* = 8.7 Hz, 2H), 7.3−7.18 (m, 5H), 6.98 (d, *J* = 8.7 Hz, 2H), 4.99 (d, *J* = 8.1 Hz, 1H), 4.80−4.77 (m, 1H), 3.87 (s, 3H), 3.83−3.74 (m, 4H), 3.70−3.56 (m, 6H) 3.14 (dd, *J* = 8.1, 14.7 Hz, 1H), 3.02−2.69 (m, 9H), 2.40 (s, 3H), 1.83−1.74 (m, 1H), 0.90 (d, *J* = 6.3 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 162.9, 155.5, 137.4, 129.9, 129.4 (×2C), 128.4, 126.4, 114.3, 77.2, 72.3, 69.6, 67.6, 59.0, 55.6, 55.1, 53.6, 44.0, 35.6, 29.7, 27.2, 20.2, 19.9. HRMS-ESI (*m*/*z*): (M + Na)$^+$ calcd for $C_{30}H_{46}N_3O_8S$, 608.3006; found, 608.3009.

Determination of X-ray Structure of 3d-Bound HIV Protease. The HIV-1 protease construct with the substitutions Q7K, L33I, L63I, C67A, and C95A to optimize protein stability[33] was expressed and purified as described.[34] Crystals were grown by the hanging drop vapor diffusion method using a 1:15 molar ratio of protease at 2.0 mg/mL and inhibitor dissolved in dimethylsulfoxide. The reservoir contained 0.1 M sodium acetate buffer (pH = 4.2) and 1.2 M NaCl, 10% DMSO. Crystals were transferred into a cryoprotectant solution containing the reservoir solution and 20−30% (v/v) glycerol, mounted on a nylon loop and flash-frozen in liquid nitrogen. X-ray diffraction data were collected on the SER-CAT beamline of the Advanced Photon Source, Argonne National Laboratory. Diffraction data were processed using HKL2000,[35] resulting in an R_{merge} value of 8.0% (41.1%) for 110362 unique reflections between 50 and 1.00 Å resolution with a completeness of 88.4% (52.6%), where the values in parentheses are for the final highest resolution shell. Data were reduced in space group $P2_12_12$ with unit cell dimensions of a = 57.96 Å, b = 86.41 Å, c = 46.03 Å with one dimer in the asymmetric unit. The structure was solved by molecular replacement using the CPP4i suite of programs,[36,37] with the structure of the D30N mutant of HIV protease in complex with GRL-98065 (2QCI)[34] as the starting model. The structure was refined using SHELX97[38] and refitted manually using the molecular graphics programs O[39] and COOT.[40] Alternate conformations were modeled for the protease residues when obvious in the electron density maps. Anisotropic atomic displacement parameters (B-factors) were refined for all atoms including solvent molecules. Hydrogen atoms were added at the final stages of the refinement. The identity of ions and other solvent molecules from the crystallization conditions was deduced from the shape and peak height of the $2F_o - F_c$ and $F_o - F_c$ electron density, the hydrogen bond interactions, and interatomic distances. The solvent structure was refined with two sodium ions, three chloride ions, and 219 water molecules including partial occupancy sites. The final R_{work} was 14.7% and R_{free} was 17.5% for all data between 10 and 1.00 Å resolution. The rmsd values from ideal bonds and angle distances were 0.017 Å and 0.034 Å, respectively. The average *B*-factor was 11.4 and 16.5 Å^2 for protease main chain and side chain atoms, respectively, 12.9 Å^2 for inhibitor atoms, and 22.6 Å^2 for solvent atoms. The X-ray crystal structure of the **3d**-bound HIV-1 protease has been deposited in the Protein Data Bank (PDB)[41] with accession code 3DJK.

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Supporting Information Available: HPLC and HRMS data of inhibitors **3a**−**m**; crystallographic data collection and refinement statistics. This material is available free of charge via the Internet at http://pubs.acs.org.

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