Rapid Discovery and Structure−Activity Profiling of Novel Inhibitors of Human Immunodeficiency Virus Type 1 Protease Enabled by the Copper(I)-Catalyzed Synthesis of 1,2,3-Triazoles and Their Further Functionalization

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Building from the results of a computational screen of a range of triazole-containing compounds for binding efficiency to human immunodeficiency virus type 1 protease (HIV-1-Pr), a novel series of potent inhibitors has been developed. The copper(I)-catalyzed azide−alkyne cycloaddition (CuAAC), which provides ready access to 1,4-disubstituted-1,2,3-triazoles, was used to unite a focused library of azide-containing fragments with a diverse array of functionalized alkyne-containing building blocks. In combination with direct screening of the crude reaction products, this method led to the rapid identification of a lead structure and readily enabled optimization of both azide and alkyne fragments. Replacement of the triazole with a range of alternative linkers led to greatly reduced protease inhibition; however, further functionalization of the triazoles at the 5-position gave a series of compounds with increased activity, exhibiting K_i values as low as 8 nM.

Introduction

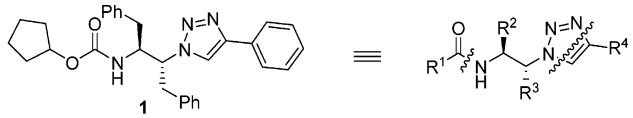
The global AIDS epidemic has claimed the lives of more than 20 million people since 1981. Another 40 million are now living with HIV, and most of these are likely to develop AIDS over the course of the next decade. Despite the various treatment protocols available, including the mainstream, highly active antiretroviral therapy (HAART),[1] the number of people infected with HIV continues to rise. The most recent UNAIDS/WHO estimates show that, in 2004 alone, 4.9 million people were newly infected with HIV.[2] HIV-1 protease[3] has been recognized as an important target for inhibition of viral replication. Although ten inhibitors have been approved by the FDA since 1995, and a number more are currently undergoing clinical evaluation, their success has been undermined by rapid mutation of the virus.[4] The alarming rate at which strains of HIV-1 that are resistant to the currently available drugs and their combinations are emerging, underscores the urgent need for new, broad-spectrum protease inhibitors, which are effective against the new mutants as well as the wild-type virus.

Herein we report the use of several click chemistry[5] techniques to aid the rapid identification and optimization of a novel series of HIV-1-Pr inhibitors. The copper(I)-catalyzed azide−alkyne cycloaddition (CuAAC)[6] has cemented its position at the heart of click chemistry due to its extremely broad scope, the orthogonality of the azide and alkyne functionalities to a diverse range of functional groups and reaction conditions, and the unique properties of the triazole products. In combination with direct screening of the crude reaction mixtures, it has proven to be a powerful approach for the rapid discovery of novel, biologically active molecules.[7] In this fashion, focused libraries of alkyne- and azide-bearing fragments, which themselves exhibited only minimal inhibitory activities, were combined under copper(I) catalysis, and the crude reaction products were directly screened for protease inhibition. Products exhibiting the highest inhibition values were then independently synthesized to confirm their activity and used as the basis for further fragment optimization. After identification of the azide- and alkyne-containing fragments resulting in the most potent inhibitors, the triazole linker itself was either replaced or further functionalized to give a series of highly active compounds with K_i values against HIV-1 protease as low as 8 nM.

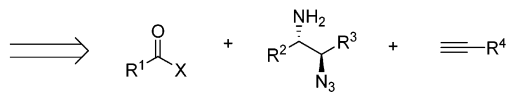
Results and Discussion

An initial lead structure was chosen from an in silico screen of an array of triazole-containing candidate structures. Thus, computational docking of an initial set of compounds into the active site of HIV-1-Pr, by use of the AutoDock program,[8] enabled calculation of their relative binding energies. Taking into account the computed binding energies as well as the potential for rapid diversification of the lead structure, compound **1** was chosen for further exploration. This structure had a relatively low computed binding energy (within the range of AutoDock standard deviation[8] from that of Amprenavir) and synthetically could readily be obtained from a core α-amino azide unit, a carbonyl-based capping group, and an alkyne (Scheme 1). Hence a small group of amino azide cores could be rapidly derivatized with activated carbonyl reagents followed by CuAAC with a library of alkynes to give a highly diverse array of potential inhibitors.

Scheme 1. Compound **1**: Its General Structure and Proposed Synthesis from an Amino Azide Core, an Activated Carbonyl Compound, and a Terminal Alkyne



Computed binding energy = -15.7 kcal/mol
c.f. Amprenavir = -16.5 kcal/mol



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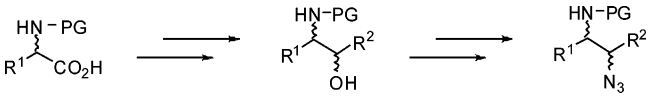
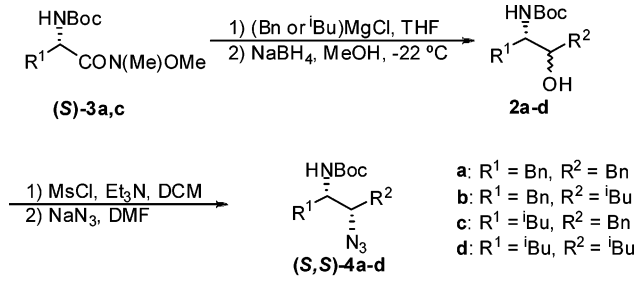
Scheme 2. Planned Synthesis of α-Amino Azide Cores[a]



[a] PG, protecting group.

Scheme 3. Synthesis of Syn α-Amino Azides



compd	crude ratio	isolated yield %	
	anti:*syn*-**2**[a]	*anti*-**2**[b]	*syn*-**4**[c]
a	90:10	61	58
b	83:17	51	38
c	88:12	64	59
d	>95:5	44	41

[a] Determined from the crude ^{1}H NMR spectra. [b]Isolated yield of the isomerically pure anti amino alcohol over two steps from the corresponding Weinreb amide. [c]Isolated yield of the isomerically pure syn amino azide over two steps from the corresponding anti amino alcohol.

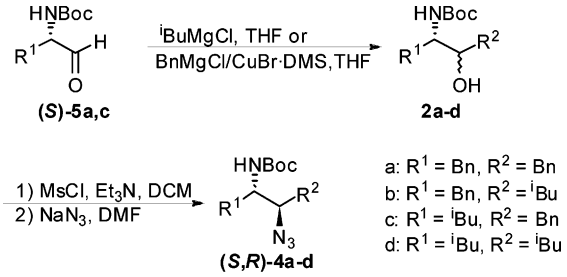
Synthetically, the α-amino azides were the most challenging fragments to obtain. Both enantiomers of both the syn and anti isomers of the amino azides were desired in order to fully probe the structural space. Although a number of selective routes to these compounds can be envisaged (for example, asymmetric functionalization of the corresponding alkenes),[9] the selective manipulation of α-amino acid derivatives[10] was the most convenient for our purposes, enabling synthesis of both diastereomers incorporating a range of substituents. Thus, suitable amino acid derivatives were selectively converted to the corresponding amino alcohols, which, after activation, readily gave the required amino azides (Scheme 2).

For the initial screening process we opted to make the compounds with R^1 and R^2 = ^{i}Bu or Bn, the *N*-Boc protecting group was chosen due to its ease of removal. Starting from the naturally occurring enantiomers of isoleucine and phenylalanine, all eight regio- and diastereoisomers of the amino azides were synthesized on approximately 1 g scale. Representative enantiomeric compounds were also synthesized starting from the unnatural amino acid derivatives.

Despite a large body of literature on the selective synthesis of α-amino alcohols[10,11] the majority of the compounds we required had not been previously described in the literature. Their syntheses, based on modified literature procedures, are described below. The anti amino alcohols (*S*,*R*)-**2a**−**d** were readily obtained by chelation-controlled reduction of the corresponding α-amino ketones[12] which were themselves obtained by the addition of benzyl or isobutylmagnesium chloride to the Weinreb amide derivative of *N*-Boc-L-phenylalanine (*S*)-**3a** or *N*-Boc-L-isoleucine (*S*)-**3c**. Mesylation under standard conditions followed by displacement of the mesylate group with sodium azide gave the corresponding syn amino azides (*S*,*S*)-**4a**−**d** in average to good yield (Scheme 3).[13]

The syn amino alcohols (*S*,*S*)-**2a**−**d** were obtained with reasonable selectivity by chelation-controlled addition of either isobutylmagnesium chloride or the cuprate reagent derived from benzylmagnesium chloride and copper bromide−dimethyl sulfide complex[14] to the *N*-Boc-protected amino aldehydes, *N*-Boc-L-phenylalaninal (*S*)-**5a** or *N*-Boc-L-isoleucinal (*S*)-**5c**.[15] Interestingly, use of either benzylmagnesium chloride or the isobutyl cuprate reagent was not successful. Mesylation of the product alcohols (*S*,*S*)-**2a**−**d** under standard conditions followed by displacement of the mesylate group with sodium azide furnished the corresponding anti amino azides (*S*,*R*)-**4a**−**d** in acceptable yield (Scheme 4).

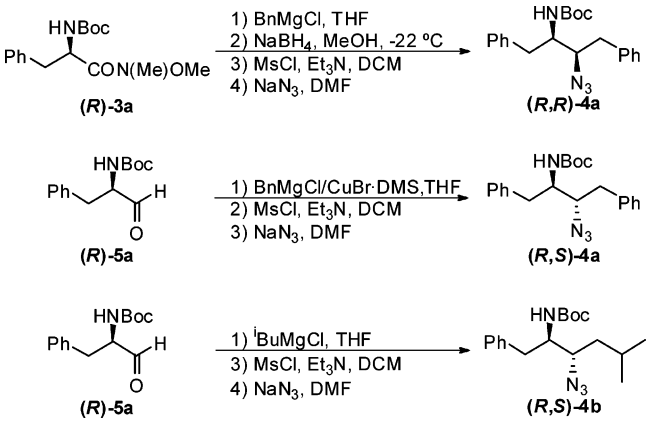
Scheme 4. Synthesis of Anti α-Amino Azide



compd	crude ratio.	isolated yield %	
	syn:*anti* -**2**[a]	*syn*-**2**[b]	*anti*-**4**[c]
a	80:20	47	67
b	88:12	47	42
c	80:20	55	71
d	-[d]	63	50

[a] Determined from the crude ^{1}H NMR spectra. [b]Isolated yield of the isomerically pure syn amino alcohol. [c]Isolated yield of the isomerically pure anti amino azide over two steps from the corresponding syn amino alcohol. [d]Not determined.

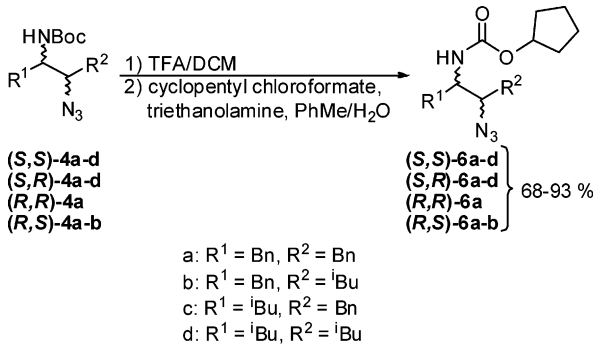
Scheme 5. Synthesis of α-Amino Azides from D-Phenylalanine Derivatives



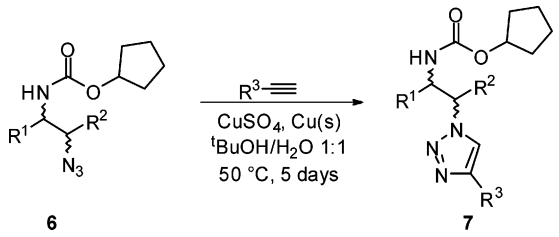
Three enantiomers of **4** were also synthesized, both to allow determination of their biological activities and to confirm the enantiomeric purity of our compounds by chiral HPLC analysis. The syn and anti compounds with R^1 = R^2 = Bn, (*R*,*R*)-**4a** and (*R*,*S*)-**4a**, and also the anti compound with R^1 = Bn and R^2 = ^{i}Bu, (*R*,*S*)-**4b**, were synthesized following the routes described above, starting from the unnatural amino acid derivatives *N*-Boc-D-phenylalanine *N*-methoxy-*N*-methylamide (*R*)-**3a**, and *N*-Boc-D-phenylalaninal (*R*)-**5a** (Scheme 5). Chiral HPLC analysis[16] of the three pairs of enantiomers confirmed their enantiomeric purity (ee > 98%), confirming that no racemization had occurred during any of our three synthetic routes.

The 11 *N*-Boc-protected amino azides **4** were then converted to their corresponding cyclopentyl carbamates **6** for initial fragment screening. Thus, cleavage of the *N*-Boc protecting groups with trifluoroacetic acid (TFA) in dichloromethane (DCM) followed by reaction of the free amines with cyclopentyl chloroformate under biphasic conditions provided the desired

Scheme 6. Synthesis of Cyclopentyl Carbamates (**6**)



Scheme 7. Synthesis of a Screening Library



products (**6**) in high yield and over 95% purity (as determined by liquid chromatographic−mass spectrometric analysis, LC-MS) after a simple aqueous workup (Scheme 6).

The amino azide derivatives (**6**) were then subjected to CuAAC with a selection of 69 terminal alkynes incorporating a diverse range of functionalities,[16] producing a library of triazoles with general structure **7** (Scheme 7). A solution of each azide core in ^{t}BuOH was added individually to a separate array of reaction tubes, each containing a solution of a single alkyne in ^{t}BuOH. An aqueous solution of $CuSO_4$ and a small piece of copper wire were added to generate a constant source of Cu(I). The tubes were sealed and shaken at 50 °C for 5 days, after which time LC-MS analysis indicated complete conversion of the starting azide to the corresponding triazole product in the vast majority of cases. The crude reaction mixtures were diluted to 5 μM into 96-well plates and assayed directly for their inhibitory activity against HIV-1-Pr.[17] Five of these compounds, (*S*,*S*)-**7a**−**e** (Figure 1), were found to give over 20% inhibition (Figure 1). All of the hits contained an *S*,*S*-configured syn amino azide fragment and an alkyne fragment based on the propargylpiperazine motif.

Synthesis and isolation of the two most potent compounds, (*S*,*S*)-**7d** and (*S*,*S*)-**7e**, proved these were genuine hits with K_i values of 98 ± 2 nM and 86 ± 9 nM, respectively (Scheme 8).

After identification of the initial hits, two focused libraries were synthesized to rapidly optimize both the alkyne and the azide-containing fragments. Optimization of the former was achieved by reaction of the dibenzyl syn amino azide (*S*,*S*)-**4a** with an array of 36 propargylpiperazine and -piperidine derivatives in the same manner as described above to give an array of 36 triazoles (*S*,*S*)-**11**.[16] A number of new hits were identified; all the most potent of which contained an arylpiperazine moiety (selected examples are shown in Table 1). The parent 4-phenylpiperazine [Table 1, compound (*S*,*S*)-**11a**] maintained good activity; however, alteration of this structural motif gave greatly reduced inhibition [(*S*,*S*)-**11b**−**e**]. Incorporation of 4-heteroarylpiperazines also resulted in greatly reduced activity [(*S*,*S*)-**11f**]. Variation of the degree and nature of substitution on the phenyl ring was well tolerated [(*S*,*S*)-**11g**−**k**], with 2,5-disubstitution tending to give the more potent compounds [(*S*,*S*)-**11j,k**]. Again, the most potent compounds were individually synthesized and isolated, and their K_i values were determined (Table 1).

The azide-containing fragment was profiled by replacing the cyclopentyl carbamate group that had been used initially with a range of alternative carbonyl-based caps. Thus, free amine (*S*,*S*)-**12a** was combined with an array of acyl chlorides, isocyanates, chloroformates, and *O*-succinamidyl carbonates under biphasic conditions to give a selection of 23 amides, ureas, and carbamates [(*S*,*S*)-**13**] in high yield and again over 95% purity (as determined by LC-MS analysis) after a simple aqueous workup. The azides [(*S*,*S*)-**13**] thus obtained were reacted in

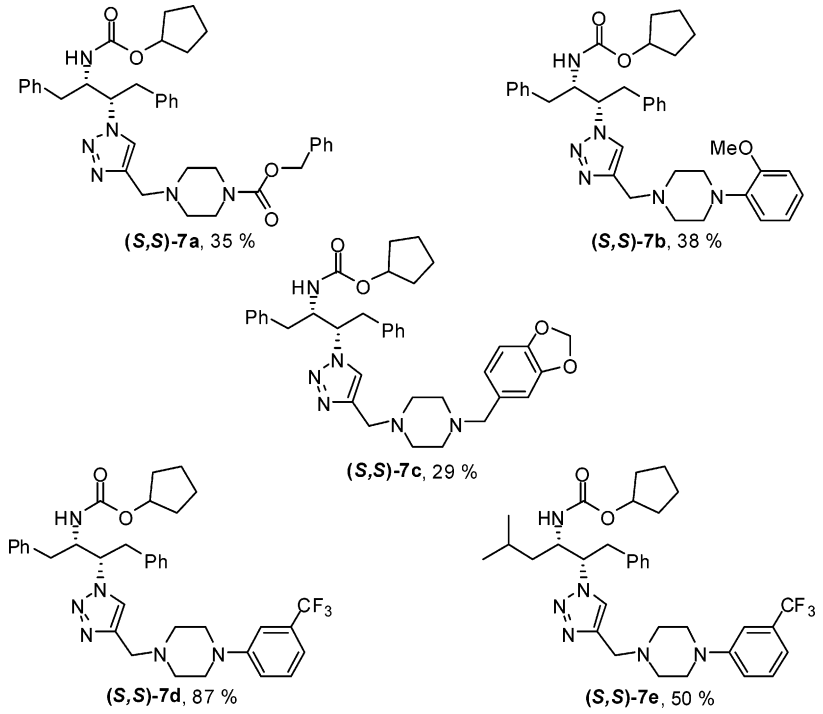
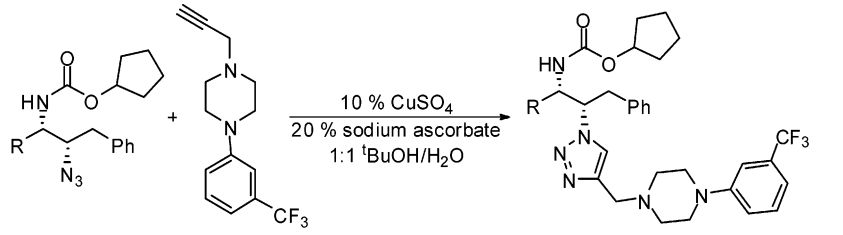


Figure 1. Structures and percentage inhibition of HIV-1-Pr for initial hit compounds at 5 μM concentration of the crude reaction mixtures.

Scheme 8. Synthesis and K_i Values of Triazole Products



Scheme 9. Exploration of the Azide-Containing Fragment

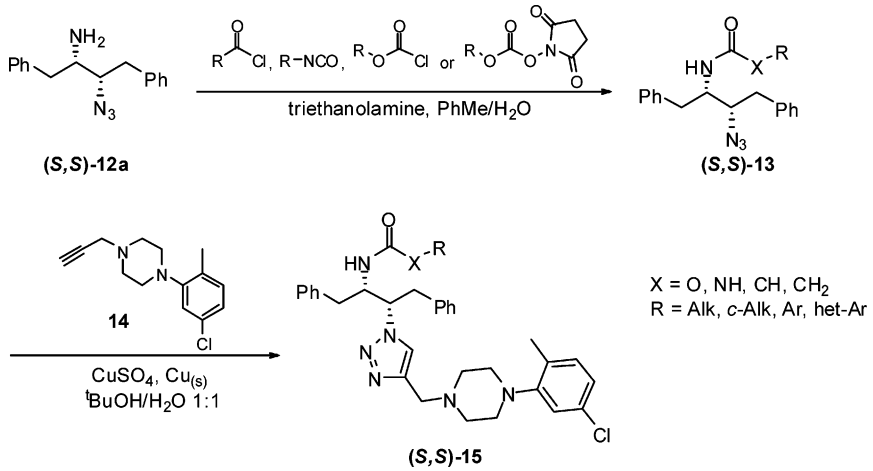
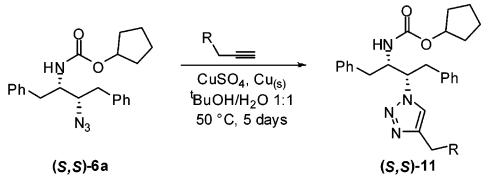


Table 1. Percentage Inhibition of HIV-1 PR by Selected Crude Reaction Mixtures at 5 μM and K_i Values for Selected Isolated Products



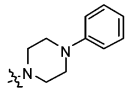
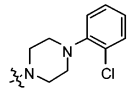
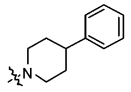
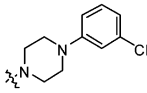
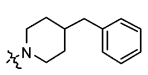
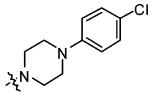
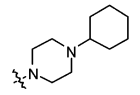
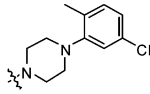
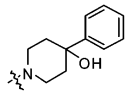
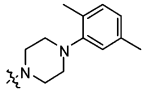
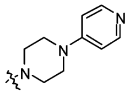
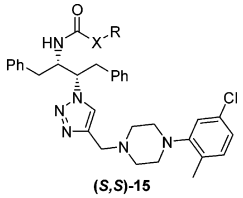
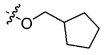
compd	R	% inhibition	compd	R	% inhibition	K_i
a		82	g		76	
b		67	h		93	
c		70	i		77	
d		22	j		94	23 ± 4 nM
e		20	k		94	32 ± 3 nM
f		12				

Table 2. Percentage Inhibition of Selected Crude Reaction Mixtures at 5 μM and K_i Values for Selected Isolated Products



compd	X-R	% inhibition	K_i
a		28	>2.5 μM
b		19	
c		73	
d		76	
e		71	83 ± 14 nM
f		31	

parallel with alkyne **14**, as described above, to form a further array of triazoles with general structure (*S*,*S*)-**15** (Scheme 9).

The crude reaction mixtures were again diluted to 5 μM and screened directly for HIV-1-PR inhibition (selected examples are shown in Table 2). Surprisingly, none of the amide or urea derivatives showed any observable inhibition at 5 μM [for example, Table 2, compounds (*S*,*S*)-**15a,b**]. A number of small alkyl carbamate derivatives [(*S*,*S*)-**15c**−**e**] showed similar activ-

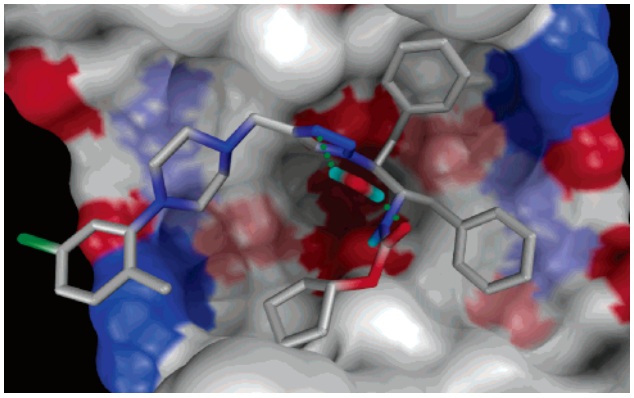


Figure 2. Inhibitor (*S*,*S*)-**11j** computationally docked into the HIV-1-Pr active site, showing hydrogen bonds from the triazole *N*-3 and carbamate oxygen to the active-site water as green spheres. Protease flap regions are removed for clarity.

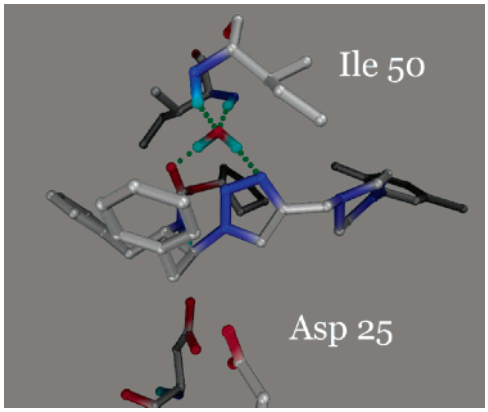


Figure 3. Detail of inhibitor (*S*,*S*)-**11j** computationally docked into the HIV-1-Pr active site. Protease amino acids Asp25, Asp25′, Ile50, and Ile50′ are shown. Hydrogen bonds between both the ligand and protease, and the active-site water are shown as green spheres. The triazole is positioned in proximity to the catalytic aspartic acid residues, suggesting possible beneficial interactions upon incorporation of a small polar group at *C*-5.

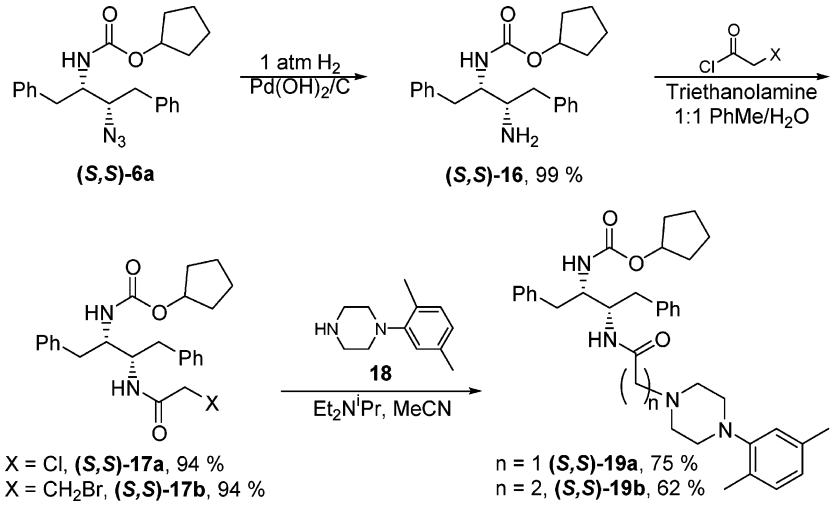
ity to (*S*,*S*)-**11j** (94% inhibition at 5 μM), but incorporation of an aryl group led to much reduced activity [(*S*,*S*)-**15f**]. To confirm these results, several of the inhibitors were synthesized and isolated, and their K_i values were determined (Table 2). None of the capping groups we tried gave compounds that exhibited as high a protease inhibition as (*S*,*S*)-**11j**, which contained the initially chosen cyclopentyl carbamate.

It was noteworthy that the azide and the alkyne fragments from which the most active compound [*S*,*S*)-**11j**] was assembled exhibited only minimal inhibitory activity themselves (azide (*S*,*S*)-**4a** $K_i = 31 \pm 22$ μM, alkyne **14** showed no observable inhibition even at 250 μM); the azide, which was the more active of the two building blocks, was over 1000 times less active than the final product. Computational docking of (*S*,*S*)-**11j** into the protease active site by use of AutoDock indicated that the compound adopted a conformation in which *N*-3 of the triazole and the carbonyl oxygen of the carbamate formed hydrogen bonds with the water molecule in the active site (Figure 2). Furthermore, no direct interaction between the inhibitor and the two aspartate residues in the active site was observed. This was in stark contrast to the currently licensed inhibitors, all of which contain a polar group, for example a hydroxyl, that acts as a transition-state mimic and strongly interacts with these residues. We reasoned that incorporation of a suitably positioned small polar group into our inhibitors could enable interaction with the aspartates, thereby increasing the binding energy (Figure 3). We envisioned two strategies for the rapid synthesis of analogues to accomplish this task: (a) replacement of the triazole with alternative, readily formed linkers and (b) direct modification of the 1,4-triazole unit to incorporate additional functionality.

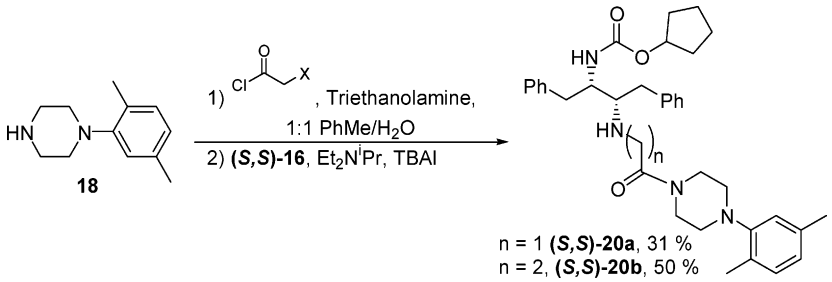
Since the 1,2,3-triazole heterocycle has been shown to be a viable isostere of the amide bond,[18] we were interested to see whether replacement of the triazole in (*S*,*S*)-**11j** with a two- or three-carbon amide-containing linker would still give effective protease inhibition. We chose to base our initial analogues on compound (*S*,*S*)-**11k**, which contained a 2,5-dimethylphenylpiperazine, rather than the slightly more active chloro derivative (*S*,*S*)-**11j** to avoid possible complications with strongly basic reaction conditions we planned to use later. The initial catalytic hydrogenation of the azide (*S*,*S*)-**4a** with $Pd(OH)_2/C$ gave the free amine (*S*,*S*)-**16** in 99% yield. Acylation with chloroacetyl chloride or 3-bromopropionyl chloride then furnished the halogenated amides (*S*,*S*)-**17a,b**, which were directly reacted with arylpiperazine **18** to furnish the desired compounds (*S*,*S*)-**19a,b** in high yield (Scheme 10). The isomeric amides (*S*,*S*)-**20a,b** were readily prepared in a similar fashion (Scheme 11).

The HIV-1-PR inhibition assay revealed that all four amide derivatives exhibited greatly reduced activity compared to the parent triazole: only minimal protease inhibition was observed at 25 μM concentration. We also synthesized the 1,5-disubstituted triazole regioisomer (*S*,*S*)-**21** in a selective manner, using the recently developed ruthenium-catalyzed triazole formation

Scheme 10. Synthesis of Amides (*S*,*S*)-**19a,b**



Scheme 11. Synthesis of Amides (*S,S*)-**20a,b**



Scheme 12. Synthesis of 1,5-Disubtituted Triazole (*S,S*)-**21**

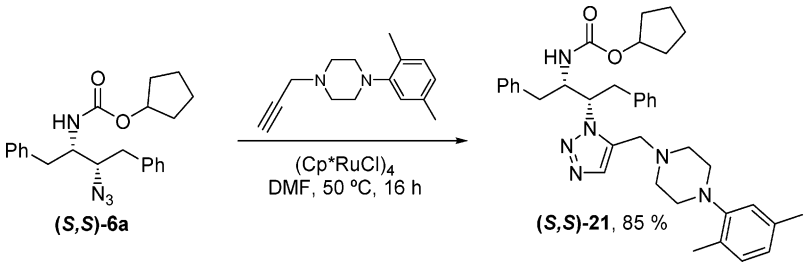
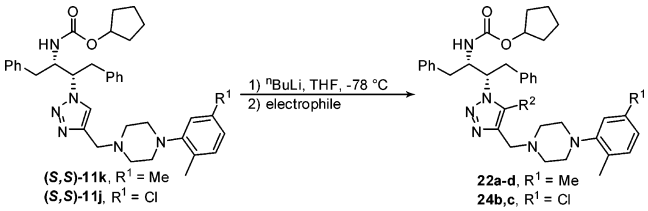


Table 3. Direct Functionalization of 1,4-Triazoles at the 5-Position

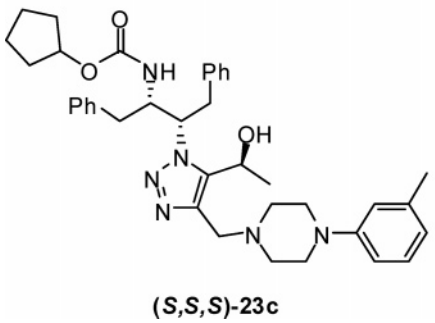


product	R^1	electrophile	R^2	yield (%)	K_i
(*S,S*)-**22a**	Me	TMS-Cl	TMS	58	>2.5 μM
(*S,S*)-**22b**	Me	*p*-CH_2O	-CH_2OH	53	14 ± 1 nM
(*S,S,S*)-**22c**	Me	MeCHO	(*S*)-CH(OH)Me	65[a]	10 ± 1 nM[b]
(*S,S,R*)-**22c**	Me	MeCHO	(*R*)-CH(OH)Me	23[c]	25 ± 3 nM[d]
(*S,S,S*)-**22d**	Me	EtCHO	(*S*)-CH(OH)Et	45[a]	27 ± 1 nM[b]
(*S,S,R*)-**22d**	Me	EtCHO	(*R*)-CH(OH)Et	15[c]	42 ± 5 nM[d]
(*S,S*)-**24b**	Cl	*p*-CH_2O	-CH_2OH	38	8 ± 0.5 nM
(*S,S,S*)-**24c**	Cl	MeCHO	(*S*)-CH(OH)Me	58[a]	21 ± 2 nM[b]
(*S,S,R*)-**24c**	Cl	MeCHO	(*R*)-CH(OH)Me	16[c]	28 ± 6 nM[d]

[a] Isolated yield of major, least polar *S,S,S* alcohol isomer. [b] K_i of major, least polar, *S,S,S* alcohol isomer. [c] Isolated yield of minor, most polar, *S,S,R* alcohol isomer [d] K_i or minor, most polar, *S,S,R* alcohol isomer.

reaction (Scheme 12).[19] Unsurprisingly, this compound also exhibited much lower protease inhibition (IC_{50} > 25 μM) than the parent 1,4-isomer.

These results indicated that the 1,4-disubstituted triazole linkage was crucial for efficient binding to the active-site residues. Therefore, we chose to install an additional small and polar substituent at the triazole *C*-5 position by direct quenching of a 5-metalated species. It has been previously demonstrated that a range of *N*-1-substituted triazoles can be selectively metalated at the 5-position and subsequently functionalized with suitable electrophiles.[20] There are also several isolated examples of the metalation of 1,4-disubstituted triazoles at the 5-position.[20a,21] However, these studies were carried out on very simple, minimally functionalized substrates. Furthermore, all of them contained at least one aryl substituent directly bonded to the triazole ring. The recent discovery of selective routes for the formation of 1,4-disubstituted triazoles[6] combined with direct deprotonation and quenching at *C*-5 creates a powerful method for the selective synthesis of 1,4,5-trisubstituted triazoles. We were therefore pleased to find that treatment of (*S,S*)-**11k** with 2.2 equiv of *n*-BuLi at −78 °C gave the dianion, which could be trapped with trimethylsilyl chloride (TMS-Cl) to give the 5-silylated triazole (*S,S*)-**22a** as the major product (Table 3). A small amount of disilylated product incorporating a second TMS group on the carbamate nitrogen was also isolated, but it could be readily converted to (*S,S*)-**22a** by stirring with aqueous HCl. No alternative products with silicon incorporated at any of the five potentially acidic benzylic positions were observed. Quenching of the dianion with paraformaldehyde gave the hydroxymethyl derivative (*S,S*)-**22b**. Two further hydroxyl-containing derivatives, **22c,d**, were synthesized by quenching of the dianion



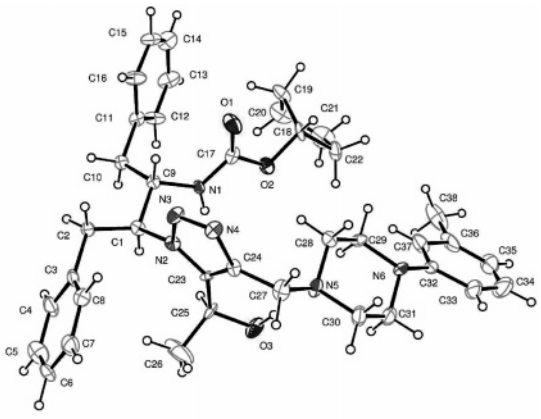


Figure 4. Compound (*S,S,S*)-**23c** structure and ORTEP drawing derived from X-ray crystallographic analysis.

with acetaldehyde or propionaldehyde, respectively. These latter reactions gave rise to readily separable mixtures of the two possible diastereomeric alcohols favoring the all-*S* products (*S*,*S*,*S*)-**22c,d** over (*S*,*S*,*R*)-**22c,d** by approximately 3:1. The configurations of the diastereomeric products were assigned after acquisition of an X-ray crystal structure of a closely related analogue (*S*,*S*,*S*)-**23c** (Figure 4).[16] Selective deprotonation was even possible in the presence of the reactive aryl chloride in (*S*,*S*)-**11j**; the triazolyllithium reagent was then quenched with paraformaldehyde or acetaldehyde, yielding (*S*,*S*)-**24b** or (*S*,*S*,*S*)- and (*S*,*S*,*R*)-**24c**, respectively (Table 3). As predicted from the docking calculations, incorporation of small polar groups gave increased inhibitory activity: the 5-hydroxymethyl compounds, (*S*,*S*)-**22b** and (*S*,*S*)-**24b,** were approximately 3 times more potent than the corresponding 5-unsubstituted triazoles. The compounds containing the larger hydroxyethyl or hydroxypropyl substituents (**22c,d**, and **24c**) tended to give slightly weaker inhibition, with the major *S*,*S*,*S*, isomers being more active than the minor *S*,*S*,*R* diastereomers.

Conclusions

Among many factors that determine success of a combinatorial search for novel compounds with desired activity, two stand out: the degree of *diversity* of the blocks that can be brought to bear and the *speed* with which synthesis, screening for function, and lead optimization can be performed. The greater the variety of scaffolds and functional groups that can be employed in the *rapid* construction of candidate compounds, the more likely it is that new and useful function will be discovered. In this study, the fidelity and robustness of the CuAAC process enabled the discovery of a novel series of HIV-1 protease inhibitors with low nanomolar activities. It was used to assemble the initial screening library from diverse arrays of highly functionalized azide- and alkyne-containing fragments. Since no protecting groups were required and byproducts were minimal, the crude reaction mixtures were screened directly for protease inhibition, leading to rapid identification of fragments that produced highly potent inhibitors upon their unification. The optimization of the initial hits was accomplished by repetition of this process. Replacement or modification of the triazole fragment in the hit compounds revealed that it is more than a simple connector and is, in fact, essential for the activity of the hits. For example, its replacement with an amide greatly reduced the potency of the candidate compounds, whereas functionalization of the triazole ring itself led to inhibitors with increased potency. This general strategy of using the versatile CuAAC reaction to discover and optimize the initial fragments, followed by replacement or derivatization of the 1,4-triazole linkage to maximize the compound's desired properties, should be useful in facilitating rapid discovery of novel lead structures against a wide range of targets.

Experimental Section

General Procedures. Reagents and solvents were purchased from commercial sources and were used as received. Reaction progress was monitored by thin-layer chromatography (TLC) on Merck silica gel 60 F-254 with detection by UV. Silica gel 60 (Merck 40−63 μm) was used for column chromatography. Melting points are uncorrected and were determined by use of a Thomas-Hoover, uni-melt, capillary melting point apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded with Bruker DRX-600, Bruker DRX-500, or Bruker AMX-400 spectrometers. Proton magnetic resonance (^{1}H NMR) spectra were recorded at 600, 500, or 400 MHz. Data are presented as follows: chemical shift (parts per million, ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sep = septet, m = multiplet, br = broad), coupling constant, *J* (hertz), and integration. Carbon magnetic resonance (^{13}C NMR) spectra were recorded at 150, 125, or 100 MHz. Data for ^{13}C NMR are reported in terms of chemical shifts (parts per million, ppm), and multiplicity (as above) followed by coupling constant (hertz) for fluorine-containing compounds. Most of the carbamate-containing products described here are observable by NMR at room temperature as mixtures of carbamate rotamers, generally in ratios of over 9:1. In these cases only signals for the major rotamer are listed. The signals for the pairs of rotameric compounds coalesced when the spectra were recorded at elevated temperatures; however, this often resulted in very broad signals. High-resolution mass spectra (HRMS) were recorded at the mass spectrometry facility at The Scripps Research Institute, La Jolla, CA. Elemental analyses were performed by Midwest Microlab, LLC, Indianopolis, IN. X-ray crystallographic analysis was carried out at the University of California, San Diego small molecule X-ray crystallography facility. Enantiomeric excesses were determined by chiral HPLC analysis. Assays were performed on a Shimadzu A10 system equipped with a diode array detector. Details of columns, eluent systems, and retention times are given in the respective experimental procedures. HPLC homogeneities were determined by use of an Agilent 1100 LC/MSD with an Agilent 1100 SL mass spectrometer. System A: Zorbax 4.6 mm × 30 mm, SB-C18 reverse-phase column, preceded by a Phenomenex C18 guard column, eluting with 10−100% MeCN (+0.05% TFA) in 0.05% TFA, linear gradient over 10 min and then isocratic for 5 min, 0.5 mL/min flow rate with UV detection at 254 nm. System B: Zorbax 4.6 mm × 150 mm, SB-C18 reverse-phase column, preceded by a Phenomenex C18 guard column, eluting with 10−100% MeOH (+0.05% TFA) in 0.05% TFA, linear gradient over 10 min and then isocratic for 10 min, 0.5 mL/min flow rate with UV detection at 254 nm. Fluorescence measurements were conducted on a Hitachi F2000 fluorescence spectrophotometer or a Packard fluorescence spectrophotometer (Fusion universal microplate analyzer) for microtiter plate assays.

Computational Docking Protocol. Atomic coordinates for the HIV-1 protease were obtained from the Protein Data Bank, PDB code 1HPV.[22] The ligand and crystallographic waters were removed with the exception of the water bridging the flaps. Polar hydrogens were added and Kollman charges were assigned to all atoms. Affinity grids centered on and encompassing the active site were calculated with 0.375 Å spacing by use of Autogrid3.[8] For the ligands, atomic coordinates were generated and initial molecular conformations minimized by use of ChemBats3D (CambridgeSoft). Gasteiger charges were assigned to all atoms and rotatable bonds were assigned with AutoDockTools. Autodock version 3.0.5 was used to evaluate ligand binding energies over the conformational search space by use of the Lamarckian genetic algorithm. Default docking parameters were used with the following exceptions: ga_pop_size, 150; ga_num_evals, 1750000; ga_run, 20.

[(1*S*,2*S*)-2-Azido-1,2-dibenzylethyl]carbamic Acid *tert*-Butyl Ester [(*S*,*S*)-4a].[13] To a solution of (*S*)-**3a** (2.71 g, 8.80 mmol, 1 equiv) in THF (24 mL) at 0 °C was added BnMgCl (20.2 mL of a 1.31 M solution in THF, 26.4 mmol, 3.0 equiv). The reaction mixture was slowly allowed to warm to room temperature and stirred for a further 3 h before being poured into 1 M HCl (15 mL). The mixture was extracted with Et_2O (3 × 20 mL), and the combined organic extracts were dried over $MgSO_4$ before being concentrated under reduced pressure to furnish the crude product. Flash chromatography (20% EtOAc in hexanes) furnished the desired ketone[12] (2.86 g, 96%).

To a solution of the ketone obtained above (2.81 g, 8.29 mmol, 1 equiv) in MeOH (58 mL) at −22 °C was added $NaBH_4$ (0.94 g, 25 mmol, 3 equiv). The reaction was maintained at −22 °C for 30 min and then allowed to warm to room temperature before being quenched by pouring into a saturated solution of NH_4Cl (60 mL). The reaction mixture was extracted with Et_2O (4 × 100 mL), and the combined organic extracts were washed with 1 M HCl (100 mL) and saturated $NaHCO_3$ solution (100 mL) before being concentrated under vacuum to furnish the crude amino alcohol **2a**

as a 9:1 mixture of diastereomers in favor of the anti isomer[12] as determined by ^{1}H NMR. Recrystallization from benzene afforded the pure anti isomer (*S*,*R*)-**2a** (1.82 g, 64%).

A solution of the amino alcohol (*S*,*R*)-**2a** obtained above (534 mg, 1.57 mmol, 1.0 equiv) in DCM (16 mL) was cooled to 0 °C before being treated with Et_3N (1.16 mL, 8.34 mmol, 1.2 equiv) followed by MsCl (592 μL, 17.7 mmol, 1.1 equiv). The reaction was maintained at 0 °C for 1 h and then allowed to warm to room temperature and stirred for a further 1 h before being diluted with DCM (35 mL) and washed with 1 M HCl (50 mL), saturated $NaHCO_3$ solution (50 mL), and finally brine (50 mL). The organic portion was dried over $MgSO_4$ and concentrated under reduced pressure before being purified by flushing through a short pad of silica (20% EtOAc in hexanes) to furnish the desired mesylate (597 mg, 91%).

To a solution of the mesylate obtained above (1.65 g, 3.93 mmol, 1.0 equiv) in DMF (20 mL) was added NaN_3 (358 mg, 5.50 mmol, 1.4 equiv). The reaction was heated to 60 °C for 16 h before being cooled to room temperature, diluted with Et_2O (60 mL), and washed with H_2O (5 × 60 mL) followed by brine (60 mL). The organic portion was dried over $MgSO_4$ and concentrated under reduced pressure before being purified by flash chromatography (10% EtOAc in hexanes) to furnish the title compound as a white solid (956 mg, 64%; mp 49−50 °C, ee > 98%[23]). $[\alpha]_D$ +3.2 (*c* 1.0, $CDCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.30−7.14 (m, 10H), 4.72 (d, *J* = 9.6, 1H), 4.00 (br q, *J* = 7.8, 1H), 3.59 (br t, *J* = 6.6, 1H), 2.92 (dd, *J* = 13.8 and 6.6, 1H), 2.86 (d, *J* = 7.2, 2H), 2.77 (dd, *J* = 13.8 and 9.0, 1H), 1.43 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 155.4, 137.3, 137.1, 129.3, 129.1, 128.6, 128.6, 126.9, 126.6, 79.6, 65.5, 53.7, 39.8, 38.5, 28.3; HRMS [electrospray ionization (ESI)−time of flight (TOF)] calculated for $C_{21}H_{26}N_4NaO_2$ (MNa^+) 389.1948, found 389.1950.

[(1*R*,2*R*)-2-Azido-1,2-dibenzylethyl]carbamic Acid *tert*-Butyl Ester [(*R*,*R*)-4a]. The procedure for the synthesis of (*S*,*S*)-**4a** was followed, starting from (*R*)-**3a** in place of its enantiomer. Thus the ketone was obtained in 86% yield and subsequently reduced with $NaBH_4$ to give, after recrystallization from benzene, the pure anti amino alcohol (*R*,*S*)-**2a** in 64% yield. Reaction with MsCl furnished the mesylate in 82% yield. Reaction with NaN_3 then gave the title compound as a white solid (66%; mp 50−51 °C, ee > 98%[23]). $[\alpha]_D$ −3.1 (*c* 1.0, $CDCl_3$); HRMS (ESI-TOF) calculated for $C_{21}H_{26}N_4NaO_2$ (MNa^+) 389.1948, found 389.1947. All other data were identical to those for (*S*,*S*)-**4a**.

[(1*S*,2*S*)-2-Azido-1-benzyl-2-isobutylethyl]carbamic Acid *tert*-Butyl Ester [(*S*,*S*)-4b]. The procedure for the synthesis of (*S*,*S*)-**4a** was followed with ^{i}BuMgCl used in place of BnMgCl. Thus the ketone was obtained after flash chromatographic purification (15% EtOAc in hexanes) in 90% yield and subsequently reduced with $NaBH_4$ to give the amino alcohol **2b** as a 5:1 mixture of diastereomers in favor of the anti isomer (*S*,*R*)-**2b**. Recrystallization from benzene furnished the pure anti isomer (*S*,*R*)-**2b** in 57% yield. Reaction with MsCl furnished the mesylate in 65% yield. Reaction with NaN_3 then gave the title compound as a white solid (58%; mp 74−75 °C). $[\alpha]_D$ +4.8 (*c* 1.0, $CDCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.32−7.22 (m, 5H), 4.63 (d, *J* = 9.6, 1H), 3.93 (br q, *J* = 7.8, 1H), 3.44 (br t, *J* = 7.2, 1H), 2.91 (dd, *J* = 13.8 and 6.6, 1H), 2.77 (dd, *J* = 13.8 and 9.0, 1H), 1.72 (sep, *J* = 6.6, 1H), 1.47−1.40 (m, 2H), 1.40 (s, 9H), 0.85 (d, *J* = 6.6, 3H), 0.77 (d, *J* = 6.6, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 155.5, 137.6, 129.2, 128.6, 126.6, 79.5, 61.8, 53.9, 40.3, 39.6, 28.3, 24.8, 22.5, 22.2; HRMS (ESI-TOF) calculated for $C_{18}H_{28}N_4NaO_2$ (MNa^+) 355.2104, found 355.2103.

[(1*S*,2*S*)-2-Azido-2-benzyl-1-isobutylethyl]carbamic Acid *tert*-Butyl Ester [(*S*,*S*)-4c]. The procedure for the synthesis of (*S*,*S*)-**4a** was followed, starting from (*S*)-**3c** in place of (*S*)-**3a**. Thus the ketone was obtained after flash chromatographic purification (10% EtOAc in hexanes) in 86% yield and subsequently reduced with $NaBH_4$ to give the amino alcohol **2c** as a 7:1 mixture of diastereomers in favor of the anti isomer (*S*,*R*)-**2c**. Recrystallization from hexanes furnished the pure anti isomer (*S*,*R*)-**2c** in 74% yield. Reaction with MsCl furnished the mesylate in 92% yield. Reaction with NaN_3 then gave, after flash chromatographic purification (5% EtOAc in hexanes), the title compound as a white solid (64%; mp 51−53 °C). $[\alpha]_D$ −42.9 (*c* 1.0, $CDCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.34−7.24 (m, 5H), 4.53 (d, *J* = 9.6, 1H), 3.87−3.83 (m, 1H), 3.61 (ddd, *J* = 8.4, 6.0, and 2.4, 1H), 2.91 (dd, *J* = 13.8 and 6.0, 1H), 2.81 (dd, *J* = 13.8 and 9.0, 1H), 1.65−1.58 (m, 1H), 1.49−1.44 (m, 1H), 1.47 (s, 9H), 1.29 (ddd, *J* = 13.8, 8.4, and 5.4, 1H), 0.91 (d, *J* = 6.6, 3H), 0.77 (d, *J* = 7.2, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 155.6, 137.6, 129.4, 128.6, 126.8, 79.4, 68.2, 50.9, 42.6, 38.4, 28.4, 24.8, 22.9, 22.2; HRMS (ESI-TOF) calculated for $C_{18}H_{28}N_4NaO_2$ (MNa^+) 355.2104, found 355.2107.

[(1*S*,2*S*)-2-Azido-1,2-diisobutylethyl]carbamic Acid *tert*-Butyl Ester [(*S*,*S*)-4d]. The procedure for the synthesis of (*S*,*S*)-**4c** was followed, with ^{i}BuMgCl in place of BnMgCl. Thus the ketone was obtained after flash chromatographic purification (10% EtOAc in hexanes) in 65% yield and subsequently reduced with $NaBH_4$ to give the amino alcohol as a single anti diastereomer. Recrystallization from benzene furnished the pure anti compound (*S*,*R*)-**2c** in 67% yield. Reaction with MsCl furnished the mesylate in 91% yield. Reaction with NaN_3 then gave, after flash chromatographic purification (5% EtOAc in hexanes), the title compound as a white solid (45%; mp 41−42 °C). $[\alpha]_D$ −39.5 (*c* 1.0, $CDCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 4.42 (d, *J* = 9.6, 1H), 3.79−3.75 (m, 1H), 3.61 (m, 1H), 1.81 (sep, *J* = 6.6, 1H), 1.65 (sep, *J* = 6.6, 1H), 1.49−1.26 (m, 4H), 1.43 (s, 9H), 0.94−0.92 (m, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 155.7, 79.3, 64.6, 51.2, 42.5, 40.3, 28.3, 24.9, 23.1, 22.8, 22.3, 22.2; HRMS (ESI-TOF) calculated for $C_{15}H_{30}N_4NaO_2$ (MNa^+) 321.2261, found 321.2260.

[(1*S*,2*R*)-2-Azido-1,2-dibenzylethyl]carbamic Acid *tert*-Butyl Ester [(*S*,*R*)-4a]. To a suspension of CuBr·DMS (6.60 g, 32.1 mmol, 2.0 equiv) in THF (80 mL) at −78 °C was added dropwise BnMgCl (49.1 mL of a 1.31 M solution in THF, 64.2 mmol, 4.0 equiv). After complete addition, the resulting solution was stirred for a further 10 min at −78 °C before a solution of (*S*)-**5a**[24] (4.00 g, 16.1 mmol, 1.0 equiv) in THF (60 mL + 20 mL wash) was added dropwise by cannula. The reaction was maintained at −78 °C for 10 min and then allowed to warm to room temperature and stirred for a further 3h before being quenched by the addition of saturated ammonium chloride solution (250 mL). The flask was opened to the atmosphere and vigorously stirred until a deep blue coloration had developed (~1 h). The resulting biphasic suspension was filtered through a short pad of Celite to remove any precipitated solids before being extracted with Et_2O (3 × 200 mL). The combined organic extracts were dried over $MgSO_4$ before being concentrated under reduced pressure to furnish the crude alcohol **2a** as a 5:1 mixture of diastereoisomers in favor of the desired syn isomer (*S*,*S*)-**2a** as determined by ^{1}H NMR. Flash chromatography (25% EtOAc in hexanes) enabled isolation of the pure syn isomer (*S*,*S*)-**2a** (2.59 g, 47%).

The product obtained above (2.37 g, 6.95 mmol, 1.0 equiv) was dissolved in DCM (35 mL) and cooled to 0 °C before being treated with Et_3N (1.16 mL, 8.34 mmol, 1.2 equiv) followed by MsCl (592 μL, 7.65 mmol, 1.1 equiv). The reaction was maintained at 0 °C for 1 h and then allowed to warm to room temperature and stirred for a further 1 h before being diluted with DCM (35 mL) and washed with 1 M HCl (50 mL), saturated $NaHCO_3$ solution (50 mL) and finally brine (50 mL). The organic portion was dried over $MgSO_4$ and concentrated under reduced pressure before being purified by flushing through a short pad of silica (20% EtOAc in hexanes) to furnish the desired mesylate (2.50 g, 86%).

To a solution of the mesylate obtained above (2.41 g, 5.75 mmol, 1.0 equiv) in DMF (30 mL) was added NaN_3 (468 mg, 7.99 mmol, 1.4 equiv). The reaction was heated to 60 °C for 16 h before being cooled to room temperature, diluted with Et_2O (100 mL), and washed with H_2O (5 × 100 mL) followed by brine (100 mL). The organic portion was dried over $MgSO_4$ and concentrated under reduced pressure before being purified by flash chromatography (12.5% EtOAc in hexanes) to furnish the title compound as a white solid (1.64 g, 78%; mp 127−128 °C, ee > 98%[25]). $[\alpha]_D$ −38.0 (*c* 1.0, $CDCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.35−7.17 (m, 10H), 4.57 (br d, *J* = 7.2, 1H), 3.99 (br s, 1H), 3.38 (br s, 1H), 3.02 (dd,

J = 14.4 and 3.6, 1H), 2.98 (dd, J = 14.4 and 4.2, 1H), 2.85−2.72 (m, 2H), 1.34 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 155.1, 137.3, 137.3, 129.2, 129.2, 128.7, 128.5, 127.0, 126.6, 79.7, 67.1, 54.5, 38.0, 35.8, 28.2; HRMS (ESI-TOF) calculated for $C_{21}H_{26}N_4NaO_2$ (MNa^+) 389.1948, found 389.1950.

[(1*R*,2*S*)-2-Azido-1,2-dibenzylethyl]carbamic Acid *tert*-Butyl Ester [(*R*,*S*)-4a]. The procedure for the synthesis of (*S*,*R*)-**4a** was followed, starting from (*S*)-**5a**[24] in place of its enantiomer. Thus, the syn amino alcohol (*R*,*R*)-**2a** was obtained in 60% yield. Reaction with MsCl furnished the mesylate in 61% yield. Reaction with NaN_3 then gave the title compound (47%; mp 126−127 °C, ee > 98%[25]). $[\alpha]_D$ +37.4 (*c* 1.0, $CDCl_3$); HRMS (ESI-TOF) calculated for $C_{21}H_{26}N_4NaO_2$ (MNa^+) 389.1948, found 389.1952. All other data were identical to those for (*S*,*R*)-**4a**.

[(1*S*,2*R*)-2-Azido-1-benzyl-2-isobutylethyl]carbamic Acid *tert*-Butyl Ester [(*S*,*R*)-4b]. To a solution of (*S*)-**5a**[24] (4.13 g, 1.66 mmol, 1.0 equiv) in THF (166 mL) at room temperature was added dropwise ^{i}BuMgCl (24.9 mL of a 2.0 M solution in THF, 49.8 mmol, 3.0 equiv). After complete addition, the resulting solution was stirred for a further 2.5 h before being quenched by the addition of saturated ammonium chloride solution (100 mL). The reaction mixture was extracted with DCM (3 × 200 mL) and the combined organic portions were washed with brine (200 mL) before being dried over $MgSO_4$ and concentrated under reduced pressure to furnish the crude alcohol **2b** as a 7:1 mixture of diastereoisomers in favor of the desired syn isomer (*S*,*S*)-**2b** as determined by ^{1}H NMR. Flash chromatography (17.5% EtOAc in hexanes) enabled isolation of the pure syn isomer (*S*,*S*)-**2b** (2.37 g, 47%).

A solution of the amino alcohol (*S*,*S*)-**2b** obtained above (1.97 g, 6.25 mmol, 1.0 equiv) in DCM (31 mL) was cooled to 0 °C before being treated with Et_3N (1.04 mL, 7.50 mmol, 1.2 equiv) followed by MsCl (533 μL, 6.88 mmol, 1.1 equiv). The reaction was maintained at 0 °C for 1 h and then allowed to warm to room temperature and stirred for a further 1 h before being diluted with DCM (35 mL) and washed with 1 M HCl (50 mL), saturated $NaHCO_3$ (50 mL), and finally brine (50 mL). The organic portion was dried over $MgSO_4$ and concentrated under reduced pressure before being purified by flushing through a short pad of silica (20% EtOAc in hexanes) to furnish the desired mesylate (2.10 g, 87%).

To a solution of the mesylate obtained above (2.10 g, 5.44 mmol, 1.0 equiv) in DMF (30 mL) was added NaN_3 (495 mg, 7.60 mmol, 1.4 equiv). The reaction was heated to 60 °C for 16 h before being cooled to room temperature, diluted with Et_2O (100 mL), and washed with H_2O (5 × 100 mL) followed by brine (100 mL). The organic portion was dried over $MgSO_4$ and concentrated under reduced pressure before being purified by flash chromatography (12.5% EtOAc in hexanes) to furnish the title compound as a white solid (0.86 g, 48%; mp 93−94 °C, ee > 98%[26]). $[\alpha]_D$ −30.5 (*c* 1.0, $CDCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.30−7.17 (m, 5H), 4.54 (br d, J = 7.2, 1H), 3.97 (br s, 1H), 3.62 (br s, 1H), 2.89 (dd, J = 14.4 and 4.8, 1H), 2.65 (dd, J = 13.8 and 10.2, 1H), 1.84−1.77 (m, 1H), 1.56−1.37 (m, 2H), 1.34 (s, 9H), 1.00 (d, J = 6.6, 3H), 0.94 (d, J = 6.6, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 155.1, 137.5, 129.1, 128.5, 126.5, 79.6, 63.7, 54.8, 39.8, 35.7, 28.2, 25.3, 23.1, 22.0; HRMS (ESI-TOF) calculated for $C_{18}H_{28}N_4NaO_2$ (MNa^+) 355.2104, found 355.2100.

[(1*R*,2*S*)- 2-Azido-1-benzyl-2-isobutylethyl]carbamic Acid *tert*-Butyl Ester [(*R*,*S*)-4b]. The procedure for the synthesis of (*S*,*R*)-**4b** was followed, starting from (*R*)-**5a**[24] in place of its enantiomer. Thus, the syn amino alcohol (*R*,*R*)-**2b** was obtained in 45% yield. Reaction with MsCl furnished the mesylate in 60% yield. Reaction with NaN_3 then gave the title compound (60%; mp 92−94 °C, ee > 98%[26]). $[\alpha]_D$ +32.6 (*c* 1.0, $CDCl_3$); HRMS (ESI-TOF) calculated for $C_{18}H_{28}N_4NaO_2$ (MNa^+) 355.2104, found 355.2103. All other data were identical to those for (*S*,*R*)-**4b**.

[(1*S*,2*R*)-2-Azido-2-benzyl-1-isobutylethyl]carbamic Acid *tert*-Butyl Ester [(*S*,*R*)-4c]. The procedure for the synthesis of (*S*,*R*)-**4a** was followed, starting from (*S*)-**5c** in place of (*S*)-**5a**. Thus, the crude amino alcohol **2c** was obtained as a 5:1 mixture of diastereomers in favor of the syn isomer (*S*,*S*)-**2c**. Flash chromatographic separation (17.5% EtOAc in hexanes) gave the pure syn isomer (*S*,*S*)-**2c** in 55% yield. Reaction with MsCl furnished the mesylate in 93% yield. Reaction with NaN_3 then gave, after flash chromatography (10% EtOAc in hexanes), the title compound as a white solid (76%; mp 72−73 °C). $[\alpha]_D$ −47.3 (*c* 1.0, $CDCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.34−7.24 (m, 5H), 4.54 (br d, J = 8.4, 1H), 3.80−3.75 (m, 2H), 2.85 (dd, J = 14.4 and 4.2, 1H), 2.77 (dd,J = 13.8 and 10.2, 1H), 1.71−1.65 (m, 1H), 1.47−1.31 (m,2H), 1.45 (s, 9H), 0.96 (d, J = 6.6, 3H), 0.89 (d, J = 6.6, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 155.3, 137.5, 129.1, 128.7, 126.9, 79.6, 68.3, 52.1, 38.2, 37.9, 28.4, 24.7, 23.8, 21.4; HRMS (ESI-TOF) calculated for $C_{18}H_{28}N_4NaO_2$ (MNa^+) 355.2104, found 355.2107.

[(1*S*,2*R*)-2-Azido-1,2-diisobutylethyl]carbamic Acid *tert*-Butyl Ester [(*S*,*R*)-4d]. The procedure for the synthesis of (*S*,*R*)-**4b** was followed, starting from (*S*)-**5c** in place of (*S*)-**5a**. Thus, the crude amino alcohol **2d** was obtained as an undetermined mixture of diastereomers. Flash chromatographic separation (13.5% EtOAc in hexanes) gave the pure syn isomer (*S*,*S*)-**2d** in 63% yield. Reaction with MsCl furnished the mesylate in 73% yield. Reaction with NaN_3 then gave, after flash chromatography (5% EtOAc in hexanes), the title compound as a white solid (68%; mp 38−39 °C). $[\alpha]_D$ −48.6 (*c* 1.0, $CDCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 4.52 (br d, J = 8.4, 1H), 3.75−3.70 (m, 1H), 3.56 (dt, J = 9.0 and 4.2, 1H), 1.79−1.72 (m, 1H), 1.68−1.62 (m, 1H), 1.49−1.43 (m, 1H),1.45 (s, 9H), 1.32−1.16 (m, 3H), 0.98 (d, J = 6.6, 3H), 0.95 (d, J = 6.6, 3H) 0.93 (d, J = 6.6, 3H), 0.90 (d, J = 6.6, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 155.3, 79.5, 64.8, 52.2, 39.7, 38.1, 28.3, 25.3, 24.6, 23.8, 23.0, 22.1, 21.5; HRMS (ESI-TOF) calculated for $C_{15}H_{30}N_4NaO_2$ (MNa^+) 321.2261, found 321.2259.

General Procedure for Synthesis of Carbamates 6 and Amides, Ureas, and Carbamates 13. To a solution of the *N*-Boc-α-amino azide **4** (1.0 equiv) in DCM (5 mL/mmol) at 0 °C was added TFA (5 mL/mmol). The reaction was stirred at 0 °C for 30 min before being quenched by cautiously pouring into a saturated solution of $NaHCO_3$. The biphasic mixture was extracted with DCM (2 × 30 mL/mmol) and the combined organic portions were dried over $MgSO_4$ before being concentrated under reduced pressure to give the free amino azide **12**.

To a solution of the free amino azide **12** (1.0 equiv) obtained above, in toluene (10 mL/mmol), was added water (10 mL/mmol), followed by triethanolamine (1.2 equiv), and finally the required chloroformate, acyl chloride, isocyanate, or *O*-succinimidyl carbonate (1.1 equiv).[16] The reaction was stirred at room temperature for 1 h before being diluted with EtOAc (30 mL/mmol) and washed sequentially with 1 M HCl (30 mL/mmol), $NaHCO_3$ (30 mL/mmol), water (30 mL/mmol), and brine (30 mL/mmol). The organic portion was then dried over $MgSO_4$ before being concentrated under reduced pressure to give the desired products **6** or **13** in 68−93% yield over the two steps, with >95% purity as judged by LC-MS analysis.

Library Synthesis and Analysis. A solution of azide (**6**) (100 μL of a 20 mM solution in ^{t}BuOH, 2 μmol, 1.0 equiv) was added to a glass reaction tube containing a solution of an alkyne[16] (100 μL of a 24 mM solution in ^{t}BuOH, 2.4 μmol, 1.2 equiv). A solution of $CuSO_4$ (200 μL of a 0.5 mM solution in water, 0.1 μmol, 0.05 equiv) was added, followed by a small piece of copper turning to give final concentrations of: azide 5 mM, alkyne 6 mM, and $CuSO_4$ 0.25 mM in 1:1 ^{t}BuOH/H_2O. The reaction tubes were then sealed before being heated to 50 °C and shaken for 5 days. The crude reactions were analyzed by LC-MS, looking for disappearance of the azide starting material and formation of a product with the correct molecular weight. The crude reaction mixtures were then diluted to 0.5 mM with dimethyl sulfoxide (DMSO) (3.6 mL) and shaken gently until any precipitated products were redissolved. The remaining copper turning was removed and the crude DMSO solutions were further diluted to 5 μM into 96-well plates with 0.1 M MES and 0.2 M NaCl, pH 5.25 buffer, containing 5% (v/v) glycerol. To each well was added enzyme (20 μg/mL) and fluorogenic substrate (50 μM), before the plates were assayed directly for HIV-1-Pr inhibition. TL-3[27] (100 nM) was used as a positive control.

Kinetic Determinations. IC_{50} values of the isolated inhibitors against HIV-1 protease SF-2-WTQ7K-Pr[27b,28] activity were assayed by use of the fluorogenic substrate Abz-Thr-Ile-Nle/Phe-(p-NO_2)-Gln-Arg-NH_2.[17] The initial rate of substrate hydrolysis was determined at different inhibitor concentrations (1 nM−25 μM; concentrations above 25 μM were generally not assayed due to insolubility problems with some fragments) with 50 μM substrate and 20 μg/mL enzyme at 37 °C, in 0.1 M MES and 0.2 M NaCl, pH 5.25 buffer, containing 5% (v/v) glycerol. IC_{50} values were determined from a dose−response plot of the obtained data by use of the GRAFIT program (version 3.0 Erithacus Software, U.K.). K_m and V_{max} values for the fluorogenic peptide described above were determined by measuring the initial rate of hydrolysis at different substrate concentrations (2.5−100 μM) and fitting the obtained data to the Michaelis−Menten equation by use of the GRAFIT program. K_i values for the isolated inhibitors were derived from the IC_{50} values via the formula for competitive inhibitor, $K_i = IC_{50}/(1 + [S]/K_m)$.

Cyclopentyl (2*S*,3*S*)-1,4-Diphenyl-3-(4-[(4-[3-(trifluoromethyl)phenyl]piperazin-1-yl)methyl]-1*H*-1,2,3-triazol-1-yl)butan-2-ylcarbamate [(*S*,*S*)-7d]. A solution of azide (*S*,*S*)-**6a** (50 mg, 0.13 mmol, 1.0 equiv) and 1-(prop-2-ynyl)-4-[3-(trifluoromethyl)phenyl]-piperazine (36 mg, 0.13 mmol, 1.0 equiv) in ^{t}BuOH (1.3 mL) was treated with $CuSO_4$ (0.65 mL of a 0.02 M solution in H_2O, 0.013 mmol, 0.1 equiv) followed by sodium ascorbate (0.65 mL of a 0.04 M solution in H_2O, 0.026 mmol, 0.2 equiv). The reaction was stirred at room temperature for 16 h before being diluted with H_2O (15 mL); then 5 drops of 30% NH_4OH was added and the mixture was shaken vigorously for several minutes before being extracted with DCM (2 × 15 mL). The combined organic portions were washed with brine (15 mL) before being dried over $MgSO_4$ and concentrated under vacuum to give the crude product. Purification by flash chromatography (80−100% EtOAc in hexanes) furnished the title compound as a pale solid (53 mg, 63%; mp 148−150 °C). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.28−6.79 (m, 15H), 6.10 (d, J = 9.6, 1H), 5.11−5.09 (m, 1H), 4.58−4.52 (m, 1H), 4.40−4.38 (m, 1H), 3.71 (br s, 2H), 3.34 (dd, J = 13.8 and 11.4, 1H), 3.19 (br s, 4H), 4.15 (dd, J = 13.8 and 3.6, 2H), 2.83 (dd, J = 13.8 and 6.6, 1H), 2.52 (br s, 4H), 2.38 (dd, J = 13.8 and 9.6, 1H), 1.87−1.57 (m, 8H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 156.5, 151.2 136.9, 136.7, 131.4 (q, J = 32), 129.5, 129.0, 128.8, 128.7, 128.6, 126.9, 126.8, 125.4, 124.2, (q, J = 272), 118.7, 115.9, 112.1, 103.0, 77.8, 64.5, 55.0, 52.9, 52.2, 48.5, 39.6, 39.3, 32.8, 32.7, 23.7, 23.6; HRMS (ESI-TOF) calculated for $C_{36}H_{42}F_3N_6O_2$ (MH^+) 647.3321, found 647.3321. Anal. ($C_{36}H_{41}F_3N_6O_2$) C, H, N.

Cyclopentyl (2*S*,3*S*)-3-[4-([4-(5-Chloro-2-methylphenyl)piperazin-1-yl]methyl)-1*H*-1,2,3-triazol-1-yl]-1,4-diphenylbutan-2-ylcarbamate [(*S*,*S*)-11j]. The procedure for the synthesis of (*S*,*S*)-**7d** was followed using **14** in place of 1-(prop-2-ynyl)-4-(3-(trifluoromethyl)phenyl)piperazine. Purification by flash chromatography on silica gel (50% EtOAc in hexanes) furnished the title compound as a pale pink solid (81%; mp 139−140 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.30−6.79 (m, 14H), 6.12 (d, J = 10.0, 1H), 5.11−5.08 (m, 1H), 4.58−4.52 (m, 1H), 4.39−4.37 (m, 1H), 3.72 (br s, 2H), 3.34 (dd, J = 14.0 and 11.0, 1H), 3.14 (dd, J = 14.0 and 4.0, 1H), 2.86 (br s, 4H), 2.83 (dd, J = 14.0 and 6.5, 1H), 2.52 (br s, 4H), 2.38 (dd, J = 13.5 and 9.0, 1H), 2.23 (s, 3H), 1.87−1.55 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 156.4, 152.4, 142.9, 136.9, 136.7, 131.9, 131.6, 130.7, 129.0, 128.8, 128.7, 128.5, 126.8, 126.8, 125.4, 122.9, 119.4, 77.8, 64.4, 55.0, 53.0, 52.8, 51.3, 39.6, 39.2, 32.8, 32.7, 23.6, 23.6, 17.4; HRMS (ESI-TOF) calculated for $C_{36}H_{44}ClN_6O_2$ (MH^+) 627.3214, found 627.3215. Anal. ($C_{36}H_{44}ClN_6O_2$) C, H, N.

Cyclopentyl (2*S*,3*S*)-3-[4-([4-(2,5-Dimethylphenyl)piperazin-1-yl]methyl)-1*H*-1,2,3-triazol-1-yl]-1,4-diphenylbutan-2-ylcarbamate [(*S*,*S*)-11k]. A solution of azide (*S*,*S*)-**6a** (200 mg, 0.53 mmol, 1.0 equiv) and 1-(2,5-dimethylphenyl)-4-(prop-2-ynyl)-piperazine (121 mg, 0.53 mmol, 1.0 equiv) in ^{t}BuOH (5.3 mL) was treated with $CuSO_4$ (2.65 mL of a 0.02 M solution in H_2O, 0.053 mmol, 0.1 equiv) followed by sodium ascorbate (2.65 mL of a 0.04 M solution in H_2O, 0.11 mmol, 0.2 equiv). The reaction was stirred for 24 h before being diluted with H_2O (30 mL) and NH_4OH (2 mL of a 30% aqueous solution), causing the product to precipitate. The mixture was stirred vigorously for 10 min before the precipitate was collected by filtration, washed with NH_4OH (30 mL of a 2 M aqueous solution) and water (30 mL). The collected product was dried under high vacuum to furnish the title compound without need for further purification, as a pale solid (313 mg, 98%; mp 148−150 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.30−6.79 (m, 14H), 6.13 (d, J = 10.0, 1H), 5.12−5.08 (m, 1H), 4.59−4.53 (m, 1H), 4.40−4.36 (m, 1H), 3.71 (s, 2H), 3.35 (dd, J = 14.0 and 11.0, 1H), 3.14 (dd, J = 14.0 and 4.0, 1H), 2.89 (br s, 4H), 2.84 (dd, J = 14.0 and 6.5, 1H), 2.52 (br s, 4H), 2.38 (dd, J = 14.0 and 9.0, 1H), 2.31 (s, 3H), 2.25 (s, 3H), 1.92−1.55 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 156.5, 151.2, 143.1, 137.0, 136.7, 136.0, 130.8, 129.3, 129.0, 128.8, 128.7, 128.5, 126.8, 126.8, 125.3, 123.8, 119.7, 77.8, 64.4, 55.0, 53.1, 53.1, 51.5, 39.6, 39.3, 32.8, 32.7, 23.7, 23.6, 21.2, 17.4; HRMS (ESI-TOF) calculated for $C_{37}H_{47}N_6O_2$ (MH^+) 607.3755, found 607.3766. Anal. ($C_{37}H_{46}N_6O_2$) C, H, N.

Cyclopentyl (2*S*,3*S*)-3-Amino-1,4-diphenylbutan-2-ylcarbamate [(*S*,*S*)-16]. A solution of azide (*S*,*S*)-**6a** (510 mg, 1.35 mmol) in MeOH (14 mL) in a 100 mL round-bottom flask was treated with $Pd(OH)_2$ on carbon (98 mg of 20% w/w, 0.14 mmol, 10 mol %). The reaction flask was purged with H_2 and the reaction was allowed to stir under an atmosphere of H_2 for 2 h. The reaction mixture was filtered through a plug of Celite, washing and rinsing with MeOH; concentration under reduced pressure then gave the crude product. Purification by flushing through a short plug of silica with 5% MeOH in EtOAc removed the hydrazine byproduct and furnished the title compound as a white solid (470 mg, 99%; mp 85−87 °C). $[\alpha]_D$ −16.6 (*c* 1.0, $CDCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.29−7.12 (m, 10H), 5.27 (d, J = 8.4, 1H), 5.07−5.05 (m, 1H), 3.93 (br q, J = 7.2, 1H), 3.11−3.08 (m, 1H), 2.92 (dd, J = 13.8 and 7.2, 1H), 2.80 (dd, J = 13.8 and 4.2, 1H), 2.77 (dd, J = 13.8 and 7.8, 1H), 2.53 (dd, J = 13.2 and 9.6, 1H), 1.85−1.50 (m, 10H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 156.5, 138.7, 138.1, 129.2, 129.1, 128.5, 128.5, 126.4, 126.4, 77.3, 55.3, 53.0, 41.2, 39.4, 32.8, 32.7, 23.7, 23.6; HRMS (ESI-TOF) calculated for $C_{22}H_{29}N_2O_2$ (MH^+) 352.2223, found 353.2226.

Cyclopentyl (2*S*,3*S*)-3-(2-[4-(2,5-Dimethylphenyl)piperazin-1-yl]acetamido)-1,4-diphenylbutan-2-ylcarbamate [(*S*,*S*)-19a]. To a solution of amine (*S*,*S*)-**16** (20 mg, 0.057 mmol, 1.0 equiv) in toluene (0.3 mL) was added water (0.3 mL) followed by triethanolamine (10 μL, 0.068 mmol, 1.2 equiv). The resulting biphasic reaction mixture was treated with chloroacetyl chloride (5.5 μL, 0.060 mmol, 1.05 equiv) and stirred at room temperature for 30 min. The reaction mixture was diluted with EtOAc (10 mL) and washed with H_2O (2 × 10 mL) followed by saturated $NaHCO_3$ solution (10 mL). The organic portion was dried over $MgSO_4$ and concentrated under reduced pressure to furnish (*S*,*S*)-**17a** (23 mg, 94%), which was used directly without further purification.

The α-chloro amide (*S*,*S*)-**17a** obtained as described above (23 mg, 0.054 mmol, 1.0 equiv) was dissolved in MeCN (0.54 mL) and treated with Hünig's base (11 μL, 0.065 mmol, 1.2 equiv) followed by **18** (10.3 mg, 0.054 mmol, 1.0 equiv). The reaction was stirred at room temperature for 20 h before being diluted with water (10 mL) and extracted with DCM (2 × 10 mL). The combined organic extracts were dried over $MgSO_4$ before being concentrated under reduced pressure to give the crude product. Purification by flash chromatography (45% EtOAc in hexanes) furnished the title compound as a white solid (24 mg, 75%; mp 180−182 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.32−6.82 (m, 14H), 5.18 (d, J = 8.0, 1H), 5.01 (br s, 1H), 4.23 (br s, 1H), 4.01 (br s, 1H), 3.06−2.77 (m, 10H), 2.46−2.34 (m, 4H), 2.34 (s, 3H), 2.22 (s, 3H), 1.82−1.53 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 170.9, 156.6, 151.0, 137.8, 136.1, 130.9, 129.4, 129.2, 129.0, 128.5, 128.4, 126.5, 126.5, 124.0, 119.7, 77.5, 61.5, 55.8, 53.8, 53.1, 51.7, 39.3, 38.2, 32.7, 32.6, 23.6, 23.5, 21.2, 17.3; HRMS (ESI-TOF) calculated for $C_{36}H_{47}N_4O_3$ (MH^+) 583.3642, found 583.3641. Anal. ($C_{36}H_{46}N_4O_3$) C, H, N.

Cyclopentyl (2*S*,3*S*)-3-(3-[4-(2,5-Dimethylphenyl)piperazin-1-yl]propanamido)-1,4-diphenylbutan-2-ylcarbamate [(*S*,*S*)-19b]. The same method was followed as for (*S*,*S*)-**19a** but using 3-bromopropionyl chloride in place of chloroacetyl chloride to furnish, after purification by flash chromatography (EtOAc), the title compound as a white solid (20 mg, 62% over two steps; mp 124−128 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.54 (d, J = 6.5, 1H), 7.26−7.16 (m, 10H), 7.06 (d, J = 7.5, 1H), 6.81 (d, J = 7.5, 1H), 6.75 (s, 1H), 5.63 (d, J = 8.5, 1H), 5.03−5.01 (m, 1H), 4.08−4.01 (m, 2H), 2.99−2.33 (m, 16H), 2.33 (s, 3H), 2.23 (s, 3H), 1.77−1.50 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 173.1, 156.7, 150.7, 138.5, 138.0, 136.1, 130.9, 129.2, 129.1, 129.1, 128.4, 128.4, 126.4, 124.0, 119.6, 77.4, 55.5, 53.9, 53.5, 52.8, 51.6, 39.5, 37.9, 32.8, 32.6, 32.0, 23.6, 23.5, 21.2, 17.4; HRMS (ESI-TOF) calculated for $C_{37}H_{49}N_4O_3$ (MH^+) 597.3805, found 597.3804. HPLC homogeneity 97.0% (system A), 95.3% (system B).

Cyclopentyl (2*S*,3*S*)-3-(2-[4-(2,5-Dimethylphenyl)piperazin-1-yl]-2-oxoethylamino)-1,4-diphenylbutan-2-ylcarbamate [(*S*,*S*)-20a]. To a solution of **18** (1.0 g, 5.3 mmol, 1.0 equiv) in toluene (20 mL) was added water (20 mL) followed by triethanolamine (0.84 mL, 6.3 mmol, 1.2 equiv). The resulting biphasic reaction mixture was treated dropwise with chloroacetyl chloride (0.44 mL, 5.5 mmol, 1.05 equiv) and stirred at room temperature for 5 h. The reaction mixture was diluted with EtOAc (50 mL) and washed with H_2O (3 × 30 mL). The organic portion was dried over $MgSO_4$ and concentrated under reduced pressure to furnish the α-chloro amide (1.4 g, quant), which was used directly without further purification.

The α-chloro amide obtained above (13 mg, 0.05 mmol, 1.0 equiv) was dissolved in MeCN (0.5 mL) and treated with Hünig's base (11 μL, 0.06 mmol, 1.2 equiv) followed by amine (*S*,*S*)-**16** (18 mg, 0.05 mmol, 1.0 equiv) and a catalytic amount of TBAI. The reaction was heated to 55 °C for 64 h and then allowed to cool to room temperature before being diluted with water (10 mL) and extracted with DCM (2 × 10 mL). The combined organic extracts were dried over $MgSO_4$ before being concentrated under reduced pressure to give the crude product. Purification by flash chromatography (38% EtOAc in hexanes) furnished the title compound as a clear film (9 mg, 31%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.28−7.10 (m, 10H), 7.08 (d, J = 7.2, 1H), 6.84 (d, J = 7.2, 1H), 6.78 (s, 1H), 5.17 (d, J = 7.8, 1H), 5.03−5.01 (m, 1H), 3.99 (br q, J = 7.2, 1H), 3.80−3.71 (m, 2H), 3.49 (d, J = 15.6, 1H), 3.40−3.35 (m, 2H), 3.30 (d, J = 15.6, 1H), 2.89−2.74 (m, 9H), 2.31 (s, 3H), 2.27 (s, 3H), 1.84−1.48 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 168.9, 156.4, 150.5, 138.7, 138.4, 136.3, 131.0, 129.4, 129.3, 129.1, 128.5, 128.3, 126.3, 126.2, 124.5, 119.9, 77.3, 61.2, 54.0, 51.7, 51.6, 49.8, 44.9, 42.5, 39.0, 38.8, 32.8, 32.6, 23.7, 23.6, 21.1, 17.3; HRMS (ESI-TOF) calculated for $C_{36}H_{47}N_4O_3$ (MH^+) 583.3642, found 583.3639. HPLC homogeneity 93.0% (system A), 90.1% (system B).

Cyclopentyl (2*S*,3*S*)-3-(3-[4-(2,5-Dimethylphenyl)piperazin-1-yl]-3-oxopropylamino)-1,4-diphenylbutan-2-ylcarbamate [(*S*,*S*)-20b]. To a solution of **18** (1.0 g, 5.3 mmol, 1.0 equiv) in toluene (20 mL) was added water (20 mL) followed by triethanolamine (0.84 mL, 6.3 mmol, 1.2 equiv). The resulting biphasic reaction mixture was treated dropwise with 3-bromopropionyl chloride (0.59 mL, 5.5 mmol, 1.05 equiv) and stirred at room temperature for 30 min. The reaction mixture was diluted with EtOAc (50 mL) and washed with H_2O (2 × 40 mL) followed by saturated $NaHCO_3$ solution (40 mL). The organic portion was dried over $MgSO_4$ and concentrated under reduced pressure to furnish the β-bromo amide (1.7 g, quant), which was used directly without further purification.

The β-bromo amide obtained as described above (16 mg, 0.05 mmol, 1.0 equiv) was dissolved in MeCN (0.5 mL) and treated with Hünigs base (11 μL, 0.06 mmol, 1.2 equiv) followed by amine (*S*,*S*)-**16** (18 mg, 0.05 mmol, 1.0 equiv) and a catalytic amount of TBAI. The reaction was heated to 55 °C for 24 h, a further portion of the β-bromo amide (64 mg, 0.2 mmol, 4.0 equiv) was then added, and the reaction was stirred for a further 72 h before being allowed to cool to room temperature. The reaction mixture was diluted with water (10 mL) and extracted with DCM (2 × 10 mL). The combined organic extracts were dried over $MgSO_4$ before being concentrated under reduced pressure to give the crude product. Purification by flash chromatography (60−100% EtOAc in hexanes) furnished the title compound as a clear film (15 mg, 50%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.28−7.07 (m, 11H), 6.84 (d, J = 8.0, 1H), 6.79 (s, 1H), 5.15−5.02 (br m, 2H), 3.97−3.50 (br m, 6H), 2.99−2.39 (br m, 12H), 2.30 (s, 3H), 2.28 (s, 3H), 1.84−1.55 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 170.2, 156.4, 150.6, 138.8, 138.4, 136.3, 131.0, 129.4, 129.3, 129.1, 128.4, 128.3, 126.2, 126.1, 124.4, 120.0, 77.1, 60.8, 53.9, 51.9, 51.6, 45.9, 44.7, 42.1, 39.1, 32.8, 32.6, 23.7, 23.6, 21.1, 17.4; HRMS (ESI-TOF) calculated for $C_{37}H_{49}N_4O_3$ (MH^+) 596.3799, found 596.3798. HPLC homogeneity 95.0% (system A), 96.4% (system B).

Cyclopentyl (2*S*,3*S*)-3-[5-([4-(2,5-Dimethylphenyl)piperazin-1-yl]methyl)-1*H*-1,2,3-triazol-1-yl]-1,4-diphenylbutan-2-ylcarbamate [(*S*,*S*)-21]. A solution of azide (*S*,*S*)-**6a** (25 mg, 0.07 mmol, 1.0 equiv) and 1-(2,5-dimethylphenyl)-4-(prop-2-ynyl)piperazine (15 mg, 0.07 mmol, 1.0 equiv) in DMF (0.7 mL) was treated with $(Cp^*RuCl)_4$ (3.6 mg, 0.003 mmol, 0.2 equiv of Ru). The reaction flask was flushed with N_2 and the reaction was heated to 50 °C for 16 h before being allowed to cool to room temperature. The reaction mixture was diluted with water (10 mL) and extracted with DCM (2 × 10 mL). The combined organic extracts were dried over $MgSO_4$ before being concentrated under reduced pressure to furnish the crude product. Purification by flash chromatography (30% EtOAc in hexanes) furnished the title compound as a pale solid (34 mg, 85%; mp 71−74 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.47 (s 1H), 7.30−6.90 (m, 11H), 6.79 (d, J = 7.5, 1H), 6.74 (s, 1H), 6.23 (d, J = 9.5, 1H), 5.04−4.99 (m, 1H), 4.75−4.71 (m, 1H), 4.67−4.61 (m, 1H), 3.36−3.28 (m, 2H), 2.80−2.30 (m, 12H), 2.28 (s, 3H), 2.19 (s, 3H), 1.81−1.54 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 156.2, 150.8, 137.2, 137.1, 136.1, 135.2, 133.2, 130.8, 129.2, 129.1, 129.0, 128.6, 128.5, 127.0, 126.6, 123.9, 119.6, 77.5, 62.8, 54.3, 53.6, 51.4, 50.0, 39.5, 38.6, 32.8, 32.6, 23.6, 23.5, 21.1, 17.3; HRMS (ESI-TOF) calculated for $C_{37}H_{47}N_6O_2$ (MH^+) 607.3755, found 607.3759. HPLC homogeneity 94.1% (system A), 90.7% (system B).

Cyclopentyl (2*S*,3*S*)-3-[4-([4-(2,5-Dimethylphenyl)piperazin-1-yl]methyl)-5-(trimethylsilyl)-1*H*-1,2,3-triazol-1-yl]-1,4-diphenylbutan-2-ylcarbamate [(*S*,*S*)-22a]. A solution of triazole (*S*,*S*)-**11k** (20 mg, 0.033 mmol, 1.0 equiv) in THF (0.7 mL) was cooled to −78 °C before being treated dropwise with *n*-BuLi (38 μL of a 1.9 M solution in hexanes, 0.073 mmol, 2.2 equiv). The solution was allowed to stir for 5 min at −78 °C before being treated with TMS-Cl and allowed to warm to room temperature. After being allowed to stir for 30 min at room temperature, the reaction was quenched by addition of water (5 mL) and extracted with DCM (2 × 10 mL). The combined organic extracts were dried over $MgSO_4$ before being concentrated under reduced pressure to furnish the crude product. Purification by flash chromatography (15−20% EtOAc in hexanes) furnished the title compound as a pale film (13 mg, 58%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.26−6.73 (m, 13H), 6.32 (d, J = 10.2, 1H), 5.01−4.99 (m, 1H), 4.66−4.60 (m, 2H), 3.72 (d, J = 12.6, 1H), 3.66 (d, J = 12.6, 1H), 3.47 (dd, J = 13.8 and 10.2, 1H), 3.16 (dd, J = 13.8 and 3.6, 1H), 2.92−2.51 (br m, 8H), 2.47 (dd, J = 13.8 and 6.6, 1H), 2.39 (dd, J = 13.8 and 8.4, 1H), 2.30 (s, 3H), 2.27 (s, 3H), 1.80−1.50 (m, 8H), −0.07 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 156.4, 151.3, 151.1, 137.1, 136.8, 136.0, 135.5, 130.9, 129.3, 129.3, 129.1, 128.6, 128.6, 127.0, 126.7, 123.6, 119.5, 77.5, 63.9, 54.9, 54.3, 53.4, 51.5, 40.4, 38.3, 32.7, 32.6 23.6, 23.5, 21.2, 17.5, −0.5; HRMS (ESI-TOF) calculated for $C_{40}H_{55}N_6O_2Si$ (MH^+) 679.4156, found 679.4146. HPLC homogeneity 95.5% (system A), 94.7% (system B).

Cyclopentyl (2*S*,3*S*)-3-[4-([4-(2,5-Dimethylphenyl)piperazin-1-yl]methyl)-5-(hydroxymethyl)-1*H*-1,2,3-triazol-1-yl]-1,4-diphenylbutan-2-ylcarbamate [(*S*,*S*)-22b]. A solution of triazole (*S*,*S*)-**11k** (50 mg, 0.083 mmol, 1.0 equiv) in THF (1.5 mL) was cooled

to −78 °C before being treated dropwise with *n*-BuLi (85 μL of a 2.5 M solution in hexanes, 0.21 mmol, 2.5 equiv). The solution was allowed to stir for 5 min at −78 °C before being transferred by cannula onto *p*-CH_2O (25 mg, 0.83 mmol, 10 equiv) at 0 °C. The reaction rapidly turned orange, then brown over 20 min, and then again became colorless after 40 min. After being allowed to stir for a further 20 min, the reaction was quenched by addition of water (5 mL) and extracted with DCM (2 × 15 mL). The combined organic layers were dried over $MgSO_4$ before being concentrated under reduced pressure to furnish the crude product. Purification by preparative TLC (70% EtOAc in hexanes) furnished the title compound as a clear film (28 mg, 53%). ^{1}H NMR (600 MHz, C_6D_6) δ = 7.17−6.39 (m, 14H), 5.32−5.30 (m, 1H), 4.81−4.77 (m, 1H), 4.17−4.12 (m, 1H), 3.88 (d, *J* = 14.4, 1H), 3.67 (d, *J* = 13.2, 1H), 3.56 (d, *J* = 13.2, 1H), 3.43 (d, *J* = 14.4, 1H), 3.33, (dd, *J* = 13.8 and 11.8, 1H), 2.94 (dd, *J* = 13.8 and 3.6, 1H), 2.90 (dd, *J* = 13.8 and 6.6, 1H), 2.71−2.57 (m, 4H), 2.42 (dd, *J* = 13.8 and 9.0, 1H), 2.34−2.21 (m, 4H), 2.20 (s, 3H), 2.14 (s, 3H), 1.80−1.29 (m, 9H); ^{13}C NMR (150 MHz, C_6D_6) 156.7, 151.3, 141.8, 137.9, 137.6, 137.2, 136.2, 131.2, 129.7, 129.4, 129.3, 129.0, 128.3, 127.1, 126.9, 124.6, 120.3, 77.8, 66.2, 56.2, 54.3, 54.2, 53.2, 51.7, 40.2, 39.6, 33.1, 33.0, 24.0, 23.9, 21.2, 17.6; HRMS (ESI-TOF) calculated for $C_{38}H_{49}N_6O_3$ (MH^+) 637.3866, found 637.3864. HPLC homogeneity 97.4% (system A), 96.9% (system B).

Cyclopentyl (2*S*,3*S*)-3-[4-([4-(2,5-Dimethylphenyl)piperazin-1-yl]methyl)-5-[(*S*)-1-hydroxyethyl]-1*H*-1,2,3-triazol-1-yl]-1,4-diphenylbutan-2-ylcarbamate [(*S*,*S*,*S*)-22c] and Cyclopentyl (2*S*,3*S*)-3-[4-([4-(2,5-Dimethylphenyl)piperazin-1-yl]methyl)-5-[(*R*)-1-hydroxyethyl]-1*H*-1,2,3-triazol-1-yl]-1,4-diphenylbutan-2-ylcarbamate [(*S*,*S*,*R*)-22c]. A solution of triazole (*S*,*S*)-**11k** (30 mg, 0.05 mmol, 1.0 equiv) in THF (1 mL) was cooled to −78 °C before being treated dropwise with *n*-BuLi (58 μL of a 1.9 M solution in hexanes, 0.11 mmol, 2.2 equiv). The solution was allowed to stir for 5 min at −78 °C before being treated with acetaldehyde (8.5 μL, 0.15 mmol 3.0 equiv). The reaction was maintained at −78 °C for 5 min and then allowed to warm to room temperature. After being allowed to stir for a further 30 min, the reaction was quenched by addition of water (5 mL) and extracted with DCM (2 × 15 mL). The combined organic extracts were dried over $MgSO_4$ before being concentrated under reduced pressure to furnish the crude product, which ^{1}H NMR indicated was an approximately 3:1 mixture of diastereomers. Purification by flash chromatography (30−50% EtOAc in hexanes) enabled separation of both the major, least polar *S*,*S*,*S* isomer as a white solid (21 mg, 65%; mp 193−195 °C) and the minor, more polar *S*,*S*,*R* isomer contaminated with an unknown impurity. Preparative TLC (8% MeOH in DCM) of the minor product enabled isolation of the pure compound (7.5 mg, 23%) as a clear film The configuration of the newly formed stereogenic center was assigned by analogy to that of (*S*,*S*,*S*)-**23c**, which was confirmed by the acquisition of an X-ray crystal structure.[16]

Data for major, least polar *S*,*S*,*S* isomer: ^{1}H NMR (600 MHz, C_6D_6) δ = 7.31 (d, *J* = 7.2, 2H), 7.21 (t, *J* = 7.2, 2H), 7.04−7.00 (m, 2H), 6.87−6.85 (m, 3H), 6.76 (d, *J* = 7.2, 1H), 6.64−6.61 (m, 2H), 6.52−6.50 (m, 2H), 5.33−5.30 (m, 1H), 4.77−4.72 (m, 1H), 4.35 (dt, *J* = 11.4 and 3.6, 1H), 4.30 (q, *J* = 6.6, 1H), 3.64 (d, *J* = 13.2, 1H), 3.57 (d, *J* = 13.2, 1H), 3.53 (dd, *J* = 13.8 and 11.4, 1H), 2.97 (dd, *J* = 13.8 and 3.6, 1H), 2.80 (dd, *J* = 13.8 and 6.6, 1H), 2.70−2.63 (m, 4H), 2.43 (dd, *J* = 13.8 and 8.4, 1H), 2.41−2.26 (m, 4H), 2.17 (s, 3H), 2.11 (s, 3H), 1.82−1.28 (m, 9H), 0.61 (d, *J* = 6.6, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ = 156.6, 151.2, 142.0, 140.9, 137.8, 137.5, 136.2, 131.2, 129.7, 129.6, 129.4, 129.1, 128.8, 127.1, 127.0, 124.5, 120.3, 77.8, 62.3, 60.8, 57.1, 54.6, 53.3 (b), 51.7, 40.1, 39.8, 33.1, 33.0, 24.0, 23.9, 23.0, 21.2, 17.5; HRMS (ESI-TOF) calculated for $C_{39}H_{51}N_6O_3$ (MH^+) 651.4023, found 651.4024. HPLC homogeneity 97.0% (system A), 95.4% (system B).

Data for minor, more polar *S*,*S*,*R* isomer: ^{1}H NMR (600 MHz, C_6D_6) δ = 7.11 (t, *J* = 7.2, 2H), 7.06−7.01 (m, 4H), 6.94 (t, *J* = 7.2, 2H), 6.88 (t, *J* = 7.2, 1H), 6.79 (d, *J* = 7.8, 1H), 6.76 (d, *J* = 7.2, 2H), 6.71 (s, 1H), 6.13 (d, *J* = 9.6, 1H), 5.18−5.14 (m, 1H), 4.75−4.69 (m, 1H), 4.45 (dt, *J* = 10.2 and 4.2, 1H), 4.28 (q, *J* = 6.6, 1H), 3.67 (d, *J* = 13.2, 1H), 3.61 (d, *J* = 13.2, 1H), 3.42 (dd, *J* = 13.8 and 12.0, 1H), 3.14 (dd, *J* = 13.8 and 4.8, 1H), 2.77−2.71 (m, 2H), 2.70 (dd, *J* = 13.8 and 5.4, 1H), 2.63−2.59 (m, 2H), 2.51 (dd, *J* = 13.8 and 10.2, 1H), 2.29 (br s, 4H), 2.24 (s, 3H), 2.16 (s, 3H), 1.74−1.50 (m, 7H), 0.1.31−1.25 (m, 2H), 1.26 (d, *J* = 6.6, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ = 156.6, 151.4, 141.4, 140.6, 137.7, 137.0, 136.2, 131.2, 129.7, 129.5, 129.3, 128.8, 128.7, 127.0, 126.8, 124.6, 120.4, 77.7, 63.4, 61.1, 55.3, 54.4, 53.3 (b), 51.8, 40.0, 39.0, 33.0, 32.9 24.2, 23.9, 23.8, 21.2, 17.6; HRMS (ESI-TOF) calculated for $C_{39}H_{51}N_6O_3$ (MH^+) 651.4023, found 651.4018. HPLC homogeneity 96.2% (system A), 96.0% (system B).

Cyclopentyl (2*S*,3*S*)-3-[4-([4-(2,5-Dimethylphenyl)piperazin-1-yl]methyl)-5-[(*S*)-1-hydroxypropyl]-1*H*-1,2,3-triazol-1-yl]-1,4-diphenylbutan-2-ylcarbamate [(*S*,*S*,*S*)-22d] and Cyclopentyl (2*S*,3*S*)-3-[4-([4-(2,5-Dimethylphenyl)piperazin-1-yl]methyl)-5-[(*R*)-1-hydroxypropyl]-1*H*-1,2,3-triazol-1-yl]-1,4-diphenylbutan-2-ylcarbamate [(*S*,*S*,*R*)-22d]. A solution of triazole (*S*,*S*)-**11k** (60 mg, 0.10 mmol, 1.0 equiv) in THF (2 mL) was cooled to −78 °C before being treated dropwise with *n*-BuLi (116 μL of a 1.9 M solution in hexanes, 0.22 mmol, 2.2 equiv). The solution was allowed to stir for 5 min at −78 °C before being treated with propionaldehyde (22 μL, 0.30 mmol 3.0 equiv). The reaction was maintained at −78 °C for 5 min and then allowed to warm to room temperature. After being allowed to stir for a further 30 min, the reaction was quenched by addition of water (5 mL) and extracted with DCM (2 × 15 mL). The combined organics were dried over $MgSO_4$ before being concentrated under reduced pressure to furnish the crude product, which ^{1}H NMR indicated was an approximately 3:1 mixture of diastereomers. Purification by preparative TLC (45% EtOAc in hexanes) enabled separation of both the major, least polar *S*,*S*,*S* isomer (30 mg, 45%) and the minor, more polar *S*,*S*,*R* isomer (10 mg, 15%) as clear films.

Data for major, least polar *S*,*S*,*S* isomer: ^{1}H NMR (600 MHz, C_6D_6) δ = 7.31−6.55 (m, 14H), 5.33−5.30 (m, 1H), 4.78−4.72 (m, 1H), 4.39 (dt, *J* = 10.8 and 3.6, 1H), 4.06 (dd, *J* = 9.6 and 3.6, 1H), 3.64 (d, *J* = 13.2, 1H), 3.58 (d, *J* = 13.2, 1H), 3.55 (dd, *J* = 13.8 and 10.8, 1H), 3.03 (dd, *J* = 13.8 and 3.6, 1H), 2.75 (dd, *J* = 13.8 and 6.6, 1H), 2.71−2.65 (m, 4H), 2.45 (dd, *J* = 13.8 and 8.4, 1H), 2.43−2.24 (m, 4H), 2.18 (s, 3H), 2.12 (s, 3H), 1.81−1.17 (m, 11H), 0.77 (t, *J* = 7.2, 3H); ^{13}C NMR (150 MHz, C_6D_6) 156.6, 151.2, 141.4, 141.2, 137.8, 137.6, 136.2, 131.1, 129.6, 129.5, 129.4, 129.0, 128.8, 127.1, 126.9, 124.5, 120.3, 77.8, 66.2, 62.3, 57.0, 54.5, 51.6, 39.9, 39.6, 33.1, 33.0, 30.2, 24.0, 23.9, 21.1, 17.9, 11.1; HRMS (ESI-TOF) calculated for $C_{40}H_{53}N_6O_3$ (MH^+) 665.4179, found 665.4178. HPLC homogeneity 100% (system A), 95.3% (system B).

Data for minor, most polar *S*,*S*,*R* isomer: ^{1}H NMR (600 MHz, C_6D_6) δ = 7.29−6.72 (m, 13H), 6.06 (d, *J* = 9.6, 1H), 5.19−5.16 (m, 1H), 4.76−4.71 (m, 1H), 5.13 (dt, *J* = 9.6 and 4.8, 1H), 4.11 (dd, *J* = 7.8 and 3.6, 1H), 3.65 (d, *J* = 13.2, 1H), 3.62 (d, *J* = 13.2, 1H), 3.41 (dd, *J* = 13.8 and 10.8, 1H), 3.13 (dd, *J* = 13.8 and 4.8, 1H), 2.77−2.54 (m, 6H), 2.29 (br s, 4H), 2.26 (s, 3H), 2.17 (s, 3H), 1.74−1.26 (m, 11H), 0.99 (t, *J* = 7.2, 3H); ^{13}C NMR (150 MHz, C_6D_6) 156.5, 151.5, 141.0, 140.6, 137.8, 136.9, 136.2, 131.2, 129.7, 129.4, 129.3, 128.8, 128.7, 127.0, 126.8, 124.6, 120.4, 77.7, 66.3, 63.3, 55.3, 54.6, 51.8, 40.0, 38.8, 33.0, 32.9, 31.1, 23.9, 23.8, 21.3, 17.6, 10.4; HRMS (ESI-TOF) calculated for $C_{40}H_{53}N_6O_3$ (MH^+) 665.4179, found 665.4175. HPLC homogeneity 100% (system A), 100% (system B).

Cyclopentyl (2*S*,3*S*)-3-[4-([4-(5-Chloro-2-methylphenyl)piperazin-1-yl]methyl)-5-(hydroxymethyl)-1*H*-1,2,3-triazol-1-yl]-1,4-diphenylbutan-2-ylcarbamate (*S*,*S*)-24b. The same method was followed as for the synthesis of (*S*,*S*)-**22b** but starting from triazole (*S*,*S*)-**11j** in place of triazole (*S*,*S*)-**11k**. Purification of the crude product by preparative TLC on neutral alumina (50% EtOAc in hexanes) furnished the title compound as a pale solid (58%; mp 85−87 °C). ^{1}H NMR (600 MHz, C_6D_6) δ = 7.15 (br s, 2H), 7.04−

7.00 (m, 3H), 6.91 (dd, J = 8.1 and 1.8, 1H), 6.82 (d, J = 1.8, 1H), 6.79−6.74 (m, 4H), 6.62 (br d, J = 9.6, 1H), 6.38 (br d, J = 6.6 Hz, 2H), 5.33−5.32 (m, 1H), 4.80−4.79 (m, 1H), 4.13 (br d, J = 11.4, 1H), 3.86 (d, J = 15.0, 1H), 3.62 (d, J = 13.2, 1H), 3.52 (d, J = 13.2, 1H), 3.41 (d, J = 14.4, 1H), 3.30 (dd, J = 13.2 and 12.0, 1H), 2.91 (td, J = 13.2 and 3.6, 2H), 2.45−2.40 (m, 5H), 2.15 (br s, 4H), 1.98 (s, 3H), 1.80−1.78 (m, 1H), 1.71−1.68 (m, 3H), 1.60−1.58 (m, 2H), 1.35−1.30 (m, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ = 156.7, 152.4, 138.0, 137.5, 137.2, 132.3, 131.0, 129.4, 129.3, 129.0, 128.6, 128.3, 127.2, 126.9, 123.7, 120.1, 77.9, 62.2, 56.2, 54.2, 52.9, 51.1, 40.2, 39.6, 33.1, 33.0, 24.0, 23.9, 17.4; HRMS (ESI-TOF) calculated for $C_{37}H_{46}ClN_6O_3$ (MH^+) 657.3314, found 657.3311. HPLC homogeneity 95.5% (system A), 97.0% (system B).

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Supporting Information Available: Elemental analysis results and HPLC homogeneity data for selected products; details of library synthesis; synthetic procedures and characterization data for compounds (*S*,*S*)-**7e**, (*S*,*S*)-**15a**, (*S*,*S*)-**15e**, (*S*,*S*,*S*)-**24c**, and (*S*,*S*,*R*)-**24c**; and synthesis details, characterization, and X-ray crystallographic data for compound (*S*,*S*)-**23c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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