Use of a Dipeptide Chemical Library in the Development of Non-Peptide Tachykinin NK_3 Receptor Selective Antagonists

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The use of a dipeptide library as the source of a micromolar chemical lead compound for the human tachykinin NK_3 receptor is described. The screening of a dipeptide library through a cloned human NK_3 receptor binding assay resulted in the identification of Boc(*S*)Phe(*S*)PheNH_2 (**1**), which has subsequently been developed, following a 'peptoid' design strategy, into a series of high-affinity NK_3 receptor selective antagonists. The structure−activity relationship of the C-terminal portion of this dipeptide lead was first explored and led to the identification of the urea derivative Boc(*S*)Phe(*R*)αMePheNH$(CH_2)_7$NHCONH_2 (**41**, PD157672). This modified dipeptide has a K_e of 7 nM in blocking senktide-induced increases in intracellular calcium levels in human NK_3 receptors stably expressed in CHO cells. Subsequent optimization of the N-terminal BocPhe group and the αMePhe residue side chain of **41** led to the identification of [*S*-(*R**,*S**)]-[2-(2,3-difluorophenyl)-1-methyl-1-[(7-ureidoheptyl)carbamoyl]ethyl]carbamic acid 2-methyl-1-phenylpropyl ester (**60**, PD161182), a non-peptide NK_3 receptor selective antagonist. Compound **60** blocks the senktide-evoked increases in intracellular calcium levels in cloned human NK_3 receptors stably expressed in CHO cells with K_e of 0.9 nM.

Introduction

The medicinal chemistry community has been quick to recognize, and subsequently exploit, the concept of large combinatorial chemical libraries as a means of rapid chemical lead identification. Since Houghton,[1] Hruby,[2] and Fodor's[3] key initial publications in this area, the scope of this technology has been significantly broadened to encompass the rapid synthesis of arrays of both peptide[1−3] and non-peptide[4−8] compound collections generated by resin or solution phase chemical techniques.

Whichever library type is chosen, it must serve to provide a collection of compounds which are capable of interacting with the biological target of interest at a detectable level. The compounds must also provide suitable starting points for subsequent optimization into a credible drug candidate. With these points in mind, we have recently described a dipeptide library.[9] The construction of such a library was considered useful as a potential source of novel lead structures since: (a) dipeptides have been shown, by us[10] and other groups,[11] to be an excellent starting point for drug design, (b) sufficient quantity of compound, even for *in vivo* profiling, can easily be prepared at relatively low cost, (c) no specialized equipment is required for the synthesis of such a library, (d) a library containing only 256 compounds can provide a data set that spans a broad spectrum of physicochemical properties in a minimum number of compounds, and (e) no deconvolution is required to identify the lead structures.

The key requirement of the library so constructed was that the greatest possible diversity of physical properties should be contained in a minimum set of compounds. For this purpose a factorial design using the minimum analogue peptide sets (MAPS)[12] in the principal properties of the amino acids was used to select a library of 256 N-protected dipeptides.

Subsequent hits obtained from the screening of this library in neuropeptide receptor assays were found to contain predominantly lipophilic amino acids (unpublished data). A second library of 64 dipeptides enriched in lipophilic side chains was therefore prepared in order to exploit this observation. These compounds are a set of Boc-protected dipeptide amides constructed from all combinations of the lipophilic amino acids Trp, Phe, Tyr, Val, Leu, Met, Ala, and Thr.

Active interest in the tachykinin research area[13−15] is reflected in the large number of recent publications describing non-peptide receptor antagonists. The majority of these describe NK_1 and NK_2 receptor selective ligands.[16] Recently the first non-peptide NK_3[17] receptor selective antagonist has been revealed. Our interest in this field has been illustrated by the rational design of both NK_1[18] and NK_2[19] receptor antagonists following a 'peptoid' design strategy. This 'peptoid' design strategy therefore became the starting point for our NK_3 receptor program and is summarized in Scheme 1.

In the development of our NK_1 and NK_2 receptor antagonists, a key step in the 'peptoid' design strategy was the identification of a dipeptide lead. In the case of our NK_3 receptor program, we took the opportunity to investigate whether the initial steps in our 'peptoid' design strategy, *i.e.*, the preparation of N- and C-terminal deletions, and the alanine scan could be superseded by the screening of our dipeptide libraries.

This paper describes the implementation of the dipeptide libraries in the identification of a micromolar affinity NK_3 receptor lead. The subsequent development of this dipeptide lead into high-affinity modified dipeptide[20] and non-peptide[21] nanomolar NK_3 selective receptor antagonists is reported.

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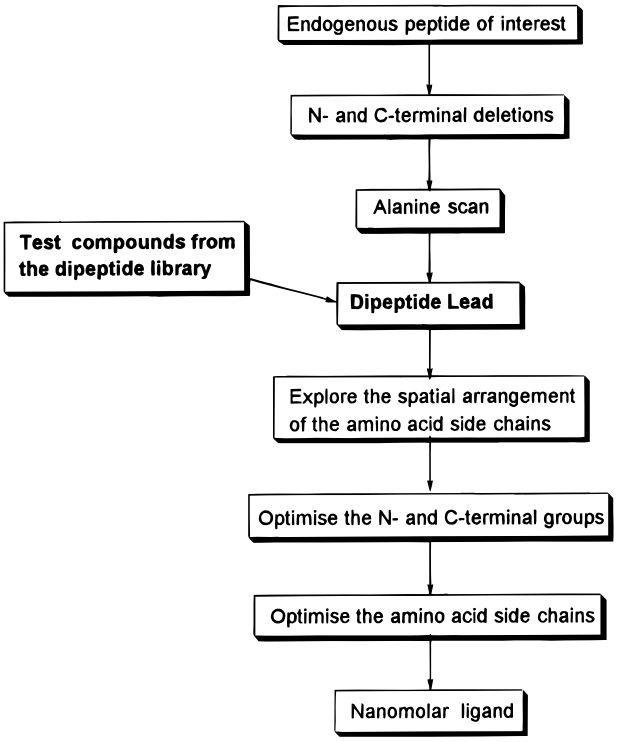
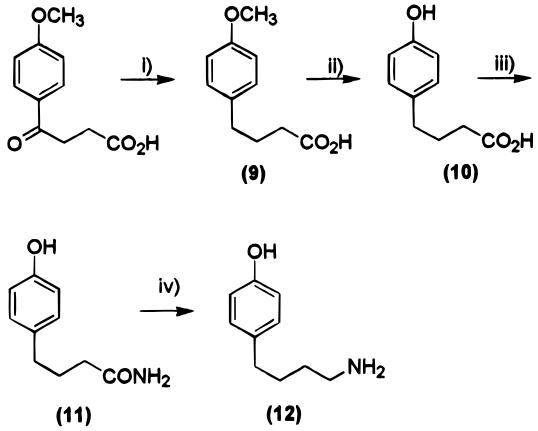
Scheme 1. Peptoid Design Strategy



Scheme 2. Synthesis of Intermediate **12**[a]

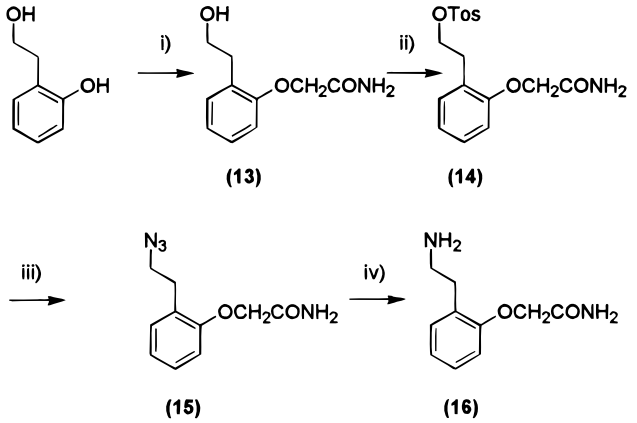


[a] (i) KOH, N_2H_4, diethylene glycol, 180 °C, 2 h (71%); (ii) 48% HBr, AcOH, 116 °C, 6 h (91%); (iii) DCCI, pentafluorophenol, EtOAc, 4 h, NH_3, 12 h (82%); (iv) 2 M borane−methyl sulfide complex in THF, 65 °C, 6 h (23%).

Chemistry

The Boc dipeptides **1**−**4** were purchased from Neosystem Laboratoire. The dipeptide library compounds **5** and **6** and the *N*- and α-methyl dipeptides **1a**−**j** were prepared by standard peptide-coupling procedures using pentafluorophenyl ester or 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) activation. Schemes 2 and 3 describe the syntheses of the C-terminal fragments **12** and **16** which were subsequently coupled to Boc(*S*)Phe(*R*)αMePheOH[22] using HBTU activation. The sulfonamide derivative **39** was prepared by the treatment of Boc(*S*)Phe(*R*)αMePheNH-$(CH_2)_7NH_2$ with methanesulfonyl chloride and pyridine in dichloromethane as outlined in Scheme 4. The (7-aminoheptyl)urea was prepared from 1,7-diaminoheptane and then coupled to Boc(*S*)Phe(*R*)αMePheOH[22] as shown in Scheme 5. Scheme 6 depicts the synthesis of the monoamino acid compounds. The [(isopropylbenzyl)oxy]carbonyl moiety is introduced by coupling the *p*-nitrophenyl carbonate of the 2-methyl-1-phenyl-1-propanol to the appropriate amino acid methyl ester. In the case of the side-chain-substituted αMePhe residues, the resulting diastereoisomers were separated at this stage by column chromatography. The esters were then hydrolyzed with lithium hydroxide, and the (7-aminoheptyl)urea moiety was coupled to the acids using HBTU activation.

Scheme 3. Synthesis of Intermediate **16**[a]



[a] (i) 2-Bromoacetamide, K_2CO_3, 2-butanone, 80 °C, 4 h; (ii) *p*-toluenesulfonyl chloride, DMAP, DCM, pyridine, 16 h (81%); (iii) NaN_3, DMF, 75 °C, 2 h (77%); (iv) Lindlar catalyst, MeOH, H_2, 44 psi, 25 °C, 18 h.

Biology

The human CHO NK_3 receptor binding assay was carried out as described previously,[23] as were the NK_1 and NK_2 binding assays.[18,19] The procedures employed in the *in vitro* functional assays have been published and are referenced in Table 8.

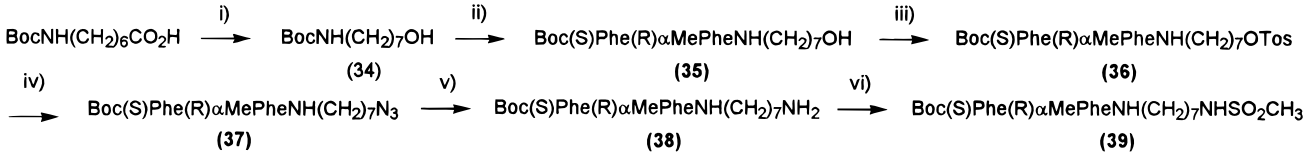
Results and Discussion

Screening of the dipeptide libraries in a cloned human NK_3 receptor binding assay resulted in the identification of a number of micromolar hits (Table 1). All hits with >10 μM affinity for the NK_3 receptor contain two aromatic amino acid residues and as a consequence came predominantly from the 64-membered lipophilic dipeptide library described above. From these hits Boc-(*S*)Phe(*S*)PheNH$_2$ (**1**) with an IC_{50} of 1550 nM was selected as the lead compound. This compound is selective for the NK_3 receptor over the NK_1 and NK_2 receptors, for which the IC_{50} values are >10 μM in both cases.

Following the identification of a dipeptide lead, the next step in our peptoid design strategy is the exploration of the spatial arrangement of the amino acid side chains and protecting groups. Conformational constraint can be built into the peptide backbone by the strategic placement of methyl groups. This approach has been successful in the improvement of the binding affinity of initial leads in our NK_1,[18] NK_2,[19] and CCK[10] receptor programs. Compounds were therefore prepared in which single methyl groups were appended on the nitrogen atom or α-carbon of the amino acid residues (Table 2).

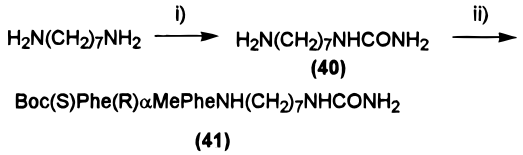
Unfortunately, no increase in binding affinity was observed as a result of the methylations. The C-terminal α-methyl compound Boc(*S*)Phe(*RS*)αMePheNH$_2$

Scheme 4. Synthesis of **39**[a]



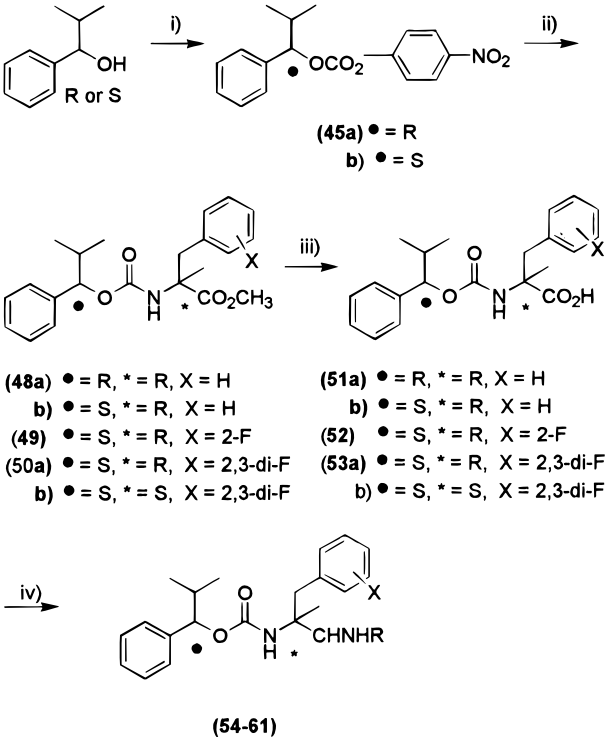
[a] (i) (a) EtOCOCl, NMM, THF, 0 °C, 1 h, (b) $LiBH_4$, THF, 3 h (96%); (ii) (a) TFA, DCM, 1 h, (b) Boc(*S*)Phe(*R*)αMePheOH, DCCI, HOBt, DMF, 15 h (67%); (iii) *p*-toluenesulfonyl chloride, NEt_3, DCM, DMAP, 15 h; (iv) NaN_3, DMF, 60 °C, 3 h (69%); (v) Lindlar catalyst, EtOH, H_2, 40 psi, 30 °C, 6 h (76%); (vi) methanesulfonyl chloride, pyridine, DCM, 15 h (21%).

Scheme 5. Synthesis of **41**[a]



[a] (i) Trimethylsilyl isocyanate, THF, 2 h (90%); (ii) Boc(*S*)-Phe(*R*)αMePheOH, HBTU, DIPEA, DMF, 2 h (47%).

Scheme 6. Synthesis of **54**−**61**[a]



[a] (i) *p*-Nitrophenyl chloroformate, pyridine, DCM, 24 h (92%); (ii) (*R*)-αMePheOCH$_3$, **46** or **47**, DMF, 3 days (26−78%); (iii) LiOH, THF/H_2O, 48 h (86−93%); (iv) RNH_2, HBTU, DIPEA, DMF, 2−18 h (29−70%).

(**1d**, IC_{50} = 1520 nM) did however display similar binding affinity to that of the parent compound. This compound was selected as the new lead on the basis that the α-methyl may impart some *in vivo* stability.[24]

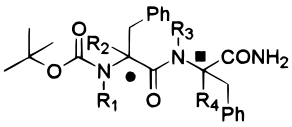
The next step in our strategy is the optimization of the N- and C-terminal groups. In order to identify suitable binding moieties for N- and C-terminal modifications of Boc(*S*)Phe(*RS*)αMePheNH$_2$ (**1d**), we considered the hypothesis that the PhePhe sequence in our ligand mimics the binding characteristics of the same sequence in [(4-hydroxyphenyl)acetyl]PhePheGlyLeuMetNH$_2$ (**7**),[25] NKB, and senktide (Figure 1). If this hypothesis is valid, it should be possible to increase the binding affinity of the dipeptide **1d** by appending binding groups and/or side chain moieties from these peptides.

Table 1. Micromolar Hits Identified from Screening the Dipeptide Library against the Human NK_3 Receptor

compd no.	structure	IC_{50}, nM[a]
1	Boc(*S*)Phe(*S*)PheNH$_2$	1550
2	Boc(*S*)Trp(*S*)PheNH$_2$	2080
3	Boc(*S*)Phe(*S*)TrpNH$_2$	9610
4	Boc(*S*)Phe(*S*)TyrNH$_2$	8620
5	$(CH_3)_2CH(CH_2)_2$COTrpTrpNH$_2$	1760
6	$(CH_3)_2CH(CH_2)_2$COPheTrpNH$_2$	3270

[a] IC_{50} is the concentration (nM) producing half-maximal inhibition of the specific binding of [^{125}I][MePhe^7]NKB to NK_3 binding sites in cloned NK_3 receptors stably expressed in CHO cells. Values shown represent the geometric mean of three to six experiments.[23]

Table 2. Methylation of the Dipeptide Lead Boc(*S*)Phe(*S*)PheNH$_2$



compd no.	R^1	R^2	R^3	R^4	●	■	IC_{50}, nM[a]
1	H	H	H	H	*S*	*S*	1550
1a	CH_3	H	H	H	*RS*	*S*	>10 000
1b	H	CH_3	H	H	*RS*	*S*	>10 000
1c	H	H	CH_3	H	*S*	*RS*	>10 000
1d	H	H	H	CH_3	*S*	*RS*	1520
1e	CH_3	H	H	H	*RS*	*R*	>10 000
1f	H	CH_3	H	H	*RS*	*R*	>10 000
1g	H	H	CH_3	H	*R*	*RS*	>10 000
1h	H	H	H	CH_3	*R*	*RS*	>10 000
1i	H	H	H	CH_3	*S*	*S*	1490
1j	H	H	H	CH_3	*S*	*R*	1830

[a] See footnote a, Table 1.

1d	Boc(S)**Phe(RS)αMePhe**NH$_2$
7	4-hydroxy-phenylacetyl**PhePhe**GlyLeuMetNH$_2$
NKB	AspMetHisAsp**PhePhe**ValGlyLeuMetNH$_2$
Senktide	SuccAsp**PheNMePhe**GlyLeuMetNH$_2$

Figure 1. Structure of **1d**, **7**, neurokinin B, and senktide.

The smallest of these peptides (**7**), *i.e.*, the compound containing the smaller number of residues, was chosen as a template. The affinity of this pentapeptide derivative for the NK_3 receptor (IC_{50} = 112 nM[23]) has been attributed to a specific binding interaction of the N-terminal (4-hydroxyphenyl)acetyl group, as the pentapeptide itself has been shown to have significantly lower affinity (IC_{50} = 10 000 nM). This moiety was therefore appended to the N- and C-termini of the dipeptide **1d** (Table 3).

Appending the (4-hydroxyphenyl)acetyl moiety to the N-terminal of **1d** led to a significant drop in NK_3 receptor binding affinity (**8**, IC_{50} = 5890 nM). In contrast appending this group at the C-terminal re-

Table 3. NK_3 Receptor Binding Affinities

compd no.	structure	IC_{50}, nM[a]
1d	Boc(*S*)Phe(*RS*)αMePheNH$_2$	1520
8[b]	Ph(4-OH)CH$_2$CO(*S*)Phe(*RS*)αMePheNH$_2$	5890
17	Boc(*S*)Phe(*RS*)αMePheNHCH$_2$Ph(4-OH)	425
18	Boc(*S*)Phe(*R*)αMePheNH(CH$_2$)$_4$Ph(4-OH)	39
19	Boc(*S*)Phe(*RS*)αMePheNHCH$_2$Ph	1080
20	Boc(*S*)Phe(*RS*)αMePheNH(CH$_2$)$_4$Ph	162
21	Boc(*S*)Phe(*RS*)αMePheNH(CH$_2$)$_7$OH	111
22	Boc(*S*)Phe(*RS*)αMePheNH(CH$_2$)$_8$OH	92
23	Boc(*S*)Phe(*RS*)αMePheNH(CH$_2$)$_9$OH	106
24	Boc(*S*)Phe(*S*)αMePheNH(CH$_2$)$_8$OH	1690
25[b]	Boc(*S*)Phe(*R*)αMePheNH(CH$_2$)$_8$OH	40
26	Boc(*S*)Phe(*RS*)αMePheNH(CH$_2$)$_8$CH$_3$	439
27[b]	Boc(*S*)Phe(*RS*)αMePheNH(CH$_2$)$_7$CO$_2$H	229
28[b]	Boc(*S*)Phe(*RS*)αMePheNH(CH$_2$)$_8$OMe	101

[a] See footnote a, Table 1. [b] Synthesis as described in ref 22.

sulted in an *ca.* 3-fold increase in NK_3 receptor binding affinity (**17**, IC_{50} = 425 nM). Increasing the methylene chain length in compounds of this nature led to an improvement in binding affinity, with four methylenes being optimal (**18**, IC_{50} = 39 nM). As the replacement of the phenol moiety with a phenyl group in both cases (**19** and **20**) led to a decrease in affinity, the hydroxyl moiety was considered to be important in the binding interaction of these ligands. A series of alkyl alcohols with varying chain lengths were therefore prepared. The optimum chain length for these compounds was identified in **22**, the 8-amino-1-octanol derivative which has an IC_{50} of 92 nM; the shorter 7-amino-1-heptanol (**21**) and the longer 9-amino-1-nonanol (**23**) derivatives have slightly lower affinities (111 and 106 nM, respectively).

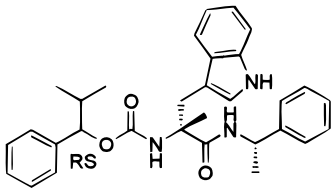
The compounds so far described with the exception of **18** are all equal mixtures of two diastereoisomers having a racemic center at the αMePhe residue. The individual stereoisomers of **22** were prepared to determine the stereochemical preference of these ligands with respect to NK_3 receptor affinity. The preferred stereochemistry was found to be *S*,*R* at the two centers, respectively. The dipeptide with this stereochemistry (**25**) has an IC_{50} of 40 nM in comparison to the equivalent *S*,*S*-isomer **24** which has an IC_{50} of 1690 nM (Table 3).

The hydroxyl moiety in the amino alcohol series is strongly implicated in participating in the binding interaction with the NK_3 receptor as the alkyl derivative **26** shows much reduced binding affinity (IC_{50} = 439 nM; *cf.* **22**, IC_{50} = 92 nM; Table 3). In order to optimize the binding interaction of the hydroxyl group, the nature of this interaction was investigated with the preparation of the corresponding hydrogen bond-accepting methyl ether and hydrogen bond-donating carboxylic acid derivatives (Table 3). The methyl ether **28** was found to have a similar binding affinity (IC_{50} = 101 nM) to the alcohol **22**, while the carboxylic acid analogue **27** binds with a lower affinity (IC_{50} = 229 nM). These observations led to the postulation that the hydroxyl group is interacting as a hydrogen bond acceptor in these ligands. A series of derivatives were therefore prepared in which the hydroxyl function is replaced with selected hydrogen bond-accepting groups.[26] A number of such compounds which bind to the human NK_3 receptor with IC_{50} values in the 20−30 nM range were identified. Among these compounds, the urea derivative **41**, Boc-(*S*)Phe(*R*)αMePheNH(CH$_2$)$_7$NHCONH$_2$, displays the highest binding affinity (IC_{50} = 16 nM).

Table 4. NK_3 Receptor Binding Affinities

compd no.	structure	IC_{50}, nM[a]
25[b]	Boc(*S*)Phe(*R*)αMePheNH(CH$_2$)$_8$OH	40
29	Boc(*S*)Phe(*RS*)PheNH(CH$_2$)$_8$OH	4310
30[b]	Boc(*S*)Phe(*R*)αMePheNH(CH$_2$)$_8$CONH$_2$	39
31[b]	Boc(*S*)Phe(*R*)αMePheNH(CH$_2$)$_8$CONHCH$_3$	18
32	Boc(*S*)Phe(*R*)αMePheNH(CH$_2$)$_8$CON(CH$_3$)$_2$	28
33[b]	Boc(*S*)Phe(*R*)αMePheNH(CH$_2$)$_8$SO$_2$Me	28
39	Boc(*S*)Phe(*R*)αMePheNH(CH$_2$)$_7$NHSO$_2$Me	31
41	Boc(*S*)Phe(*R*)αMePheNH(CH$_2$)$_7$NHCONH$_2$	16
42[b]	Boc(*S*)Phe(*R*)αMePheNH(CH$_2$)$_2$Ph(4-OCH$_2$CONH$_2$)	67
43	Boc(*S*)Phe(*R*)αMePheNH(CH$_2$)$_2$Ph(2-OCH$_2$CONH$_2$)	119

[a] See footnote a, Table 1. [b] Synthesis as described in ref 22.



(44)

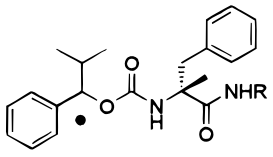
Figure 2. Structure of [2-(1*H*-indol-3-yl)-1-methyl-1-[(1-phenylethyl)carbamoyl]ethyl]carbamic acid 2-methyl-1-phenylpropyl ester (**44**).

In order to reduce the chain flexibility of these poly(methylene) compounds, we prepared analogues in which a phenyl ring was introduced within the alkyl chain. Although the analogues prepared showed no improvement in binding affinity, a preference for the *para* substitution (**42**) over the *ortho* substitution (**43**) was observed. This result suggests that the C-terminal segment may bind in an extended conformation (Table 4).

The contribution to receptor binding affinity of the α-methylation at the C-terminal phenylalanine residue was re-examined by the preparation of the non-α-methyl compound **29**. The binding affinity of this ligand is 4310 nM, which compares to 92 nM for the α-methylated analogue **22**. In these compounds where the C-terminal group plays a major role in the binding affinity of the ligand, the presence of the α-methyl group is crucial, presumably in restricting the number of conformations available to these ligands.[27]

Having optimized the C-terminal portion of our dipeptide lead, our next objective as outlined in our 'peptoid' design strategy was to examine the N-terminal portion of our compounds. A key consideration was to convert these modified dipeptides into non-peptide derivatives, and to this end the replacement of the N-terminal Boc(*S*)Phe moiety was investigated. An interesting lead in this area came in the form of **44** (Figure 2) which was prepared as part of our NK_1 receptor program. In addition to having the targeted NK_1 receptor affinity (IC_{50} = 1400 nM), this monoamino acid derivative was noted to also have micromolar affinity for the NK_3 receptor (IC_{50} = 1200 nM). The possible relationship between this monoamino acid derivative and our modified dipeptides was investigated by the substitution of the (*R*)αMeTrp residue in **44** by the (*R*)αMePhe residue found in the dipeptide ligands (Table 5). In order to determine which stereochemistry is required at the N-terminal [(isopropylbenzyl)oxy]-carbonyl moiety for NK_3 receptor affinity, both stereoisomers at this center were prepared. The compound

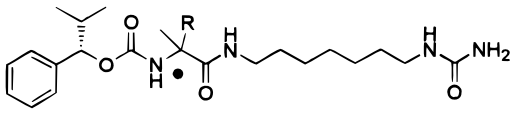
Table 5. NK_3 Receptor Binding Affinities



compd no.	●	R	IC_{50}, nM[a]
54	*R*	-(*S*)CH(CH_3)Ph	74
55	*S*	-(*S*)CH(CH_3)Ph	>10 000
56	*R*	-$(CH_2)_8$OH	350
57	*S*	-$(CH_2)_8$OH	52
58	*S*	-$(CH_2)_7$NHCONH$_2$	57

[a] See footnote a, Table 1.

Table 6. NK_3 Receptor Binding Affinities



compd no.	●	R	IC_{50}, nM[a]
58	*R*	-CH_2Ph	57
59	*R*	-CH_2Ph(2-F)	16
60	*R*	-CH_2Ph(2,3-diF)	7
61	*S*	-CH_2Ph(2,3-diF)	1400

[a] See footnote a, Table 1.

with the *R* stereochemistry at the [(isopropylbenzyl)-oxy]carbonyl moiety (**54**) is clearly preferred, having an IC_{50} value of 74 nM, in comparison to the *S*-isomer **55**, which has an IC_{50} value of >10 000 nM. Encouraged by this increase in NK_3 receptor affinity with compound **54**, we went on to append the C-terminal groups identified as optimum in our modified dipeptides. Appending the 8-amino-1-octanol moiety found in **25** results in a marginal increase in NK_3 receptor affinity (**57**, IC_{50} = 52 nM). The observed binding affinity of **57** is very similar to that of **25** (IC_{50} = 40 nM), suggesting that the (*S*)-[(isopropylbenzyl)oxy]carbonyl group is a good replacement for the N-terminal Boc(*S*)-Phe moiety in the dipeptide ligands. Interestingly, when the C-terminal α-methylbenzylamine is replaced by the 8-amino-1-octanol group, a switch in the preferred stereochemistry at the N-terminal for optimal NK_3 receptor binding affinity is observed. In these compounds the *S*,*R* isomer has highest affinity for the NK_3 receptor. The replacement of the 8-amino-1-octanol group with the (7-aminoheptyl)urea group found in **41** results in no further increase in NK_3 receptor affinity (**58**, IC_{50} = 57 nM).

The final stage in our peptoid design strategy is the optimization of the amino acid side chains. The central αMePhe phenyl ring structure−activity relationship (SAR) was investigated using a Topliss[28] type approach. This lead to the identification of a 2-chlorinated compound with a 2-fold increase in NK_3 receptor affinity. The 2-position was further investigated by the preparation of a number of halogen and alkyl 2-substituted αMePhe derivatives. Substitution in this position with fluorine increases NK_3 receptor affinity just over 3-fold (**59**, IC_{50} = 16 nM); see Table 6. Affinity is further increased in the 2,3-difluoro analogue **60** (IC_{50} = 7 nM). The stereochemistry at the two chiral centers was confirmed as *S*,*R* from an X-ray crystallographic structure of compound **50a**.

Both the modified dipeptide ligands, *e.g.*, **25** and **41**, and the non-peptide ligands **59** and **60** show good selectivity for the NK_3 receptor over NK_1 and NK_2 receptors in human and hamster preparations, respectively (Table 7). It is interesting to note that while the dipeptide ligands **25** and **41** have low affinity for the rat NK_3 receptor (IC_{50} = 2790 and 1730 nM, respectively), the non-peptide ligands **59** and **60** have appreciable affinity for the rat NK_3 receptor (IC_{50} = 83 and 30 nM, respectively).

Table 7. Tachykinin Receptor Selectivity

compd no.	binding affinities (IC_{50}, nM)				
	NK_1[a](IM9)	NK_2[b](HUB)	NK_3[c] (GP)	NK_3[d] (CHO)	NK_3[e](rat)
NKB	98	3.6	2	9.7	
senktide	>10 000		12	22	11
25	>10 000	6160 (3840−9990)	22 (12−51)	40 (26−61)	2790 (2000−3700)
41	>10 000	6540 (4100−9700)	9 (5−13)	16 (8−24)	1730 (1100−2200)
59	2200 (750−3700)	1500 (1300−1700)	14 (8−18)	16 (14−20)	83 (44−156)
60	3000 (2900−3100)	790 (480−1100)	4 (1−6)	7 (6−9)	30 (13−78)

[a] Values shown represent the geometric mean of three separate experiments carried out using [^{125}I]Bolton-Hunter substance P to label NK_1 binding sites in human lymphoma IM9 cells.[18] [b] Values shown represent the geometric mean of three separate experiments carried out using [^{125}I]NKA to label NK_2 binding sites in membranes prepared from hamster urinary bladder.[19] [c] Values shown represent the geometric mean of three to six separate experiments carried out using [^{125}I][MePhe^7]NKB to label NK_3 binding sites in guinea pig cortical membranes.[23] [d] See footnote a, Table 1. [e] Values shown represent the geometric mean of three to six separate experiments carried out using [^{125}I][MePhe^7]NKB to label NK_3 binding sites in rat cortical membranes.[23]

Table 8. *In Vitro* Functional Data

compd no.	*in vitro* functional assays (K_e, nM)			
	CHO[a] cells	GP[b] ileum	GP[c] hab	rat hab[d]
25	29 (25−35)	14 (8−40)	54 (34−108)	
41	7 (2−22)	42 (26−130)	16 (12−21)	
59	2 (2−11)		13 (5−21)	
60	0.9 (0.5−1.5)		6 (4−7)	19 (10−34)

[a] Inhibition of senktide-evoked increases in intracellular calcium levels in cloned human NK_3 receptors stably expressed in CHO cells measured using the fluorescent indicator Fura2.[29] Equilibrium constants shown represent the mean of at least three separate experiments. [b] Isomeric contractions were recorded from longitudinal muscle myenteric plexus preparations with responses to the NK_3 receptor selective agonist senktide.[30] Data represent the geometric means of individual values in at least three separate experiments. [c] Inhibition of senktide-induced increases in spontaneous firing of guinea pig habenula neurons *in vitro*.[31] Values are the mean of at least three separate experiments. [d] Inhibition of senktide-induced increases in spontaneous firing of rat habenula neurons *in vitro*.[31] Values are the mean of at least three separate experiments.

Selected ligands were tested in human and guinea pig *in vitro* functional assays. The ability of these ligands to inhibit senktide-evoked increases in intracellular calcium levels in cloned human NK_3 receptors stably expressed in CHO cells and senktide-induced increases in spontaneous firing of guinea pig habenula neurons *in vitro* was examined (Table 8). These functional assays show potent and competitive NK_3 receptor selective antagonism with these compounds. The non-peptide **60** has K_e values of 0.9 and 6 nM in these two assays, respectively. As **60** had been shown to have moderate affinity for the rat NK_3 receptor, its ability to inhibit the senktide-induced increase in the spontaneous firing of rat medial habenula neurons *in vitro* was investigated. The K_e for antagonism of senktide by **60**

in this assay is 19 nM, only some 3-fold lower than that seen in the guinea pig habenula.

Conclusion

In this paper we have described the development of a novel series of high-affinity non-peptide NK_3 receptor selective antagonists. The initial lead compound in this program was identified from the screening of a dipeptide chemical library through a human NK_3 receptor binding assay. Optimization of the C-terminal portion of this dipeptide lead resulted in the identification of a series of modified dipeptides. These compounds bind selectively to the human NK_3 receptor with comparable binding affinity to the peptide ligands neurokinin B and senktide. The C-terminal urea derivative **41** has the highest affinity for the NK_3 receptor in this series of compounds (IC_{50} = 16 nM).

These modified dipeptide ligands were then further developed following our 'peptoid' design strategy (Scheme 1). Modification of the N-terminal portion and substitution of the αMePhe residue side chain led to the identification of **60**, a true non-peptide NK_3 receptor selective antagonist. **60** has an affinity of 7 nM for the human NK_3 receptor and has been shown to be a competitive antagonist in human, guinea pig, and rat functional assays with K_e values of 0.9, 6, and 19 nM, respectively.

To our knowledge this is the first published example in which an initial hit obtained from the screening of a synthetic peptide chemical library has been developed into a high-affinity non-peptide ligand for a membrane-bound receptor. With these non-peptide NK_3 receptor antagonists now in hand, we can begin to determine whether such ligands will be of therapeutic value in such areas as analgesia,[32] schizophrenia,[17] and Parkinson's disease.[33]

Experimental Section

Melting points were determined with a Mettler FP80 or a Reichert Thermovar hot-stage apparatus. Proton NMR were recorded on a Bruker AM300 or a Varian Unity +400 spectrometer; chemical shifts are recorded in ppm downfield from tetramethylsilane. IR spectra were recorded with the compound neat on a sodium chloride disk on a Perkin-Elmer System 2000 Fourier transform spectrophotometer. Optical rotations were determined with a Perkin-Elmer 241 polarimeter. Mass spectra were recorded with a Finnigan MAT TSQ70 or Fisons VG Trio-2A instrument. Elemental analyses are within ±0.4% of theoretical values and were determined by Medac Ltd., Uxbridge, U.K. Normal Phase silica gel used for chromatography was Merck no. 9385 (230−400 mesh), and reverse phase silica gel used was Lichroprep RP-18 (230−400 mesh); both were supplied by E. Merck, A.G., Darmstadt, Germany. Anhydrous solvents were purchased in septum-capped bottles from Fluka Chemicals Ltd., Glossop, U.K.

[1-[(1-Carbamoyl-2-phenylethyl)carbamoyl]-2-phenylethyl]methylcarbamic Acid *tert*-Butyl Ester (1a). Boc-(*RS*)NMePheOH (150 mg, 0.54 mmol) was dissolved in DMF (5 mL), and DCCI (111 mg, 0.54 mmol) and HOBt (83 mg, 0.54 mmol) were added. The reaction mixture was stirred for 4 h, after which H-PheNH_2 (90 mg, 0.55 mmol) was added and stirring was continued for a further 12 h. The solvent was removed *in vacuo*, and the residue was redissolved in EtOAc (100 mL) and washed with aqueous $NaHCO_3$ (3 × 50 mL), 1 M HCl (3 × 50 mL), and water (3 × 50 mL). The organic layer was separated, dried over $MgSO_4$, and evaporated. The residue was purified by reverse phase column chromatography to afford a white solid: mp 55−60 °C; 125 mg (54%); $[\alpha]^{20}_D$ = −22.2° (*c* = 0.5, MeOH); ^{1}H-NMR (DMSO-d_6, 340 K) δ 1.26 (s, 9H), 2.46, 2.62 (2 × s, 3H), 2.65−2.95 (m, 2H), 3.00, 3.10 (m, 2H), 4.50−4.60 (m, 1H), 4.65−4.85, (m, 1H), 6.90−7.00 (m, 1H), 7.10−7.25 (m, 10H), 7.40−7.50 (m, 1H); IR (film) 3331, 2978, 1665 cm^{-1}; MS *m/e* (CI) 426 (M + H) (5), 326 (100). Anal. ($C_{24}H_{31}N_3O_4$·0.1H_2O) C, H, N.

[1-[(1-Carbamoyl-2-phenylethyl)carbamoyl]-1-methyl-2-phenylethyl]carbamic Acid *tert*-Butyl Ester (1b). Boc-(*RS*)αMePheOH (213 mg, 0.76 mmol) was dissolved in DMF (10 mL), and DCCI (157 mg, 0.76 mmol) and pentafluorophenol (140 mg, 0.76 mmol) were added. The reaction mixture was stirred for 2 h, after which the precipitate was removed by filtration. The H-PheNH_2 (138 mg, 0.84 mmol) in EtOAc (10 mL) was added, and the reaction mixture was stirred for 3 days. The solvent was removed *in vacuo*, and the residue was redissolved in EtOAc (25 mL) and washed with aqueous $NaHCO_3$ (3 × 10 mL), 1 M HCl (2 × 10 mL), and water (3 × 10 mL). The organic layer was separated, dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography, 50% EtOAc/hexane, to afford a white solid: mp 80−85 °C; 127 mg (39%); $[\alpha]^{21}_D$ = −40.4° (*c* = 0.5, MeOH); ^{1}H-NMR (DMSO-d_6) δ 0.93, 1.08 (2 × s, 3H), 1.38, 1.41 (2 × s, 9H), 2.83−3.25 (m, 4H), 4.30−4.53 (m, 1H), 6.74−6.95 (m, 3H), 7.14−7.26 (m, 10H), 7.79−7.89 (m, 1H); IR (film) 3400−3200, 1675, 1608, 1520, 1369 cm^{-1}. Anal. ($C_{24}H_{31}N_3O_4$·0.3H_2O), C, H, N.

[1-[(1-Carbamoyl-2-phenylethyl)methylcarbamoyl]-2-phenylethyl]carbamic Acid *tert*-Butyl Ester (1c). Boc-(*S*)PheOH (124 mg, 0.47 mmol) was dissolved in DMF (5 mL), and HBTU (177 mg, 0.47 mmol) and DIPEA (362 mg, 2.79 mmol) were added. The reaction mixture was stirred for 10 min, and TFA·H-(*S*)-NMePheNH_2 (150 mg, 0.51 mmol) was added. The reaction mixture was stirred for 30 min, and the solvent was then removed *in vacuo* and the residue redissolved in EtOAc (25 mL) and washed with aqueous $NaHCO_3$ (3 × 10 mL), 1 M HCl (2 × 10 mL), and water (3 × 10 mL). The organic layer was separated, dried over $MgSO_4$, and evaporated. The residue was purified by reverse phase column chromatography, 65−95% MeOH in water, to afford a white solid: mp 113−117 °C; 42 mg (21%); $[\alpha]^{20}_D$ = −29.0° (*c* = 0.5, MeOH); ^{1}H-NMR (DMSO-d_6) δ 1.27−1.30 (m, 9H), 2.19−2.44 (m, 1H), 2.69−3.02 (m, 4H), 3.14−3.34 (m, 1H), 4.20−4.50 (m, 1H), 4.81−4.99, 5.20−5.29 (m, 1H), 6.83−7.36 (m, 13H); IR (film) 3412, 3079, 1690, 1680, 1641, 1632, 1496 cm^{-1}. Anal. ($C_{24}H_{31}N_3O_4$·1.5H_2O) C, H; N: calcd, 9.29; found, 8.84.

[1-[(1-Carbamoyl-1-methyl-2-phenylethyl)carbamoyl]-2-phenylethyl]carbamic Acid *tert*-Butyl Ester (1d). The compound was prepared by the method described for **1c** in 47% yield: mp 141−143 °C; $[\alpha]^{21}_D$ = −32.0° (*c* = 0.5, MeOH); ^{1}H-NMR (DMSO-d_6) δ 1.30 (s, 9H), 1.42 (s, 3H), 2.73−3.39 (m, 4H), 4.03−4.18 (m, 1H), 7.08−7.26, (m, 13H), 7.57 (s, 1H); IR (film) 3300−3200, 1676, 1497 cm^{-1}. Anal. ($C_{24}H_{31}N_3O_4$·0.1H_2O) C, H, N.

[1-[(1-Carbamoyl-2-phenylethyl)carbamoyl]-2-phenylethyl]methylcarbamic Acid *tert*-Butyl Ester (1e). The compound was prepared by the method described for **1b** in 35% yield: mp 98−106 °C; ^{1}H-NMR (DMSO-d_6, 340 K) δ 1.19 (s, 9H), 2.41 (d, *J* = 14.2 Hz, 1H), 2.60−3.08 (m, 6H), 4.40−4.58 (m, 1H), 4.60−4.91 (m, 1H), 7.12−7.50 (m, 12H), 7.72−7.98 (m, 1H); IR (film) 3300−3000, 2930, 1667, 1516 cm^{-1}. Anal. ($C_{24}H_{31}N_3O_4$·0.6H_2O) C, H, N.

[1-[(1-Carbamoyl-2-phenylethyl)carbamoyl]-1-methyl-2-phenylethyl]carbamic Acid *tert*-Butyl Ester (1f). The compound was prepared by the method described for **1b** in 49% yield: mp 60−62 °C; $[\alpha]^{21}_D$ = +49.3° (*c* = 0.5, MeOH); ^{1}H-NMR (DMSO-d_6) δ 0.93, 1.08 (2 × s, 3H), 1.40 (s, 9H), 2.82−3.25 (m, 4H), 4.30−4.53 (m, 1H), 6.74−6.95 (m, 3H), 7.14−7.28 (m, 10H), 7.78−7.85 (m, 1H); IR (film) 3307, 2981, 1671, 1496 cm^{-1}. Anal. ($C_{24}H_{31}N_3O_4$·0.3H_2O) C, H, N.

[1-[(1-Carbamoyl-2-phenylethyl)carbamoyl]-2-phenylethyl]carbamic Acid *tert*-Butyl Ester (1g). The compound was prepared by the method described for **1c** in 33% yield: mp 47−50 °C; ^{1}H-NMR (DMSO-d_6) δ 1.10−1.37 (m, 9H), 2.19−2.42 (m, 1H), 2.59−3.04 (m, 5H), 3.13−3.40 (m, 1H), 4.20−4.70 (m, 1H), 4.82−5.28 (m, 1H), 6.88−7.39 (m, 13H); IR (film) 3308, 3196, 1680, 1640, 1496 cm^{-1}. Anal. ($C_{24}H_{31}N_3O_4$·0.25H_2O) C, H, N.

[1-[(1-Carbamoyl-1-methyl-2-phenylethyl)carbamoyl]-2-phenylethyl]carbamic Acid *tert*-Butyl Ester (1h). The compound was prepared by the method described for **1c** in 41% yield: mp 138−143 °C; $[\alpha]^{21}_D = +52.7°$ ($c = 0.5$, MeOH); ^{1}H-NMR (DMSO-d_6) δ 1.29 (s, 9H), 1.37 (s, 3H), 2.67−2.78 (m, 1H), 2.93−3.08 (m, 1H), 3.18−3.37 (m, 1H), 3.98−4.18 (m, 1H), 7.07 (d, $J = 5.9$ Hz, 1H), 7.17−7.28, (m, 12H), 7.74 (s, 1H); IR (film) 3306, 2980, 1664, 1498 cm^{-1}. Anal. ($C_{24}H_{31}N_3O_4 \cdot 0.5H_2O$) C, H, N.

[*S*-(*R,*R**)]-[1-[(1-Carbamoyl-1-methyl-2-phenylethyl)-carbamoyl]-2-phenylethyl]carbamic Acid *tert*-Butyl Ester (1i).** The compound was prepared by the method described for **1c** in 64% yield: mp 160−162 °C; $[\alpha]^{21}_D = +60.0°$ ($c = 0.5$, MeOH); ^{1}H-NMR (DMSO-d_6) δ 1.27 (s, 9H), 1.20 (s, 3H), 2.73−2.96 (m, 2H), 3.23−3.37 (m, 2H), 3.98 (m, 1H), 7.07 (d, $J = 6.2$ Hz, 2H), 7.19−7.28 (m, 11H), 7.77 (s, 1H); IR (film) 3306, 2980, 1665, 1498 cm^{-1}. Anal. ($C_{24}H_{31}N_3O_4$) C, H, N.

[*R*-(*R,*S**)]-[1-[(1-Carbamoyl-1-methyl-2-phenylethyl)-carbamoyl]-2-phenylethyl]carbamic Acid *tert*-Butyl Ester (1j).** The compound was prepared by the method described for **1c** in 58% yield: mp 191−195 °C; $[\alpha]^{21}_D = +4.0°$ ($c = 0.5$, MeOH); ^{1}H-NMR (DMSO-d_6) δ 1.16, 1.28 (2 × s, 9H), 1.36, 1.50 (2 × s, 3H), 2.58−2.79 (m, 1H), 3.13−3.35 (m, 3H), 4.08−4.17 (m, 1H), 7.08−7.26 (m, 13H), 7.73 (s, 1H); IR (film) 3172, 1674, 1655, 1541 cm^{-1}. Anal. ($C_{24}H_{31}N_3O_4$) C, H, N.

4-(4-Methoxyphenyl)butyric Acid (9). 4-(4-Methoxyphenyl)-4-oxobutyric acid[34] (3.46 g, 16.6 mmol), hydrazine monohydrate (1.61 mL, 33 mmol), and KOH pellets (3.77 g, 66 mmol) were heated under reflux in diethylene glycol (20 mL) for 1.5 h. The temperature was increased to 180 °C for 2 h, during which time the hydrazine and water distilled over. On cooling additional hydrazine (1.61 mL) was added, and the process was repeated; 10% citric acid solution (130 mL) was added, and the mixture was extracted with ether (3 × 200 mL). The organic layer was washed with water and dried over $MgSO_4$, the solvent was evaporated, and the residue was purified by column chromatography, ether/hexane (2:3), to give a white solid: 2.30 g (71%); ^{1}H-NMR ($CDCl_3$) δ 1.93 (q, 2H), 2.35 (t, 2H), 2.61 (t, 2H), 3.78 (s, 3H), 6.82 (d, 2H), 7.08 (d, 2H); IR (film) 2936, 1707 cm^{-1}. MS *m*/*e* (CI) 194 (M), 177 (100).

4-(4-Hydroxyphenyl)butyric Acid (10). 9 (1.0 g, 5 mmol) was dissolved in 48% HBr (50 mL) and glacial acetic acid (80 mL), and the solution was heated under reflux for 6 h. The solution was poured onto ice (300 mL) and stirred for a further 12 h. The mixture was extracted with ether (3 × 300 mL), and the combined extracts were washed with water (3 × 200 mL). The organic layer was dried over $MgSO_4$, and the solvent was evaporated to given an oil which was purified by reverse phase chromatography, 10−80% methanol/water. A white solid was obtained: 0.82 g (91%); ^{1}H-NMR ($CDCl_3$) δ 1.77 (q, 2H), 2.16 (t, 2H), 2.45 (t, 2H), 6.63 (d, 2H), 6.86 (d, 2H), 8.16 (s, 1H); MS *m*/*e* (CI) 181 (M + H), 163 (100).

4-(4-Hydroxyphenyl)butyramide (11). 4-(4-Hydroxyphenyl)butyric acid **10** (0.80 g, 4.4 mmol), DCCI (0.92 g, 4.4 mmol), and pentafluorophenyl (0.82 g, 4.4 mmol) were dissolved in EtOAc (80 mL), and the solution was stirred for 4 h. The precipitate was removed by filtration, and the filtrate was concentrated *in vacuo*. The residue was dissolved in DCM (60 mL), and ammonia gas was bubbled through the solution for 1 h. Stirring was continued for a further 12 h, and the solvent was then evaporated. The residue was purified by column chromatography, 6% MeOH/DCM, to give a white solid: 0.70 g (82%); ^{1}H-NMR (DMSO-d_6) δ 1.66 (m, 2H), 1.98 (t, 2H), 2.39 (t, 2H), 6.20 (m, 3H), 6.91 (d, 2H), 7.17 (s, 1H), 9.05 (s, 1H); IR (film) 3357, 3183, 1676, 1608 cm^{-1}.

4-(4-Aminobutyl)phenol (12). BSM (2 M) in THF (3.23 mL, 6.5 mmol) was added dropwise to a solution of **11** (0.50 g, 2.8 mmol) in THF (25 mL) under N_2. The reaction mixture was heated under reflux for 6 h and then cooled to room temperature. MeOH (3 mL) was added, and the solution was stirred overnight. Dry HCl gas was bubbled through the solution for 20 min, and the solution was then reheated under reflux for 1 h. The solvent was removed *in vacuo*, and the residue was dissolved in EtOAc (100 mL) and washed with 2 M HCl (2 × 60 mL). The pH of the aqueous phase was adjusted to 10 with solid Na_2CO_3, and the mixture was then extracted with EtOAc (3 × 100 mL). The organic layer was dried, and the solvent was evaporated to give a solid: 105 mg (23%); ^{1}H-NMR (DMSO-d_6) δ 1.28 (m, 2H), 1.46 (t, 2H), 2.39 (t, 2H), 3.50 (m, 2H), 6.60 (d, 2H), 6.90 (d, 1H); IR (film) 3313, 2924, 1576, 1462 cm^{-1}.

2-[2-(2-Hydroxyethyl)phenoxy]acetamide (13). Potassium carbonate (1.20 g, 8.7 mmol) was added to a solution of 2-(2-hydroxyethyl)phenol (1.20 g, 8.7 mmol) and 2-bromoacetamide (1.32 g, 8.7 mmol) in 2-butanone (25 mL). The suspension was heated under reflux for 4 h and stirred at room temperature for 15 h. The solid was removed by filtration, and the filtrate was concentrated *in vacuo*. Purification by column chromatography, 5% MeOH/EtOAc, gave a white solid: 1.50 g (88%); ^{1}H-NMR (DMSO-d_6) δ 2.75 (t, 2H), 3.55 (m, 2H), 4.38 (s, 2H), 4.57 (m, 1H), 6.75−7.15 (m, 4H), 7.30 (br s, 1H), 7.37 (br s, 1H); IR (film) 3377, 1682, 1590, 1040 cm^{-1}.

Toluene-4-sulfonic Acid 2-[2-(Carbamoylmethoxy)-phenyl]ethyl ester (14). *p*-Toluenesulfonyl chloride (1.77 g, 9.3 mmol) in DCM (25 mL) was added dropwise over 2 h to a solution of the alcohol **13** (1.45 g, 7.4 mmol) and DMAP (1.13 g, 9.3 mmol) in DCM (75 mL) at 0 °C. The reaction mixture was stirred at room temperature for 16 h and then washed with 10% citric acid (2 × 50 mL) and water (50 mL). The organic layer was dried over $MgSO_4$, and the solvent was removed *in vacuo* to give a residue which was purified by column chromatography, 60% EtOAc/hexane, to give an oil: 2.10 g (81%); ^{1}H-NMR (DMSO-d_6) δ 2.36 (s, 3H), 2.91 (t, 2H), 4.18 (t, 2H), 4.29 (s, 2H), 6.72−7.62 (m, 10H); IR (film) 3330, 2916, 1684, 1585, 1357, 1175 cm^{-1}.

2-[2-(2-Azidoethyl)phenoxy]acetamide (15). 14 (2.05 g, 5.9 mmol) and NaN_3 (0.42 g, 6.5 mmol) were dissolved in DMF (20 mL), and the reaction mixture was heated to 75 °C for 2 h. The solution was cooled to room temperature and poured onto ice (120 mL). The aqueous phase was then extracted with ether (3 × 100 mL) and dried over $MgSo_4$, and the solvent was removed *in vacuo* to give a white solid which was used without purification: 0.99 g (77%); ^{1}H-NMR (DMSO-d_6) δ 2.88 (t, 2H), 3.50 (t, 2H), 4.42 (s, 2H), 6.80−7.40 (m, 6H); IR (film) 2924, 2104, 1694 cm^{-1}; MS *m*/*e* (CI) 221 (M + H), 107 (100).

2-[2-(2-Aminoethyl)phenoxy]acetamide (16). A solution of the azide **15** (205 mg, 0.9 mmol) in MeOH (40 mL) was treated with Lindlar catalyst (100 mg) and hydrogen gas at 44 psi, 25 °C, for 18 h. After removal of the catalyst by filtration through Kieselguhr, the solvent was removed *in vacuo* to give a gum (182 mg), which was used without purification: ^{1}H-NMR (DMSO-d_6) δ 2.60−2.80 (m, 4H), 4.39 (s, 2H), 6.80−7.20 (m, 4H), 7.36 (br s, 1H), 7.42 (br s, 1H); IR (film) 3297, 2927, 1682 cm^{-1}.

[1-[[1-[(4-Hydroxybenzyl)carbamoyl]-1-methyl-2-phenylethyl]carbamoyl]-2-phenylethyl]carbamic Acid *tert*-Butyl Ester (17). The compound was prepared by coupling *p*-hydroxybenzylamine[35] to Boc(*S*)Phe(*RS*)αMPheOH[22] by the procedure described for **1a**. The product was purified by column chromatography, 50% EtOAc/hexane, to give the compound: 97 mg (37%); mp 86−90 °C; ^{1}H-NMR ($CDCl_3$) δ 1.26, 1.28 (2 × s, 9H), 1.50, 1.59 (2 × s, 3H), 2.73−3.08 (m, 3H), 3.32−3.41 (m, 1H), 3.98−4.39 (m, 3H), 4.88, 4.99 (2 × d, $J = 5.2$ Hz, 1H), 5.89, 6.27 (2 × s, 1H), 6.72−7.32 (m, 14H); IR (film) 3329, 1689, 1673, 1650, 1516 cm^{-1}. Anal. ($C_{24}H_{31}N_3O_4 \cdot 0.1H_2O$) C, H, N.

[*R*-(*R,*S**)]-[1-[[1-[[4-(4-Hydroxyphenyl)butyl]carbamoyl]-1-methyl-2-phenylethyl]carbamoyl]-2-phenylethyl]-carbamic Acid *tert*-Butyl Ester (18).** The amine **12** was coupled to Boc(*S*)Phe(*SR*)αMePheOH[22] using HOBt activation as described for **1a**. The compound was purified by column chromatography, 5% MeOH/DCM, to give a white solid: 105 mg (61%); mp 66−71 °C; $[\alpha]^{23}_D = +10.4°$ ($c = 1.0$, MeOH); ^{1}H-NMR (DMSO-d_6) δ 1.04−1.45 (m, 16H), 2.40 (t, $J = 6.8$ Hz, 2H), 2.60−3.18 (m, 6H), 4.08−4.15 (m, 1H), 6.60−7.22 (m, 15H), 7.51 (s, 1H), 7.71 (s, 1H), 9.02 (s, 1H); IR (film) 3347, 2927, 1693, 1652, 1515 cm^{-1}; MS *m*/*e* (CI) 574 (M + H), 474, 166, 134 (100). Anal. ($C_{34}H_{43}N_3O_5$) C, H, N.

[1-[[1-(Benzylcarbamoyl)-1-methyl-2-phenylethyl]carbamoyl]-2-phenylethyl]carbamic Acid *tert*-Butyl Ester

(19). The compound was prepared by coupling benzylamine to Boc(*S*)Phe(*RS*)αMePheOH[22] using DCCI/pentafluorophenol as described for **1b**. The crude material was purified by reverse phase chromatography to give the required compound in 89% yield: mp 60−62 °C; ^{1}H-NMR (DMSO-d_6) δ 1.73, 1.80 (2 × s, 9H), 1.32, 1.36 (2 × s, 3H), 2.60−2.34 (m, 4H), 4.06−4.36 (m, 1H), 6.92−7.30 (m, 15H), 7.89, 7.93 (2 × s, 1H), 8.15 (m, 1H); MS *m*/*e* (CI) 516 (M + H), 416, 309, 281, 134 (100). Anal. ($C_{31}H_{36}N_3O\cdot0.3H_2O$) C, H, N.

[1-[[1-Methyl-2-phenyl-1-[(4-phenylbutyl)carbamoyl]-ethyl]carbamoyl]-2-phenylethyl]carbamic Acid *tert*-Butyl Ester (20). The compound was prepared by coupling 4-phenylbutylamine to Boc(*S*)Phe(*RS*)αMePheOH[22] using HBTU activation as described for **1c**. The compound was purified by column chromatography, 50% EtOAc/hexane, to give a white solid: 180 mg (65%); mp 66−70 °C; ^{1}H-NMR ($CDCl_3$) δ 1.28 (m, 2H), 1.31, 1.35 (2 × s, 9H), 1.48, 1.57 (2 × s, 3H), 1.52 (m, 2H), 2.61 (t, J = 8 Hz, 2H), 2.75−3.40 (m, 6H), 4.05 (m, 1H), 4.83, 4.92 (2 × d, J = 7 Hz, 1H), 5.86, 6.18 (2 × s, 1H), 6.50, 6.66 (2 × s, 1H), 6.94 (br s, 2H), 7.10−7.35 (m, 13H); IR (film) 3327, 1688, 1652, 1497 cm^{-1}. Anal. ($C_{34}H_{43}N_3O_4\cdot0.5H_2O$) C, H, N.

[1-[[1-[(7-Hydroxyheptyl)carbamoyl]-1-methyl-2-phenylethyl]carbamoyl]-2-phenylethyl]carbamic Acid *tert*-Butyl Ester (21). The compound was prepared as described for **35** using Boc(*S*)Phe(*RS*)αMePheOH[22] to give a white solid: 80 mg (59%); ^{1}H-NMR ($CDCl_3$) δ 1.18−1.56 (m, 22H), 2.75−3.49 (m, 6H), 3.63 (t, J = 6.5 Hz, 2H), 3.98−4.12 (m, 1H), 4.84, 4.92 (2 × d, J = 7 Hz, 1H), 5.87, 6.18 (2 × s, 1H), 6.50, 6.64 (2 × s, 1H), 6.95 (m, 2H), 7.16−7.36 (m, 8H); IR (film) 3339, 2931, 1687, 1648, 1533 cm^{-1}; MS *m*/*e* (FAB) 540 (M$^+$), 440, 134. Anal. ($C_{31}H_{45}N_3O_5\cdot0.35H_2O$) C, H, N.

[1-[[1-[(8-Hydroxyoctyl)carbamoyl]-1-methyl-2-phenylethyl]carbamoyl]-2-phenylethyl]carbamic Acid *tert*-Butyl Ester (22). 8-Amino-1-octanol[22] was coupled to Boc(*S*)Phe(*RS*)αMePheOH[22] by the method described for **1c** to give a white solid: 60 mg (22%); mp 46−48 °C; ^{1}H-NMR ($CDCl_3$) δ 1.32−1.66 (m, 25H), 2.75−3.43 (m, 6H), 3.63 (t, J = 6.5 Hz, 2H), 4.00−4.10 (m, 2H), 4.86, 4.96 (2 × d, J = 7 Hz, 1H), 5.86, 6.20 (2 × s, 1H), 6.52, 6.65 (2 × s, 1H), 6.95 (m, 2H), 7.16−7.34 (m, 8H); IR (film) 3340, 2931, 1690, 1650, 1530 cm^{-1}; MS *m*/*e* (FAB) 555 (M + H), 454, 307, 28. Anal. ($C_{32}H_{47}N_3O_5\cdot0.8H_2O$) C, H, N.

[1-[[1-[(9-Hydroxynonanyl)carbamoyl]-1-methyl-2-phenylethyl]carbamoyl]-2-phenylethyl]carbamic Acid *tert*-Butyl Ester (23). 9-Amino-1-nonanol was coupled to Boc(*S*)-Phe(*RS*)αMePheOH[22] by the method described for **1c** to give a white solid: 189 mg (55%); mp 58−63 °C; ^{1}H-NMR ($CDCl_3$) δ 1.20−1.65 (m, 26H), 2.75−3.40 (m, 6H), 3.63 (t, J = 7 Hz, 2H), 4.05 (m, 1H), 4.83, 4.93 (2 × br s, 1H), 5.88, 6.21 (2 × s, 1H), 6.49, 6.63 (2 × s, 1H), 6.96 (m, 2H), 7.15−7.35 (m, 8H); IR (film) 3339, 2929, 2836, 1682, 1651, 1531 cm^{-1}. Anal. ($C_{33}H_{49}N_3O_5\cdot0.2H_2O$) C, H, N.

[*S*-(*R,*R**)]-[1-[[1-[(8-Hydroxyoctyl)carbamoyl]-1-methyl-2-phenylethyl]carbamoyl]-2-phenylethyl]carbamic Acid *tert*-Butyl Ester (24).** 8-Amino-1-octanol[22] was coupled to Boc(*S*)Phe(*S*)αMePheOH[36] using HBTU as described for **1c** to give a white solid: 460 mg (42%); mp 108−114 °C; $[\alpha]^{20}_D$ = +49.9° (*c* = 0.5, MeOH); ^{1}H-NMR ($CDCl_3$) δ 1.30−1.58 (m, 26H), 2.85−3.95 (m, 6H), 3.64 (t, J = 6.4 Hz, 2H), 4.10 (m, 1H), 4.85 (m, 1H), 6.15 (s, 1H), 6.50 (s, 1H), 6.95 (m, 2H), 7.16−7.33 (m, 8H); IR (film) 3326, 2978, 2856, 1678, 1651, 1532 cm^{-1}; MS *m*/*e* (CI) 555 (M + H), 554, 454, 146, 134 (100). Anal. ($C_{32}H_{47}N_3O_5$) C, H, N.

[1-[[1-Methyl-1-(nonylcarbamoyl)-2-phenylethyl]carbamoyl]-2-phenylethyl]carbamic Acid *tert*-Butyl Ester (26). The compound was prepared by coupling nonylamine to Boc(*S*)Phe(*RS*)αMePheOH[22] using HBTU as described for **1c**. The crude material was purified by column chromatography to give a white solid: 134 mg (48%); mp 63−68 °C; ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, J = 7 Hz, 3H), 1.25 (m, 14H), 1.33, 1.37 (2 × s, 9H), 1.45, 1.55 (2 × s, 3H), 2.70−3.20 (m, 5H), 3.37 (m, 1H), 4.05 (m, 1H), 4.85 (m, 1H), 5.85, 6.20 (2 × s, 1H), 6.45, 6.60 (2 × s, 1H), 6.95 (m, 2H), 7.15−7.40 (m, 8H); IR (film) 3307, 2927, 2855, 1671, 1645, 1531 cm^{-1}. Anal. ($C_{33}H_{49}N_3O_4$) C, H, N.

[1-[[1-[(8-Hydroxyoctyl)carbamoyl]-2-phenylethyl]carbamoyl]-2-phenylethyl]carbamic Acid *tert*-Butyl Ester (29). 8-Amino-1-octanol[22] was coupled to Boc(*S*)Phe(*RS*)-PheOH[36] using DCCI/HOBt as described for **1a**. The crude product was purified by reverse phase chromatography to give a white solid: 20 mg (47%); mp 98−105 °C; $[\alpha]^{21}_D$ = −5.1° (*c* = 0.5, MeOH); ^{1}H-NMR ($CDCl_3$) δ 1.41−1.65 (m, 22H), 2.79−3.40 (m, 6H), 3.61−3.66 (t, J = 6.5 Hz, 2H), 4.01 (m, 2H), 4.97−5.07 (m, 1H), 5.70−6.62 (m, 2H), 6.97−7.36 (m, 10H); IR (film) 3291, 2929, 1695, 1645, 1538 cm^{-1}. Anal. ($C_{31}H_{45}N_3O_5\cdot0.55H_2O$) C, H, N.

[*R*-(*R,*S**)]-[1-[[1-[[8-(Dimethylcarbamoyl)octyl]carbamoyl]-1-methyl-2-phenylethyl]carbamoyl]-2-phenylethyl]carbamic Acid *tert*-Butyl Ester (32).** The compound was prepared by coupling dimethylamine to Boc(*S*)Phe-(*R*)αMePheOH[22] using HBTU as described for **1c**. A glass was obtained: 180 mg (88%); $[\alpha]^{22}_D$ = +8.8° (*c* = 1.0, MeOH); ^{1}H-NMR ($CDCl_3$) δ 1.20−1.65 (m, 24H), 2.30 (t, 2H), 2.75−3.44 (m, 12H), 4.03 (m, 1H), 4.95 (br s, 1H), 5.92 (br s, 1H), 6.65 (br s, 1H), 6.95−7.00 (m, 2H), 7.20−7.40 (m, 8H); IR (film) 3326, 2930, 1692, 1652 cm^{-1}. Anal. ($C_{35}H_{52}N_4O_5\cdot0.2H_2O$) C, H, N.

(7-Hydroxyheptyl)carbamic Acid *tert*-Butyl Ester (34). (*tert*-Butoxycarbonyl)-7-aminoheptanoic acid (0.45 g, 1.8 mmol) and *N*-methylmorpholine (0.22 mL, 2 mmol) were dissolved in THF (10 mL). The solution was cooled to 0 °C, and ethyl chloroformate (0.2 mL, 2 mmol) in THF (10 mL) was added dropwise over 10 min. The solution was stirred for 1 h, and the precipitate was then removed by filtration. The filtrate was recooled to 0 °C, and 1 M $LiBH_4$ in THF (3 mL, 6 mmol) was added dropwise over 5 min. The solution was stirred with slow warming to room temperature over 3 h, and the solvent was then removed *in vacuo*. The residue was dissolved in EtOAc (50 mL), washed with water (3 × 50 mL) and brine (50 mL), and then dried over $MgSO_4$. The solvent was removed *in vacuo* to given an oil, 0.40 g (96%), which was used without purification: ^{1}H-NMR ($CDCl_3$) δ 1.28−1.60 (m, 19H), 3.10 (m, 2H), 3.64 (m, 12H), 4.50 (br s, 1H); IR (film) 33.44, 2931, 2858, 1689, 1531 cm^{-1}.

[*R*-(*R,*S**)]-[1-[[1-[(7-Hydroxyheptyl)carbamoyl]-1-methyl-2-phenylethyl]carbamoyl]-2-phenylethyl]carbamic Acid *tert*-Butyl Ester (35).** (7-Hydroxyheptyl)carbamic acid *tert*-butyl ester (**34**) (0.4 g, 1.7 mmol) was dissolved in DCM (10 mL)/TFA (10 mL), and the solution was stirred for 1 h. The solvent was then removed *in vacuo*, and the residue was added to a mixture of Boc(*S*)Phe(*R*)αMePheOH[22] (0.64 g, 1.5 mmol), DCCI (0.31 g, 1.5 mmol), and HOBt (0.2 g, 1.5 mmol) in DMF (3 mL). DIPEA (0.7 mL, 4 mmol) was added, and the reaction mixture was stirred for 15 h. The precipitate was removed by filtration, and the solvent was concentrated *in vacuo*. The residue was dissolved in EtOAc (100 mL), and the solution was washed with 1 M HCl (3 × 50 mL), saturated $NaHCO_3$ (3 × 50 mL), water (3 × 50 mL), and brine (50 mL). The organic layer was dried over $MgSO_4$, and the solvent was removed *in vacuo* to give a residue which was purified by reverse phase chromatography, 0−100% MeOH/water. A white solid was obtained: 0.54 g (67%); ^{1}H-NMR ($CDCl_3$) δ 1.29−1.58 (m, 22H), 2.75−3.45 (m, 6H), 3.63 (t, J = 6.8 Hz, 2H), 4.00 (m, 1H), 4.96 (br d, 1H), 5.85 (br s, 1H), 6.65 (br s, 1H), 6.96−6.98 (m, 2H), 7.19−7.35 (m, 8H); IR (film) 3324, 3029, 2929, 1661, 1516 cm^{-1}; MS *m*/*e* (CI) 540 (M + H), 440, 134. Anal. ($C_{31}H_{45}N_3O_5\cdot0.25H_2O$) C, H, N.

[*R*-(*R,*S**)]-Toluene-4-sulfonic Acid 7-[[2-[[2-[(*tert*-Butoxycarbonyl)amino]-3-phenylpropionyl]amino]-2-methyl-3-phenylpropionyl]amino]heptyl Ester (36).** The alcohol **35** (267 mg, 0.5 mmol) was dissolved in DCM (3 mL), and *p*-toluenesulfonyl chloride (105 mg, 0.55 mmol), NEt_3 (0.08 mL, 0.6 mmol), and DMAP (catalytic) were added. The reaction mixture was stirred for 15 h and then diluted with DCM (50 mL). The solution was washed with 1 M HCl (3 × 20 mL), saturated aqueous $NaHCO_3$ (3 × 20 mL), water (3 × 20 mL), and brine (20 mL). The organic layer was dried over $MgSO_4$, and the solvent was removed *in vacuo* to give a white solid (359 mg) which was used without purification: ^{1}H-NMR ($CDCl_3$) δ 1.21−1.66 (m, 22H), 2.45 (s, 3H), 2.75−3.45 (m, 6H), 4.01 (m, 3H), 4.90 (br d, 1H), 5.85 (br s, 1H), 6.70 (br s, 1H),

6.96−6.98 (m, 2H), 7.12−7.35 (m, 10H), 7.70 (d, J = 8.4 Hz, 2H); IR (film) 3351, 2978, 2935, 1687, 1657, 1521, 1598, 1366, 1175 cm^{-1}.

[*R*-(*R,*S**)]-[1-[[1-[(7-Azidoheptyl)carbamoyl]-1-methyl-2-phenylethyl]carbamoyl]-2-phenylethyl]carbamic Acid *tert*-Butyl Ester (37).** The tosylate **36** (317 mg, 0.46 mmol) was dissolved in DMF (5 mL), and sodium azide (33 mg, 0.51 mmol) was added. The reaction mixture was heated to 60 °C, stirred for 3 h, and then cooled to room temperature and stirred for a further 15 h. The solution was poured onto ice and extracted with DCM (3 × 100 mL). The combined extracts were washed with water (3 × 100 mL) and brine (100 mL) and then dried over $MgSO_4$, and the solvent was removed *in vacuo*. The residue was purified by column chromatography, 50% ether/hexane, to give a white solid: 179 mg (69%); ^{1}H-NMR ($CDCl_3$) δ 1.30−1.60 (m, 22H), 2.75−3.45 (m, 8H), 4.00 (m, 1H), 4.90 (br d, 1H), 5.85 (br s, 1H), 6.70 (br s, 1H), 6.97−6.99 (m, 2H), 7.20−7.36 (m, 8H); IR (film) 3322, 2932, 2095, 1683, 1651, 1517 cm^{-1}.

[*R*-(*R,*S**)]-[1-[[1-[(7-Aminoheptyl)carbamoyl]-1-methyl-2-phenylethyl]carbamoyl]-2-phenylethyl]carbamic Acid *tert*-Butyl Ester (38).** A solution of the azide **37** (275 mg, 0.49 mmol) in EtOH (20 mL) was treated with Lindlar catalyst (60 mg) and hydrogen gas at 40 psi, 30 °C, for 6 h. After removal of the catalyst by filtration through Kieselguhr, the solvent was removed *in vacuo* to give a white solid (266 mg). The product was dissolved in MeOH containing 1 M HCl and purified by reverse phase chromatography, 50−100% MeOH/water, to give a white solid: 215 mg (76%); mp 94−102 °C; ^{1}H-NMR ($CDCl_3$) δ 1.20−1.50 (m, 20H), 2.84 (br t, 2H), 2.75−3.33 (m, 8H), 4.00 (m, 1H), 5.20 (br s, 1H), 6.24 (br s, 1H), 6.79 (br t, 1H), 6.97−6.99 (m, 2H), 7.18−7.33 (m, 8H), 8.34 (br s, 3H); IR (film) 3322, 2933, 1689, 1652, 1520 cm^{-1}.

[*R*-(*R,*S**)]-[1-[[1-[[7-[(-Methylsulfonyl)a**mino]heptyl]-carbamoyl]-1-methyl-2-phenylethyl]carbamoyl]-2-phenylethyl]carbamic Acid *tert*-Butyl Ester (39).** The amine **38** (100 mg, 0.2 mmol) was dissolved in pyridine, and methanesulfonyl chloride (16 μL, 0.2 mmol) in pyridine/DCM (2 mL) was added dropwise over 10 min. The solution was stirred for 15 h, and then diluted with aqueous $NaHCO_3$ (20 mL). The mixture was extracted with DCM (3 × 20 mL), and the combined extracts were washed with water (50 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo*, and the residue was purified by column chromatography, 5% MeOH/DCM, to give a white solid: 25 mg (21%); mp 55−59 °C; ^{1}H-NMR ($CDCl_3$) δ 1.20−1.60 (m, 22H), 2.95 (s, 3H), 2.72−3.45 (m, 8H), 4.00 (m, 1H), 4.84 (m, 1H), 5.02 (br d, 1H), 5.82 (br s, 1H), 6.70 (br s, 1H), 6.95−6.98 (m, 2H), 7.19−7.36 (m, 8H); IR (film) 3340, 2932, 2859, 1688, 1652, 1520 cm^{-1}. Anal. ($C_{32}H_{48}N_4O_6S\cdot0.3H_2O$) C, H, N.

(7-Aminoheptyl)urea (40). A solution of trimethylsilyl isocyanate (0.35 mL, 2.6 mmol) in anhydrous THF (75 mL) was added dropwise over 30 min to a stirred solution of 1,7-diaminoheptane (1.0 g, 7.7 mmol) in THF (25 mL). The reaction mixture was stirred at room temperature for 2 h, and water (10 mL) was then added. After stirring for a further 2 h, the solvent was removed *in vacuo*. The residue was slurried with hot EtOAc, and the solid was collected by filtration. The solid was then slurried with water (25 mL) and filtered and the solvent evaporated to give a white solid: 398 mg (90%); mp 108−114 °C; ^{1}H-NMR (DMSO-d_6) δ 1.24−1.35 (m, 10H), 2.48−2.52 (m, 2H), 2.90−2.95 (m, 2H), 5.32 (s, 2H), 5.87 (s, 1H); IR (film) 3326, 2928, 2856, 1649, 1561, 1155 cm^{-1}; MS m/e (CI) 174, 157, 144, 131, 114. Anal. ($C_8H_{19}N_3O_4\cdot0.25H_2O$) C, H, N.

[*R*-(*R,*S**)]-[1-[[1-Methyl-2-phenyl-1-[(7-ureidoheptyl)-carbamoyl]ethyl]carbamoyl]-2-phenylethyl]carbamic Acid *tert*-Butyl Ester (41).** (7-Aminoheptyl)urea (**40**) was coupled to Boc(*S*)Phe(*R*)αMePheOH[22] using HBTU as described for **1c**. Purification by column chromatography, 5% MeOH/DCM, gave a white solid: 66 mg (47%); mp 65−72 °C; ^{1}H-NMR ($CDCl_3$) δ 1.21−1.52 (m, 22H), 2.75−3.22 (m, 8H), 4.02 (m, 1H), 4.55 (br s, 2H), 5.05, 5.15 (2 × br s, 2H), 5.95 (br s, 1H), 6.80 (br s, 1H), 6.97−6.99 (m, 2H), 7.18−7.34 (m, 8H); IR (film) 3344, 2931, 1693, 1651, 1539 cm^{-1}. MS m/e (FAB) 605 (M + Na), 582 (M + H), 482, 335. Anal. ($C_{31}H_{47}N_5O_5\cdot0.4H_2O$) C, H, N.

[*R*-(*R,*S**)]-[1-[[1-[[2-(Carbamoylmethoxy)phenyl]ethyl]carbamoyl]-1-methyl-2-phenylethyl]carbamoyl]-2-phenylethyl]carbamic Acid *tert*-Butyl Ester (43).** The amine **16** was coupled to Boc(*S*)Phe(*R*)αMePheOH[22] by the procedure described for **1a**. The crude product was purified by reverse phase chromatography, 60−80% MeOH/water, to give a white solid: 180 mg (34%); mp 98−103 °C; $[\alpha]^{23}_D$ = +8.1° (c = 1.0, MeOH); ^{1}H-NMR (DMSO-d_6) δ 1.21 (s, 3H), 1.26 (s, 9H), 2.60−3.27 (m, 8H), 4.15 (m, 1H), 4.40 (s, 2H), 6.80−7.23 (m, 15H), 7.41 (s, 1H), 7.50 (s, 1H), 7.70 (m, 1H), 7.76 (s, 1H); IR (film) 3328, 2979, 1694, 1683, 1652 cm^{-1}. Anal. ($C_{34}H_{42}N_4O_6$) C, H, N.

[2-(1*H*-Indol-3-yl)-1-methyl-1-[(1phenylethyl)carbamoyl]ethyl]carbamic Acid 2-Methyl-1-phenylpropyl Ester (44). (*R*,*S*)-2-Methyl-1-phenyl-1-propanol *p*-nitrophenyl carbonate (184 mg, 0.3 mmol) was added to a stirred solution of α-amino-α-methyl-*N*-(1-phenylethyl)-[*R*-(*R**,*S**)]-1*H*-indole-3-propanamide[18] (94 mg, 0.6 mmol) in EtOAc (20 mL). A catalytic amount of DMAP was added, and the reaction mixture was stirred for 4 days. The solution was diluted with Et_2O (25 mL) and washed with 5% citric acid (3 × 25 mL) and brine (25 mL). The organic layer was dried over $MgSO_4$ and filtered and the solvent evaporated. The residue was purified by column chromatography, 33% EtOAc/hexane, to give a solid: 36 mg (25%); mp 65−75 °C; ^{1}H-NMR ($CDCl_3$) δ 0.76 (m, 3H), 0.93 (m, 3H), 1.16−1.43 (m, 3H), 1.55 (m, 3H), 2.03 (m, 1H), 3.17−3.50 (m, 2H), 4.87−4.99 (m, 1H), 5.29−5.42 (m, 2H), 6.42 (br, 1H), 6.52, 6.75 (2 × s, 1H), 7.04−7.33 (m, 13H), 7.55 (m, 1H), 7.88, 8.07 (2 × s, 1H); IR (film) 3339, 2965, 1707, 1655, 1494, 1069 cm^{-1}. Anal. ($C_{31}H_{35}N_3O_3\cdot0.2H_2O$) C, H, N.

(*R*)-Carbonic Acid 2-Methyl-1-phenylpropyl Ester 4-Nitrophenyl Ester (45a). A solution of pyridine (8.8 mL, 0.1 mmol) in anhydrous DCM (20 mL) was added dropwise over 30 min to a stirred solution of *p*-nitrophenyl chloroformate (22.2 g, 0.11 mmol) and *S*-(−)-2-methyl-1-phenyl-1-propanol (15.0 g, 0.1 mmol) in anhydrous DCM (200 mL) cooled to 0 °C. The solution was stirred for 24 h with slow warming to room temperature. The reaction mixture was diluted with DCM (200 mL) and washed with 10% HCl (3 × 100 mL) and brine (100 mL). The organic layer was dried over $MgSO_4$, the solvent was removed *in vacuo*, and the residue was purified by column chromatography, 10% EtOAc/heptane, to give a gum: 28.87 g (92%); ^{1}H-NMR ($CDCl_3$) δ 0.85 (d, J = 6.8 Hz, 3H), 1.09 (d, J = 6.8 Hz, 3H), 2.25 (m, 1H), 5.38 (d, J = 7.6 Hz, 1H), 7.26−7.41 (m, 7H), 8.24 (d, J = 9.2 Hz, 2H); IR (film) 3362, 1764, 1526, 1224, 1218 cm^{-1}. Anal. ($C_{17}H_{17}NO_5$) C, H, N.

(*S*)-Carbonic Acid 2-Methyl-1-phenylpropyl Ester 4-Nitrophenyl Ester (45b). The compound was prepared as described for **45a**; purification by column chromatography, 10% ether/hexane, gave an oil: 1.50 g (82%); ^{1}H-NMR ($CDCl_3$) δ 0.85 (d, J = 6.8 Hz, 3H), 1.09 (d, J = 6.8 Hz, 3H), 2.23 (m, 1H), 5.37 (d, J = 6.8 Hz, 1H), 7.31−7.41 (m, 7H), 8.24 (d, 2H); IR (film) 3424, 3088, 2968, 1746, 1526, 1347, 1255, 1218 cm^{-1}.

2-Amino-3-(2-fluorophenyl)-2-methylpropionic Acid Methyl Ester (46). To a suspension of (*S*)-alanine methyl ester hydrochloride (5.0 g, 36 mmol), 4-chlorobenzaldehyde (5.1 g, 36 mmol), and $MgSO_4$ (2 g) in DCM (60 mL) was added NEt_3 (5 mL, 36 mmol). The reaction mixture was stirred for 20 h, filtered, and concentrated *in vacuo*. The resulting gum was triturated with ether, and the precipitate was removed by filtration. The filtrate was concentrated to give an oil (7.9 g, 98%). The Schiff base (2 g, 8.9 mmol) was dissolved in THF (20 mL) under an atmosphere of N_2, and the solution was cooled to −78 °C; 1 M LHMDS in THF (9.8 mL, 9.8 mmol) was added dropwise, and the reaction mixture was stirred for 1 h. 2-Fluorobenzyl bromide (1.7 g, 8.9 mmol) was added dropwise in THF (5 mL), and the solution was stirred for 20 h with slow warming to room temperature. HCl (1 M, 200 mL) was then added, and stirring was continued for 2 h. The solvent was removed *in vacuo*, and the residue was partitioned between 1 M HCl (200 mL) and EtOAc (200 mL). The pH of the aqueous layer was adjusted to 8 with Na_2CO_3, and the mixture was extracted with EtOAc (3 × 100 mL). The

combined extracts were washed with water (3 × 100 mL) and dried over $MgSO_4$, and the solvent was removed *in vacuo* to give an oil: 1.54 g (82%); ^{1}H-NMR ($CDCl_3$) δ 1.39 (s, 3H), 2.93 (d, J = 13.6 Hz, 1H), 3.09 (d, J = 13.6 Hz, 1H), 3.72 (s, 3H), 7.00−7.25 (m, 4H); IR (film) 2952, 1735 cm^{-1}.

2-Amino-3-(2,3-difluorophenyl)-2-methylpropionic Acid Methyl Ester (47). The compound was prepared following the procedure described for **46**. The product was obtained as an oil: 0.38 g (73%); ^{1}H-NMR ($CDCl_3$) δ 1.40 (s, 3H), 2.96 (d, J = 13 Hz, 1H), 3.12 (d, J = 13 Hz, 1H), 3.72 (s, 3H), 6.92−7.08 (m, 3H); IR (film) 3378, 2954, 1735, 1491, 1206 cm^{-1}.

[*R*-(*R,*R**)]-2-Methyl-2-[[(2-methyl-1-phenylpropoxy)carbonyl]amino]-3-phenylpropionic Acid Methyl Ester (48a).** The carbonate **45a** (3.00 g, 9.5 mmol) and (*R*)αMePheOMe (1.84 g, 9.5 mmol) were dissolved in anhydrous DMF (20 mL), and the solution was stirred for 3 days. The solvent was removed *in vacuo*, and the residue was dissolved in EtOAc (100 mL) and washed with 10% aqueous K_2CO_3 (5 × 75 mL) and brine (75 mL). The organic layer was dried over $MgSO_4$, and the solvent was concentrated. The residue was purified by column chromatography, 10% ether/heptane, to give a white solid: 2.5 g (70%); mp 118−120 °C; $[\alpha]^{23}_D$ = +46° (c = 0.5, acetone); ^{1}H-NMR ($CDCl_3$) δ 0.83 (d, J = 6.8 Hz, 3H), 0.99 (d, J = 6.8 Hz, 3H), 1.55 (s, 3H), 2.06−2.11 (m, 1H), 3.19 (d, J = 13.4 Hz, 1H), 3.39 (d, J = 13.4 Hz, 1H), 3.75 (s, 3H), 5.41 (m, 2H), 6.96−6.98 (m, 2H), 7.18−7.37 (m, 8H); IR (film) 3353, 2959, 1732, 1714, 1497, 1451 cm^{-1}; MS *m*/*e* (CI) 370 (M + H), 238, 194, 133.

[*S*-(*R,*S**)]-2-Methyl-2-[[(2-methyl-1-phenylpropoxy)carbonyl]amino]-3-phenylpropionic Acid Methyl Ester (48b).** The compound was prepared as described for **48a** using carbonate **45b**. Column chromatography gave an oil: 1.4 g (78%); $[\alpha]^{23}_D$ = +21° (c = 0.25, acetone); ^{1}H-NMR ($CDCl_3$) δ 0.81 (d, J = 6.8 Hz, 3H), 0.98 (d, J = 6.8 Hz, 3H), 1.66 (s, 3H), 2.03−2.10 (m, 1H), 3.05 (d, J = 13.6 Hz, 1H), 3.40 (d, J = 13.4 Hz, 1H), 3.72 (s, 3H), 5.35 (d, J = 6.8 Hz, 1H), 5.55 (s, 1H), 6.76−6.77 (m, 2H), 7.08−7.40 (m, 8H); IR (film) 3423, 2960, 1740, 1721, 1496, 1451 cm^{-1}; MS *m*/*e* (CI) 370 (M + H), 238, 194, 133.

[*S*-(*R,*S**)]-3-(2-Fluorophenyl)-2-methyl-2-[[(2-methyl-1-phenylpropoxy)carbonyl]amino]propionic Acid Methyl Ester (49).** The compound was prepared as described for **48a** using carbonate **45b** and 2-fluoro-(*RS*)αMePheOMe (**46**). The two diastereoisomers were separated by column chromatography, 10% ether/heptane, and the desired product (the more polar isomer) was isolated as an oil: 165 mg (26%); ^{1}H-NMR ($CDCl_3$) δ 0.81 (d, J = 6.8 Hz, 3H), 0.97 (d, J = 6.8 Hz, 3H), 1.54 (s, 3H), 2.08 (m, 1H), 3.25 (d, J = 13.6 Hz, 1H), 3.40 (d, J = 13.4 Hz, 1H), 3.73 (s, 3H), 5.39 (m, 2H), 6.86−7.36 (m, 9H); IR (film) 3354, 2960, 1739, 1717 cm^{-1}.

[*S*-(*R,*S**)]-3-(2,3-Difluorophenyl)-2-methyl-2-[[(2-methyl-1-phenylpropoxy)carbonyl]amino]propionic Acid Methyl Ester (50a).** The compound was prepared as described for **48a** using carbonate **45b** and 2,3-difluoro-(*RS*)αMePheOMe (**47**). The two diastereomers were separated by column chromatography, 10% ether/heptane, and the desired product (the more polar isomer) was isolated as a white solid: 111 mg (35%); mp 112−115 °C; $[\alpha]^{23}_D$ = +36° (c = 0.1, MeOH); ^{1}H-NMR ($CDCl_3$) δ 0.81 (d, J = 6.8 Hz, 3H), 0.98 (d, J = 6.8 Hz, 3H), 1.54 (s, 3H), 2.07 (m, 1H), 3.29 (d, J = 14 Hz, 1H), 3.46 (d, J = 14 Hz, 1H), 3.76 (s, 3H), 5.38 (m, 2H), 6.65 (m, 1H), 6.85 (m, 1H), 7.02 (m, 1H), 7.26−7.36 (m, 5H); IR (film) 3343, 2957, 1735, 1713, 1492, 1268, 1071 cm^{-1}; MS *m*/*e* (CI) 406 (M + H), 130, 133. Anal. ($C_{22}H_{25}NO_4F_2$) C, H, N.

[*S*-(*R,*R**)]-3-(2,3-Difluorophenyl)-2-methyl-2-[[(2-methyl-1-phenylpropoxy)carbonyl]amino]propionic Acid Methyl Ester (50b).** The compound was prepared as described for **50a**. The two diastereoisomers were separated by column chromatography, 10% ether/heptane, and the desired product (the less polar isomer) was isolated as an oil: 87 mg (27%); $[\alpha]^{23}_D$ = −105° (c = 0.2, MeOH); ^{1}H-NMR ($CDCl_3$) δ 0.83 (d, J = 6.8 Hz, 3H), 0.98 (d, J = 6.8 Hz, 3H), 1.65 (s, 3H), 2.07 (m, 1H), 3.26 (d, J = 14 Hz, 1H), 3.38 (d, J = 14 Hz, 1H), 3.72 (s, 3H), 5.34 (d, J = 6.8 Hz, 1H), 5.55 (s, 1H), 6.46 (m, 1H), 6.68 (m, 1H), 6.97 (m, 1H), 7.26−7.38 (m, 5H); IR (film) 3350, 2961, 1739, 1720, 1493, 1260 cm^{-1}; MS *m*/*e* (CI) 406 (M + H), 230, 133. Anal. ($C_{22}H_{25}NO_4F_2$) C, H, N.

[*R*-(*R,*R**)]-2-Methyl-2-[[(2-methyl-1-phenylpropoxy)carbonyl]amino]-3-phenylpropionic Acid Methyl Ester (51a).** The ester **48a** (0.74 g, 2 mmol) was dissolved in THF (20 mL), and LiOH monohydrate (0.16 g, 4 mmol) in water (4 mL) was added. The reaction mixture was heated under reflux for 48 h, and the solvent was then removed *in vacuo*. The residue was partitioned between 2 M HCl (100 mL) and EtOAc (100 mL), the aqueous layer was re-extracted with EtOAc (3 × 100 mL), and the combined extracts were dried over $MgSO_4$. The solvent was removed to give a white solid: 0.6 g (86%); $[\alpha]^{23}_D$ = +44° (c = 0.4, MeOH); ^{1}H-NMR ($CDCl_3$) δ 0.82 (d, J = 6.8 Hz, 3H), 0.99 (d, J = 6.8 Hz, 3H), 1.55 (s, 3H), 2.10 (m, 1H), 3.29 (m, 2H), 5.27 (s, 1H), 5.42 (d, J = 7.2 Hz, 1H), 6.99 (m, 2H), 7.17−7.38 (m, 8H); IR (film) 3409, 2969, 1713, 1497, 1452, 1052 cm^{-1}; MS *m*/*e* (CI) 356 (M + H), 302, 266, 180, 133.

[*S*-(*R,*S**)]-2-Methyl-2-[[(2-methyl-1-phenylpropoxy)carbonyl]amino]-3-phenylpropionic Acid Methyl Ester (51b).** The compound was prepared from the ester **48b** as described for **51a**. A white solid was obtained: 1.32 g (93%); $[\alpha]^{23}_D$ = +14° (c = 0.4, MeOH); ^{1}H-NMR ($CDCl_3$) δ 0.81 (d, J = 6.8 Hz, 3H), 0.99 (d, J = 6.8 Hz, 3H), 1.67 (s, 3H), 2.10 (m, 1H), 3.13−3.42 (d × d, 2H), 5.37 (d, J = 7 Hz, 1H), 5.42 (s, 1H), 6.87 (m, 2H), 7.11−7.39 (m, 8H); IR (film) 3414, 2964, 1711, 1498, 1452, 1053 cm^{-1}; MS *m*/*e* (CI) 356 (M + H), 224, 180, 133.

[*S*-(*R,*S**)]-3-(2-Fluorophenyl)-2-methyl-2-[[(2-methyl-1-phenylpropoxy)carbonyl]amino]propionic Acid (52).** The compound was prepared as described for **51a** from ester **49**. A white solid was obtained: 127 mg (97%); ^{1}H-NMR ($CDCl_3$) δ 0.81 (d, J = 6.8 Hz, 3H), 0.98 (d, J = 6.8 Hz, 3H), 1.52 (s, 3H), 2.07 (m, 1H), 3.34 (m, 2H), 5.22 (s, 1H), 5.39 (d, J = 7 Hz, 1H), 6.85−7.38 (m, 9H); IR (film) 2964, 1714, 1494 cm^{-1}.

[*S*-(*R,*S**)]-3-(2,3-Difluorophenyl)-2-methyl-2-[[(2-methyl-1-phenylpropoxy)carbonyl]amino]propionic Acid (53a).** The compound was prepared as described for **51a** from ester **50a**. A white solid was obtained: 94 mg (94%); ^{1}H-NMR ($CDCl_3$) δ 0.80 (d, J = 6.8 Hz, 3H), 0.98 (d, J = 6.8 Hz, 3H), 1.52 (s, 3H), 2.08 (m, 1H), 3.35 (d, J = 14 Hz, 1H), 3.42 (d, J = 14 Hz, 1H), 5.21 (s, 1H), 5.38 (d, J = 6.8 Hz, 1H), 6.57 (m, 1H), 6.82 (m, 1H), 7.02 (m, 1H), 7.26−7.38 (m, 5H); IR (film) 3418, 3035, 2965, 1715, 1493 cm^{-1}.

[*S*-(*R,*R**)]-3-(2,3-Difluorophenyl)-2-methyl-2-[[(2-methyl-1-phenylpropoxy)carbonyl]amino]propionic Acid (53b).** The compound was prepared as described for **51a** from ester **50b**. A white solid was obtained: 67 mg (90%); ^{1}H-NMR ($CDCl_3$) δ 0.81 (d, J = 6.8 Hz, 3H), 0.98 (d, J = 6.8 Hz, 3H), 1.62 (s, 3H), 2.08 (m, 1H), 3.37 (s, 2H), 5.36 (m, 2H), 6.62 (m, 1H), 6.79 (m, 1H), 7.02 (m, 1H), 7.26−7.36 (m, 5H); IR (film) 2965, 1715, 1492, 1290, 1258, 1071 cm^{-1}.

[1-Methyl-2-phenyl-1-[(1-phenylethyl)carbamoyl]ethyl]carbamic Acid 2-Methyl-1-phenylpropyl Ester (54). The compound was prepared by coupling (*S*)-α-methylbenzylamine to acid **51a** by the method described for **1a**. A white solid was obtained: 41 mg (70%); mp 151−161 °C; $[\alpha]^{20}_D$ = +10° (c = 0.5, acetone); ^{1}H-NMR ($CDCl_3$) δ 0.81 (d, J = 6.8 Hz, 3H), 0.98 (d, J = 6.8 Hz, 3H), 1.32 (d, J = 6.8 Hz, 3H), 1.48 (s, 3H), 2.02−2.11 (m, 1H), 3.14 (d, J = 14 Hz, 1H), 3.28 (d, J = 14 Hz, 1H), 4.93−5.00 (m, 1H), 5.26 (m, 1H), 5.38 (d, J = 7.6 Hz, 1H), 6.39 (d, J = 7.1 Hz, 1H), 6.99−7.01 (m, 2H), 7.14−7.36 (m, 13H); IR (film) 3326, 3031, 2930, 1721, 1694, 1645, 1485, 1078 cm^{-1}; MS *m*/*e* (CI) 459 (M + H), 327, 283, 133. Anal. ($C_{29}H_{34}N_2O_3$·0.25H_2O) C, H, N.

[1-Methyl-2-phenyl-1-[(1-phenylethyl)carbamoyl]ethyl]carbamic Acid 2-Methyl-1-phenylpropyl Ester (55). The compound was prepared by coupling (*S*)-α-methylbenzylamine to acid **51b** by the method described for **1a**. A white solid was obtained: 51 mg (50%); mp 183−189 °C; $[\alpha]^{20}_D$ = +6° (c = 0.5, acetone); ^{1}H-NMR ($CDCl_3$) δ 0.78 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H), 1.38 (d, J = 6.8 Hz, 3H), 1.44 (s, 3H), 2.01−2.10 (m, 1H), 3.07 (d, J = 14 Hz, 1H), 3.33 (d, J = 14 Hz, 1H), 5.01−5.08 (m, 1H), 5.15 (s, 1H), 5.38 (d, J = 7.8 Hz, 1H), 6.41 (d, J = 7.3 Hz, 1H), 6.92 (d, J = 6.8 Hz, 2H),

7.09−7.36 (m, 13H); IR (film) 3331, 2960, 1692, 1647, 1524, 1455, 1081 cm^{-1}; MS *m/e* (CI) 459 (M + H), 327, 283, 133. Anal. ($C_{29}H_{34}N_2O_3$) C, H, N.

[*R*-(*R*,R)]-[1-[(8-Hydroxyooctyl)carbamoyl]-1-methyl-2-phenylethyl]carbamic Acid 2-Methyl-1-phenylpropyl Ester (56).** The compound was prepared by coupling 8-aminooctanol[22] to acid **51a** by the method described for **1a**. Purification by column chromatography, 33−50% EtOAc/hexane, gave a gum: 23 mg (34%); $[\alpha]^{20}_D = +9°$ (*c* = 0.8, acetone); ^{1}H-NMR ($CDCl_3$) δ 0.81 (d, *J* = 6.8 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H), 1.19−1.42 (m, 10H), 1.52−1.59 (m, 3H), 2.04−2.14 (m, 1H), 3.06−3.23 (m, 3H), 3.27 (d, *J* = 14 Hz, 1H), 3.64 (t, *J* = 6.6 Hz, 2H), 5.24 (m, 1H), 5.38 (d, *J* = 7.6 Hz, 1H), 6.01 (br, 1H), 7.00−7.02 (m, 2H), 7.18−7.36 (m, 8H); IR (film) 3366, 3031, 2930, 1720, 1649, 1488, 1078 cm^{-1}; MS *m/e* (CI) 483 (M + H), 307, 266, 133. Anal. ($C_{29}H_{42}N_2O_4 \cdot 0.5H_2O$) C, H, N.

[*S*-(*R*,S)]-[1-[(8-Hydroxyooctyl)carbamoyl]-1-methyl-2-phenylethyl]carbamic Acid 2-Methyl-1-phenylpropyl Ester (57).** The compound was prepared by coupling 8-aminooctanol[22] to acid **51b** by the method described for **1a**. Purification by column chromatography, 33−50% EtOAc/hexane, gave a gum: 24 mg (39%); $[\alpha]^{20}_D = +7°$ (*c* = 1.0, acetone); ^{1}H-NMR ($CDCl_3$) δ 0.80 (d, *J* = 6.8 Hz, 3H), 0.98 (d, *J* = 6.8 Hz, 3H), 1.19−1.42 (m, 10H), 1.50−1.62 (m, 3H), 2.08 (m, 1H), 3.08 (d, *J* = 14 Hz, 1H), 3.17−3.22 (m, 2H), 3.33 (d, *J* = 14 Hz, 1H), 3.64 (t, *J* = 6.6 Hz, 2H), 5.11 (m, 1H), 5.39 (d, *J* = 7.6 Hz, 1H), 6.17 (br, 1H), 6.94−6.95 (m, 2H), 7.14−7.38 (m, 8H); IR (film) 3363, 3031, 2856, 1719, 1649, 1494, 1079 cm^{-1}; MS *m/e* (CI) 483 (M + H), 307, 266, 133. Anal. ($C_{29}H_{42}N_2O_4 \cdot 0.5H_2O$) C, H, N.

[*S*-(*R*,S)]-[1-Methyl-2-phenyl-1-[(7-ureidoheptyl)carbamoyl]ethyl]carbamic Acid 2-Methyl-1-phenylpropyl Ester (58).** The compound was prepared by coupling the amino urea **40** to acid **51b** by the method described for **1c**. Purification by column chromatography, 80% EtOAc/heptane, gave a white solid: 30 mg (43%); mp 54−57 °C; ^{1}H-NMR ($CDCl_3$) δ 0.79 (d, *J* = 6.8 Hz, 3H), 0.98 (d, *J* = 6.8 Hz, 3H), 1.21−1.60 (m, 13H), 2.07 (m, 1H), 3.05 (d, *J* = 14 Hz, 1H), 3.32 (d, *J* = 14 Hz, 1H), 3.14−3.22 (m, 4H), 4.42 (br, 2H), 4.85 (s, 1H), 5.09 (s, 1H), 5.37 (d, *J* = 7.6 Hz, 1H), 6.28 (br, 1H), 6.92−7.38 (m, 10H); IR (film) 3347, 2931, 1713, 1651, 1538 cm^{-1}; MS *m/e* (APCI) 511 (M + H). Anal. ($C_{29}H_{42}N_4O_4 \cdot 0.6H_2O$) C, H, N.

[*S*-(*R*,S)]-[2-(2-Fluorophenyl)-1-methyl-1-[(7-ureidoheptyl)carbamoyl]ethyl]carbamic Acid 2-Methyl-1-phenylpropyl Ester (59).** The compound was prepared by coupling the amino urea **40** to acid **52** by the method described for **1c**. Purification by column chromatography, 5% MeOH/DCM, gave a white solid: 17 mg (29%); mp 67−72 °C; ^{1}H-NMR ($CDCl_3$) δ 0.81 (d, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 3H), 1.20−1.58 (m, 13H), 2.10 (m, 1H), 3.10−3.30 (m, 6H), 4.48 (br, 2H), 4.98 (s, 1H), 5.38 (m, 2H), 6.22 (br, 1H), 6.82−7.36 (m, 9H); IR (film) 3343, 2932, 2858, 1713, 1651, 1539 cm^{-1}. Anal. ($C_{29}H_{41}N_4O_4F \cdot 0.2H_2O$) C, H, N.

[*S*-(*R*,S)]-[2-(2,3-Difluorophenyl)-1-methyl-1-[(7-ureidoheptyl)carbamoyl]ethyl]carbamic Acid 2-Methyl-1-phenylpropyl Ester (60).** The compound was prepared by coupling the amino urea **40** to acid **53a** by the method described for **1c**. Purification by column chromatography, 5% MeOH/DCM, gave a white solid: 39 mg (55%); mp 59−64 °C; ^{1}H-NMR ($CDCl_3$) δ 0.80 (d, *J* = 6.8 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H), 1.26−1.57 (m, 13H), 2.09 (m, 1H), 3.19 (m, 4H), 3.26 (d, *J* = 14 Hz, 1H), 3.36 (d, *J* = 14 Hz, 1H), 4.40 (br, 2H), 4.80 (s, 1H), 5.28 (br, 1H), 5.37 (br, 1H), 6.25 (br, 1H), 6.55 (m, 1H), 6.76 (br, 1H), 7.00 (br, 1H), 7.26−7.38 (m, 5H); IR (film) 3363, 2932, 2864, 1709, 1651, 1539 cm^{-1}; MS *m/e* (APCI) 1050 (M^{2+}) 547 (M), 504. Anal. ($C_{29}H_{40}N_4O_4F_2 \cdot 0.75H_2O$) C, H, N.

[*S*-(*R*,R)]-[2-(2,3-Difluorophenyl)-1-methyl-1-[(7-ureidoheptyl)carbamoyl]ethyl]carbamic Acid 2-Methyl-1-phenylpropyl Ester (61).** The compound was prepared by coupling the amino urea **40** to acid **53b** by the method described for **1c**. Purification by column chromatography, 5% MeOH/DCM, gave a white solid: 54 mg (62%); mp 56−61 °C; ^{1}H-NMR ($CDCl_3$) δ 0.81 (d, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 3H), 1.17−1.49 (m, 8H), 1.56 (m, 5H), 2.08 (m, 1H), 3.14−3.35 (m, 6H), 4.43 (s, 2H), 4.82 (br, 1H), 5.35 (d, *J* = 7.2 Hz, 1H), 5.42 (br, 1H), 6.12 (m, 1H), 6.68 (m, 1H), 6.87 (m, 1H), 7.04 (m, 1H), 7.26−7.34 (m, 5H); IR (film) 3351, 2932, 2858, 1709, 1651, 1540 cm^{-1}; MS *m/e* (APCI) 547 (M), 504. Anal. ($C_{29}H_{40}N_4O_4F_2 \cdot 0.2H_2O$) C, H, N.

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Supporting Information Available: X-ray crystallographic coordinates and experimental parameters for compound **50a** (22 pages). Ordering information is given on any current masthead page.

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