Inhibitors of Acyl-CoA:Cholesterol O-Acyl Transferase (ACAT) as Hypocholesterolemic Agents. 8.[1] Incorporation of Amide or Amine Functionalities into a Series of Disubstituted Ureas and Carbamates. Effects on ACAT Inhibition in Vitro and Efficacy in Vivo[2]

Patrick M. O'Brien,*,† Drago R. Sliskovic,† C. John Blankley,† Bruce D. Roth,† Michael W. Wilson,† Katherine L. Hamelehle, Brian R. Krause, and Richard L. Stanfield

Departments of Chemistry and Atherosclerosis Therapeutics, Parke-Davis Pharmaceutical Research, Warner Lambert Company, 2800 Plymouth Road, Ann Arbor, Michigan 48105

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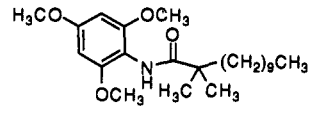
A series of disubstituted ureas containing amide or amine groups was prepared and evaluated for their ability to inhibit acyl-CoA:cholesterol O-acyl transferase in vitro and to lower plasma total cholesterol in a variety of cholesterol-fed rat models in vivo. The presence of polar or ionizable functionalities within this class of compounds may impart greater aqueous solubility to those compounds and thus allow improved transport to the enzyme location within the intestinal enterocyte. Compounds from this class exhibit good cholesterol lowering in a chronic cholesterol-fed rat model of hypercholesterolemia even when dosed in an aqueous vehicle. In general, the amine-containing compounds were more potent and efficacious than the amides in the acute rat model of hypercholesterolemia. Further structure–activity relationship studies showed that the preferred position of the amide/amine group was β to the urea moiety and not α, and that in this series, the presence of a secondary amine (or amide) proton is required for good in vitro potency. One of these compounds, **9n**(–), lowered plasma total cholesterol (–47%) and elevated high-density lipoprotein cholesterol (+256%) when dosed in an aqueous vehicle to rats with preestablished hypercholesterolemia.

Introduction

We have recently reported on a series of fatty acid anilides as potent acyl-CoA:cholesterol O-acyl transferase (ACAT) inhibitors.[3] Evidence has been provided that one of these compounds, Cl-976 (1), possesses hypolipidemic activity in rats[4] and hamsters[5] by virtue of its ability to inhibit both intestinal and liver ACAT. It also produces direct antiatherosclerotic activity in cholesterol-fed rabbits.[6]

A study of bioisosteric replacements for the amide moiety revealed that a disubstituted urea was a good bioisosteric replacement for the amide moiety.[7] The ensuing structure–activity relationship (SAR) studies revealed that the urea, substituted on one nitrogen with 2,6-diisopropylphenyl, gave compounds which were very potent ACAT inhibitors, the structural requirements for the second urea nitrogen being less stringent.[8] Compound **2** was identified from this series as a potent inhibitor of ACAT in vitro, which was efficacious in cholesterol-fed rats when dosed in an oil vehicle, but not when dosed in an aqueous vehicle.[1] This suggested an absorption problem and prompted an SAR study based on **2**, which identified **3** as another potent ACAT inhibitor, which, although not as potent as **2**, was more efficacious in several animal models, irrespective of dosing vehicle.[1] One possible explanation for the improved in vivo activity of **3** is that the dimethylamino group provides an ionizable site which, when protonated, as would be likely in the stomach, would render the compound more soluble and hydrophilic in this state and transport to the enzyme thereby facilitated. Interestingly, compounds **1**, **2**, and **3** all have similar CLOGP[9] values (6.27, 6.33, and 6.53); however, only **3** has some aqueous solubility (0.1 mg/mL).



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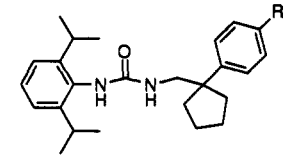
CLOGP = 6.27



2, R=H, CLOGP=6.33

3, R=N(CH3)2, CLOGP=6.53

Figure 1.

We report in this paper an alternate strategy for incorporating polar or ionizable functions into the essential substructure for the aralkylurea ACAT inhibitors represented by **2**. This consisted of replacing the spirocyclopentyl moiety with amine and amido groups of varying size and polarity and a broad range of lipophilicity as estimated by CLOGP.

Chemistry

The strategy outlined above was made possible by employing the retrosynthetic strategy illustrated in Chart 1. The amides (**7a–x, 7b′,c′,e′,k′,u′**) were synthesized by acylating (±)-2-phenylglycinonitrile (**4**) or 2-cyano-2-phenethylamine (**4′**)[10] with the appropriate acid chloride in the presence of triethylamine (Scheme 1). In the case of the heteroaryl examples **7q–x**, the α-amino nitriles (**4, 4′**) were acylated with the more readily available heteroaryl carboxylic acids, using CDI or DCC as the coupling agent. The resulting α-amido nitriles (**5a–i, k–x, 5b′,c′,e′,k′,u′**) were catalytically hydrogenated to the amines (**6a–i,k–x, 6b′,c′,e′,k′,u′**) using Raney nickel in methanolic ammonia. However, it was necessary to carry out the hydrogenation of **5j** in the presence of Pd/C under acidic conditions (sulfuric acid in methanol) in order to avoid dehaolgenation of the aliphatic bromide. Treatment of the amino deriva-

† Department of Chemistry.

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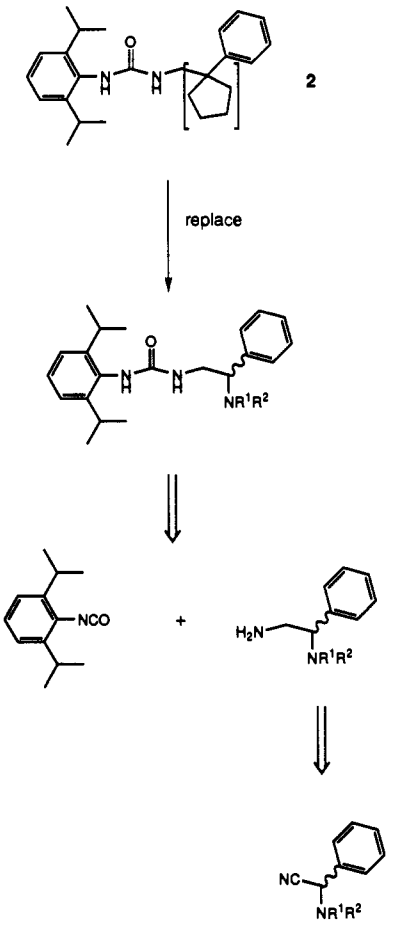
Chart 1. Retrosynthetic Pathway to Amine and Amide Analogs



tives with 2,6-diisopropylphenyl isocyanate in ethyl acetate gave the corresponding ureas (**7a–x, 7b′,c′,e′,k′,u′**).

A small series of analogs with polar terminal substitutions was prepared by reacting the bromide **7j** with various alkoxy or amine nucleophiles at elevated temperatures to give **8k–o** (Scheme 2). Oxidation of **7q** and **7u** to the corresponding *N*-oxides **7r** and **7v** was achieved with mCPBA in refluxing dichloromethane.

A regioisomer of **7k** was prepared by reversing the order of the reaction sequence in Scheme 1 for steps a–c. The α-amino nitrile **4** was coupled with 2,6-diisopropylphenyl isocyanate, followed by catalytic hydrogenation of the resulting nitrile **11** over 20% Pd/C, to give the corresponding amine **12**. Acylation of **12** with benzoyl chloride in the presence of triethylamine yielded compound **13** (R = Ph) in which the phenyl ring is now positioned α with respect to the urea moiety as opposed to β in **7k**.

Selective reduction of the alkyl (**7b–g,j, 7e′**) and aryl-substituted amides (**7k–m, 7k′**) to the corresponding amines (**9b–g,j,k–m, 9e′,k′**) was achieved by treatment with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) in refluxing toluene. Interestingly, in addition to reducing the amide carbonyl of **7j**, Red-Al also dehalogenated the terminal bromide to give the hexylamine **9j**.

9k was N-alkylated to give tertiary amines **10a** and **10b** when treated with the appropriate alkyl or benzyl halides.

Compounds possessing an asymmetric center positioned β with respect to the urea moiety were initially synthesized in racemic form. In order to assess whether the biological activity observed for these racemates resided in one particular enantiomer, a novel asymmetric synthesis (Scheme 3) was designed, thus allowing the preparation of aryl- (**9k,m–t**) and heteroaryl- (**9u–z**) substituted amines in either enantiomeric form. Commercially available (*R*)-(−)- or (*S*)-(+)-2-phenylglycinol **14** was selectively N-protected with BOC anhydride in THF, containing 4-(dimethylamino)pyridine (DMAP) as the catalyst. Alcohol **15** was then activated with methanesulfonyl chloride to give mesylate **16** which underwent nucleophilic displacement to the primary azide **17** upon treatment with sodium azide in DMF. The protected aminourea **19** was prepared by reducing **17** with lithium aluminum hydride (LAH) at 0 °C followed by coupling amine **18** with 2,6-diisopropylphenyl isocyanate. Treatment of **19** with HCl in dichloromethane effectively removed the BOC protecting group to give the penultimate aminourea. The amino moiety was condensed with a variety of aldehydes, and the resulting imines were reduced with sodium borohydride in methanol or THF to give stereoisomers **9a,k,m–z** (as determined by chiral HPLC. See the Experimental Section).

It was necessary to prepare the benzladehydes utilized for compounds **9o** and **9t** in Scheme 3 by employing the synthetic methodology shown in Scheme 4. Esterification of acid **37** was accomplished using standard conditions (HCl/MeOH): subsequent alkylation of amine **38** with formaldehyde in refluxing formic acid gave **39**. Reduction of **39** with DIBAL in CH_2Cl_2 gave the corresponding alcohol **40**, which was oxidized with MnO_2 in refluxing toluene to give **41** in quantitative yield. The (dimethylamino)methyl group of **44** was regioselectively introduced into the aryl ring of **42** employing modified Mannich reaction conditions. The resulting benzonitrile **43** was easily converted to the desired aldehyde **44** by reduction with Raney nickel in formic acid at 60 °C.

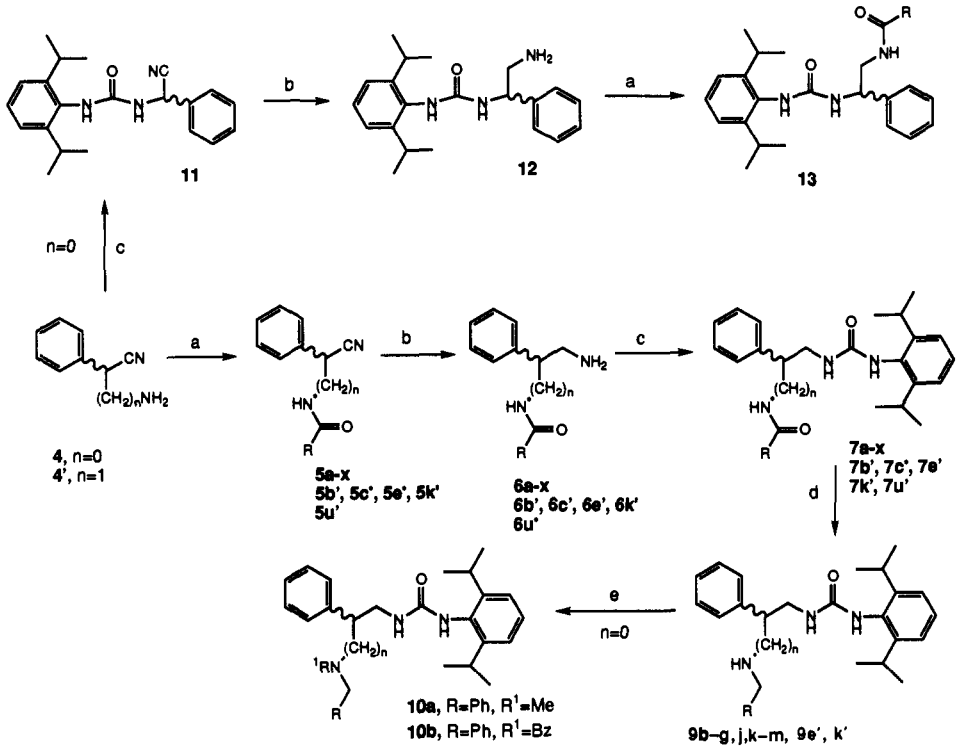
As shown in Scheme 5, the Strecker reaction was instrumental in preparing a variety of amino nitriles (**21a–e**) bearing substituents other than phenyl from appropriately substituted aldehydes and ketones (**20a–e**). These versatile intermediates were then converted to amidoureas (**24a–e**) in three steps, employing reaction conditions previously described.

The availability of BOC-protected amino acid esters (**25a–e**) provided an alternative method for varying the β substituents for the urea derivatives. The target compounds (**31a–e**) were synthesized by reducing the ester functionality (**25a–e**) to the corresponding alcohol (**26a–e**) with LAH in THF, followed by conversion of **26a–e** to the target compounds, utilizing the procedure previously described in Scheme 3.

In addition to preparing ureas, several carbamates (Scheme 6) were synthesized from intermediates (**15, 18, 6d**) previously described. Compound **15** was treated with 2,6-diisopropylphenyl isocyanate to afford the dicarbamate **32**. Subsequent deprotection of the amino moiety upon treatment with gaseous HCl in dichloromethane gave amine **33**, which was acylated with appropriately substituted acid chlorides to give amides **34a–b** or condensed with 4-(dimethylamino)benzaldehyde to give the imine, which was reduced to **34c** with sodium borohydride in methanol.

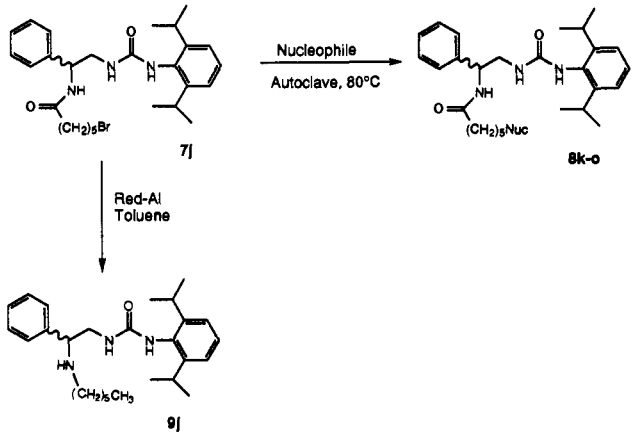
Compound **18** was coupled with 2,6-diisopropylphenyl chloroformate[11] to yield **35**. Deprotection with HCl, followed by acylation with lauroyl chloride, gave **36b**. The phenethylamine derivative **6d** was easily converted to the corresponding carbamate **36a** upon treatment with 2,6-

Scheme 1[a]



[a] (a) RCOCl, NEt_3, THF; (b) Raney Ni or Pd/C, H_2, NH_3/MeOH, 50 psi; (c) 2,6-diisopropylphenyl isocyanate, EtOAc; (d) Red-Al, toluene, reflux **9b–g,j,k–m, 9e',k'**; (e) R^1X (X = Br, I), NaH, DMF.

Scheme 2



diisopropylphenyl chloroformate in the presence of triethylamine.

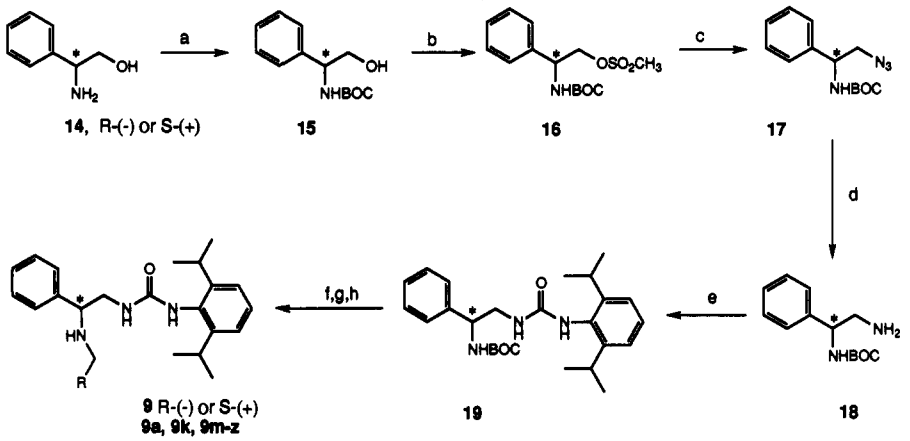
Biological Results

The compounds prepared in this study were evaluated in a two-tier assay system. This consisted of in vitro assay, in which compounds were evaluated for their ability to inhibit intestinal ACAT, using [1-^{14}C]oleoyl-CoA as enzyme substrate and microsomes from the intestines of cholesterol-fed rabbits as enzyme source.[3] The primary in vivo assay was performed in rats given a single dose of test compound by gavage suspended in carboxymethylcellulose (CMC) and Tween-20 in water, followed by a single high-fat, high-cholesterol meal.[12] The ability of the test compound to inhibit the overnight rise in plasma cholesterol that occurs in rats fed this diet was an excellent method of routinely determining the efficacy of a large number of compounds in a short period of time. Although the exact amount of food was not measured for each animal in this acute test, the stomachs were checked routinely for the presence of food to eliminate false positives. For selected compounds, a more stringent test of efficacy was performed in which the test compound was administered to rats with preestablished hypercholsterolemia. These rats were fed the same diet as above but for 14 days. During the second week, the drug was administered daily in the same vehicle. Efficacy in this model is defined as the ability to lower plasma non-HDL cholesterol and to elevate the diet-induced low levels of HDL cholesterol.[12]

This in vivo testing regimen contrasts to the one previously employed in our group in which efficacy was assessed in rats by *admixing* the compounds into the high-fat, high-cholesterol diet.[3] The earlier protocol ensured that the maximum possible amount of compound (especially lipophilic compounds) was absorbed and thus maximal efficacy was expressed. However, it soon became apparent that this protocol did not model well the situation encountered in current clinical practice. This became evident when the vehicle-dependent efficacy of compound **2** was observed.

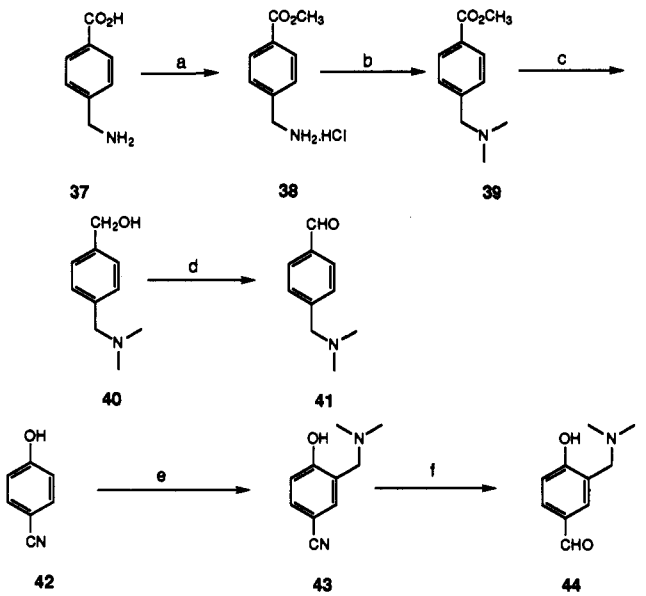
Replacement of the spirocyclopentyl moiety (positioned β to the urea moiety) of **2** by a variety of alkyl and substituted-alkyl amides gave compounds which were less active, both in vitro and in vivo (n = 0, Table 1). There was a steady increase in the potency of the alkyl amides with increasing chain length (**7a–g**). The most active compound in vivo was **7d**, which significantly lowered plasma cholesterol by 29% in cholestero-fed rats. Interestingly, the most potent compounds (**7e** and **7f**) were inactive in vivo, possibly due to their high lipophilicity (CLOGP values of 8.97 and 11.0, respectively). The introduction of polar functionalities into the alkyl chain led to considerable decreases in both lipophilicity and in vitro activity (compare **7c** and **8m** and **8n**). The primary bromoalkyl amide, **7j**, however, was as efficacious as **2** in

Scheme 3[a]



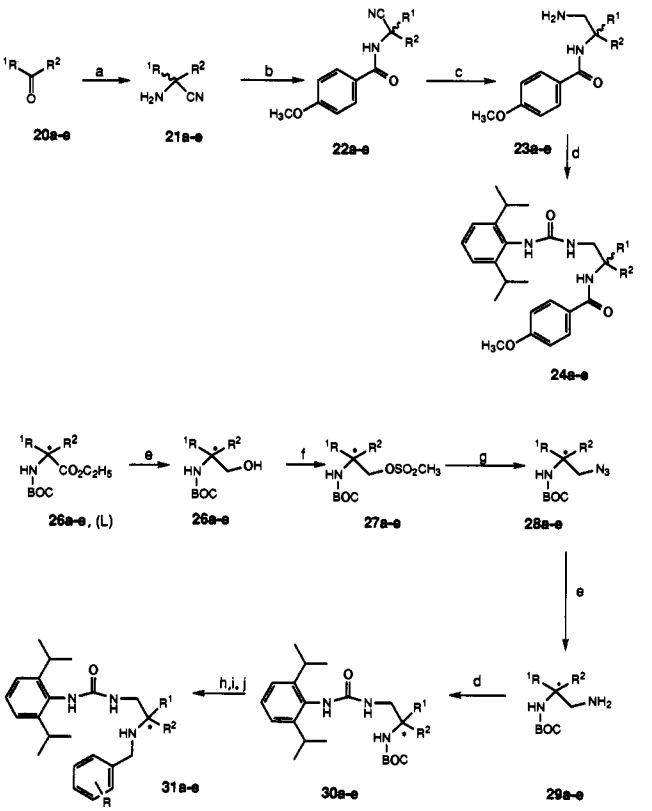
[a] (a) BOC anhydride, DMAP, THF; (b) CH_3SO_2Cl, NEt_3, CH_2Cl_2; (c) NaN_3, DMF; (d) LAH, THF; (e) 2,6-diisopropylphenyl isocyanate, EtOAc; (f) HCl, CH_2Cl_2; (g) RCHO, Na_2SO_4, MeOH; (h) $NaBH_4$, THF.

Scheme 4[a]



[a] (a) HCl, MeOH, reflux; (b) H_2CO, HCO_2H, reflux, then NaOH; (c) DIBAL, CH_2Cl_2; (d) MnO_2, toluene, reflux; (e) H_2CO, $HN(CH_3)_2$, EtOH; (f) HCO_2H, Raney Ni.

Scheme 5[a]



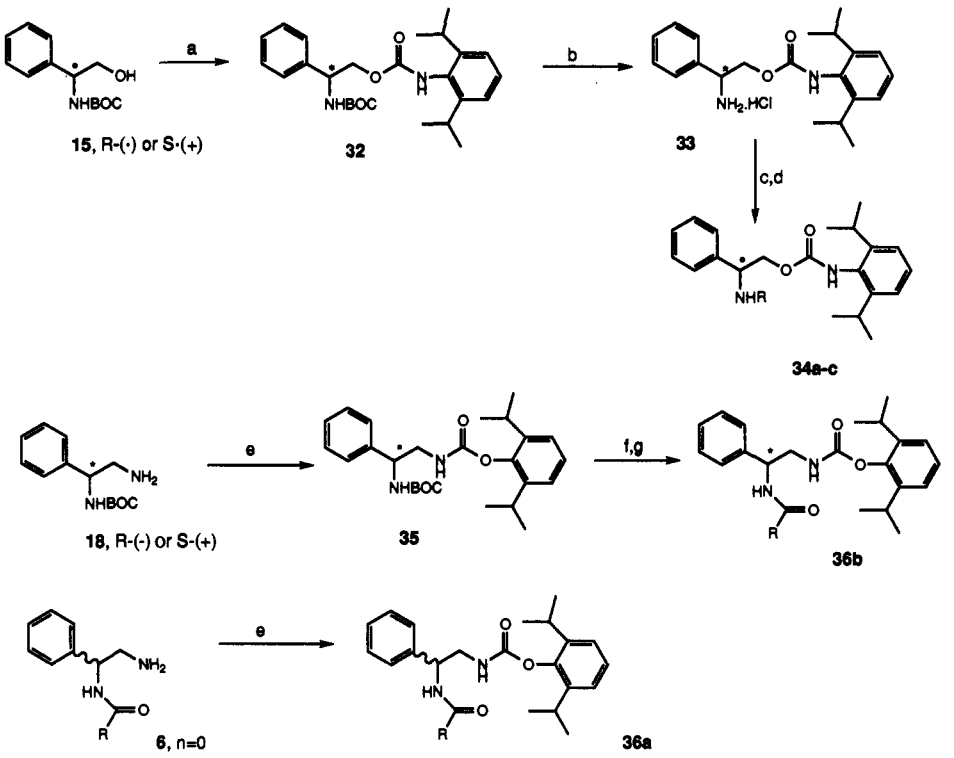
[a] (a) NaCN, NH_4Cl, NH_4OH, MeOH/H_2O; (b) 4-CH_3OPhCOCl, NEt_3, THF; (c) Raney Ni, H_2, MeOH, 50 psi; (d) 2,6-diisopropylphenyl isocyanate, EtOAc; (e) LAH, THF; (f) CH_3SO_2Cl, NEt_3, CH_2Cl_2; (g) NaN_3, DMF; (h) HCl, CH_2Cl_2; (i) RCHO, Na_2SO_4, MeOH; (j) $NaBH_4$, THF.

lowering plasma cholesterol in cholesterol-fed rats (36% vs 38%, respectively), despite being 22 times less potent in vitro. Homologation of selected compounds gave compounds **7b'**, **7c'**, and **7e'** in which the alkyl amide moiety is positioned γ to the urea moiety (n = 1, Table 1). These compounds were less active in vitro than the corresponding β-substituted compounds (**7b**, **7c**, and **7e**).

Qualitatively, this series behaves in a similar manner to that reported earlier[8] in that in vitro potency decreases with lipophilicity below a CLOGP of about 6. Above this point, high in vitro potency ceases to be dependant on lipophilicity. In vivo activity, however, is lost in the highest homologs, most likely due to excessive lipophilicity or minimal solubility.

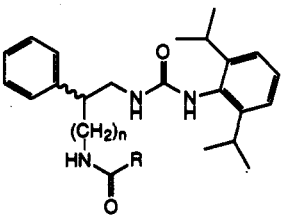
A variety of aryl and heteroaryl amides were then examined for their effects on ACAT both in vitro and in vivo (Table 2). Compound **7k**, in which the phenyl group is positioned β with respect to the urea moiety, was found to be 7 times more potent than **13** (IC_{50} = 3.6 μM), a compound in which the phenyl group is positioned α to the urea moiety; however, neither was effective in vivo. This is entirely consistent with the special benefit of the placement of the phenyl group β to the urea group identified in the earlier aralkylurea series.[8] Likewise, the homolog of **7k** (**7k'**), was 4-fold less potent in vitro. Substitution of the phenyl group in **7k** with a limited number of both electron-withdrawing (**7n** and **7o**) and electron-donating groups (**7l** and **7m**) gave no increase in potency. The result of replacing the β-phenyl moiety, of compound **7m**, with other groups is shown in Table 3. The bis-propyl analog, **24b**, was 3.6 times more potent than **7m** and more efficacious in vivo. Other modifications such as the introduction of heteroaryl, cycloalkyl, and spiro-cycloalkyl failed to give any significant increases in potency or efficacy.

Scheme 6[a]



[a] (a) 2,6-Diisopropylphenyl isocyanate, EtOAc; (b) HCl, CH_2Cl_2; (c) RCHO, Na_2SO_4, MeOH; (d) $NaBH_4$, THF; (e) 2,6-diisopropylphenyl chloroformate, EtOAc, NEt_3; (f) HCl, CH_2Cl_2; (g) RCOCl, NEt_3, THF.

Table 1. Physical and Biological Properties of Ureas Containing Alkyl-Substituted Amides

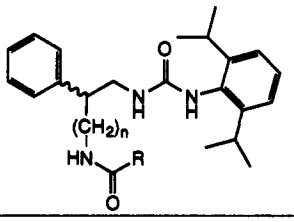


no.	R	n	formula[a]	mp, °C	IC_{50}, μM[b]	% change TC[c]	CLOGP
1, CI 976					0.073	-44*	6.27
2, PD 129337					0.017	-38*	6.33
7a	CH_3	0	$C_{23}H_{31}N_3O_2 \cdot 0.5EtOAc$	232-233	2.5	NC[d]	3.68
7b	$(CH_2)_3CH_3$	0	$C_{26}H_{37}N_3O_2$	223-225	0.43	-8	5.77
7b'	$(CH_2)_3CH_3$	1	$C_{27}H_{39}N_3O_2 \cdot 0.1H_2O$	176-177	0.61	-6	4.47
7c	$(CH_2)_5CH_3$	0	$C_{28}H_{41}N_3O_2$	187-189	0.15	NC	6.32
7c'	$(CH_2)_5CH_3$	1	$C_{29}H_{43}N_3O_2 \cdot 0.25H_2O$	195-197	0.65	NC	5.52
7d	$(CH_2)_6CH_3$	0	$C_{31}H_{47}N_3O_2$	204-205	0.59	-29*	7.91
7e	$(CH_2)_{10}CH_3$	0	$C_{33}H_{51}N_3O_2$	177-178	0.077	-16	8.97
7e'	$(CH_2)_{10}CH_3$	1	$C_{34}H_{53}N_3O_2$	157-159	0.079	NC	8.17
7f	$(CH_2)_{14}CH_3$	0	$C_{37}H_{59}N_3O_2 \cdot 0.2H_2O$	173-174	0.081	NC	11.0
7g	$(CH_2)_{16}CH_3$	0	$C_{39}H_{63}N_3O_2$	168-170	1.7	-8	12.14
7h	$(CH_2)_4CO_2CH_3$	0	$C_{28}H_{39}N_3O_4$	176-178	2.6	NC	4.18
7i	$(CH_2)CH(CH_3)(CH_2)_2CH{=}C(CH_3)_2$	0	$C_{31}H_{45}N_3O_2$	189-191	0.40	NC	7.11
7j	$(CH_2)_4CH_2Br$	0	$C_{27}H_{38}BrN_3O_2$	176-178	0.38	-36*	5.65
8k	$(CH_2)_4CH_2OCH_3$	0	$C_{28}H_{41}N_3O_3 \cdot 0.2H_2O$	186-187	0.38	NC	4.38
8l	$(CH_2)_4CH_2NH_2$	0	$C_{27}H_{40}N_4O_2 \cdot HBr, H_2O$	188-190	>5	NC	4.38
8m	$(CH_2)_4CH_2N(CH_3)_2$	0	$C_{29}H_{44}N_4O_2 \cdot 0.6HBr$	165-169	4.2	NC	4.22
8n	$(CH_2)_4CH_2N((CH_2)_2OH)_2$	0	$C_{31}H_{48}N_4O_4 \cdot 0.25H_2O$	147-150	2.8	-4	3.29
8o	$(CH_2)_4CH_2$—N N—CO_2ET	0	$C_{34}H_{51}N_5O_4 \cdot 0.3EtOAc$	163-165	2.8	NC	6.02

[a] Analytical results are within ±0.4% of the theoretical values unless otherwise noted. [b] ACAT inhibition in vitro, intestinal microsomes isolated from cholesterol-fed rabbits. Each determination performed in triplicate. See ref 3 for complete protocol. [c] Denotes percent change in total cholesterol in cholic acid (0.5%)-cholesterol (1.5%)-peanut oil (5.5%)-fed rats. See ref 12 for complete protocol. Unless otherwise noted, 50 mg/kg of inhibitor was administered as the standard dose. [d] NC denotes no change. * Denotes significantly different from control, $p < 0.05$ using analysis of variance followed by Fisher's multiple range test.

The heteroaryl amide inhibitors (**7q-x**) were more active, both in vitro and in vivo, than the alkyl and aryl amides. The 2-pyridyl analog, **7u**, was very potent in vitro but only lowered plasma cholesterol by 24% in the cholesterol fed rat. However, the corresponding *N*-oxide, **7v**, although essentially equipotent with **7u**, was more efficacious in vivo than **7u**, **1**, or **2**. In addition to this, the CLOGP value was 2.65, well below the 6-12 range previously

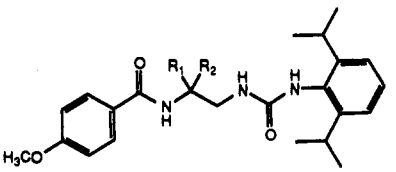
Table 2. Physical and Biological Properties of Ureas Containing Aryl- and Heteroaryl-Substituted Amides



no.	R	*n*	formula[a]	mp, °C	IC_{50}, μM[b]	% change TC[c]	CLOGP
7k	Ph	0	$C_{28}H_{33}N_3O_2 \cdot 0.1EtOAc$	249–250	0.53	NC[d]	5.37
7k'	Ph	1	$C_{29}H_{35}N_3O_2 \cdot 0.8H_2O$	156–160	1.90	NC	4.82
7l	4-CH_3Ph	0	$C_{29}H_{35}N_3O_2$	247–249	0.35	−1	5.87
7m	4-CH_3OPh	0	$C_{29}H_{35}N_3O_3$	244–245	0.33	−7	5.57
7n	4-CF_3Ph	0	$C_{29}H_{32}F_3N_3O_2$	270–272	0.51	−9	6.61
7o	2,6-Cl_2Ph	0	$C_{28}H_{31}Cl_2N_3O_2 \cdot 0.4H_2O$	230–232	1.20	NC	5.26
7p	1-naphthyl	0	$C_{32}H_{35}N_3O_2$	240–242	0.97	−14	6.55
7q	2-quinolinyl	0	$C_{31}H_{34}N_4O_2 \cdot 0.4H_2O$	193–195	0.15	−31*	5.95
7r	2-quinolinyl *N*-oxide	0	$C_{31}H_{34}N_4O_3 \cdot 0.2H_2O$	176–181	0.15	−21[e]	4.03
7s	2-indolyl	0	$C_{30}H_{34}N_4O_2 \cdot 0.2H_2O$	>225	2.3	−3	5.63
7t	2-furanyl	0	$C_{26}H_{31}N_3O_3$	190 dec	0.44	−37*	4.55
7u	2-pyridyl	0	$C_{27}H_{32}N_4O_2$	197–199	0.080	−24*	4.75
7u'	2-pyridyl	1	$C_{28}H_{34}N_4O_2$	181–184	0.30	−7	5.01
7v	2-pyridyl *N*-oxide	0	$C_{27}H_{32}N_4O_3 \cdot 0.5H_2O$	105–110	0.13	−44*	2.65
7w	4-pyridyl	0	$C_{25}H_{32}N_4O_2$	172–174	3.2	−12	4.57
7x	2-pyrazinyl	0	$C_{26}H_{31}N_5O_2$	178–181	0.44	−19*	3.73

[a–d,*] Refer to footnotes in Table 1. [e] Dosed with 30 mg/kg of test compound.

Table 3. Physical and Biological Properties of Ureas Bearing β-Substituents Other Than Phenyl



no.	R_1	R_2	formula[a]	mp, °C	IC_{50}, μM[b]	% change TC[c]	CLOGP
24a	CH_3	CH_3	$C_{25}H_{35}N_3O_3$	foam	2.5	−9[d]	4.79
24b	$(CH_2)_2CH_3$	$(CH_2)_2CH_3$	$C_{29}H_{43}N_3O_3$	161–162	0.090	−25[e]	6.90
24c	$-(CH_2)_4-$		$C_{27}H_{37}N_3O_2$	158–159	0.50	−6[e]	5.57
24d(±)	cyclohexyl	H	$C_{29}H_{41}N_3O_3$	231–232	0.25	−15[e]	6.51
24e(±)	2-Pyridyl	CH_3	$C_{29}H_{36}N_3O_3$	154–158	0.61	−23*[e]	4.51

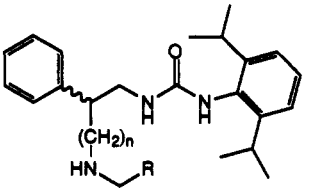
[a–e,*] Refer to footnotes in Tables 1 and 2.

discussed. Introduction of a second nitrogen atom into the pyridyl ring of **7u** gave a compound, **7x**, which was 5.5 times less potent in vitro, but equally effective in vivo. In general, compounds in these series were considerably less lipophilic (CLOGP range 3–6) than the alkyl amides in Table 1.

The most profound changes in both potency and efficacy occurred when the amides were replaced by the corresponding amines (Tables 4–6). Reduction of the amides to the corresponding amines resulted, in general, in increased potency in vitro and increased efficacy in vivo. In Table 4, for example, conversion of alkyl amide **7e** to the amine **9e** resulted in a 1.7-fold increase in potency and a dramatic increase in efficacy (from a nonsignificant 16% decrease in plasma cholesterol for **7e** to a 45% decrease for **9e**). The changes were even more dramatic for the homolog, **9e'**, which lowered plasma cholesterol by 54%, whereas the corresponding amide, **7e'**, failed to lower plasma cholesterol in cholesterol-fed rats. Most of the alkylamines examined displayed good in vivo efficacy, regardless of the chain length; however, the highly lipophilic compounds, **9f** and **9g**, were inactive in vivo, but the cyclopropylmethyl compound, **9a**, was very efficacious, despite its relatively low CLOGP of 5.25. Again, we observed an apparent dependency on lipophilicity as measured by CLOGP (6–12 range) for in vivo efficacy. Alkylation of the secondary amine moiety with methyl iodide or benzyl bromide gave compounds **10a** and **10b**, which were poor ACAT inhibitors in vitro (IC_{50}'s = >10 and 7.6 μM, respectively).

The same general observation was made with the arylamines (Table 5). Reduction to the benzylamines **9k–t** resulted in much more potent compounds which gave far superior efficacy. There was a 10-fold increase in potency observed with the conversion of benzamide **7k** to the racemic benzylamine **9k**, as well as a significant increase in efficacy. In general, there was little difference in efficacy between the enantiomers, and there was a small difference in potency between the enantiomers of **9k** (the (−) enantiomer was 1.6-fold more potent than the (+) enantiomer); however, the in vivo efficacy was comparable. This observation was also noted for **9m**, where racemate and enantiomers showed much greater plasma cholesterol lowering than **2**. For **9n**, however, the (+) enantiomer was 2-fold more potent in vitro than the (−) enantiomer. The homolog, **9k'**, was more efficacious than **9k** despite being 3-fold less potent. A variety of electron-withdrawing and electron-donating substituents on the phenyl ring were examined, and a number of them (e.g., **9l–o,r,t**) had efficacy exceeding that of **2**, and some compounds (e.g., **9l–n**) had greater potency and efficacy than **1**. A number of heterocyclic alkylamines were prepared, and surprisingly,

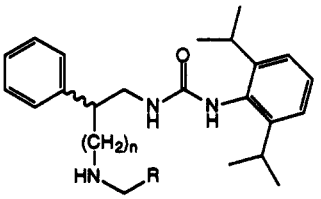
Table 4. Physical and Biological Properties of Ureas Containing Alkyl-Substituted Amines



no.	R	n	formula[a]	mp, °C	IC_{50}, μM[b]	% change TC[c]	CLOGP
9a(−)	cyclopropyl	0	$C_{25}H_{35}N_3O$	188–190	0.064	−51*[e]	5.25
9b(±)	$(CH_2)_3CH_3$	0	$C_{28}H_{39}N_3O$	178–179	0.11	−38*	6.39
9j(±)[f]	$(CH_2)_4CH_3$	0	$C_{27}H_{41}N_3O$	150–152	0.049	−41*	6.92
9c(±)	$(CH_2)_5CH_3$	0	$C_{28}H_{43}N_3O$	104–107	0.11	−25	7.45
9d(±)	$(CH_2)_8CH_3$	0	$C_{31}H_{49}N_3O$	oil[g]	0.083	−38*	7.91
9e(±)	$(CH_2)_{10}CH_3$	0	$C_{33}H_{53}N_3O$	oil[g]	0.045	−45*	10.10
9e′(±)	$(CH_2)_{10}CH_3$	1	$C_{34}H_{55}N_3O$	oil[g]	0.11	−54*	9.26
9f(±)	$(CH_2)_{14}CH_3$	0	$C_{37}H_{61}N_3O$	80–82	0.12	NC[d]	12.20
9g(±)	$(CH_2)_{16}CH_3$	0	$C_{39}H_{65}N_3O$	84–86	0.23	−3	13.30

[a–e,*] Refer to footnotes in Tables 1 and 2. [f] This compound was prepared by reductive dehalogenation of **7j**. [g] Purified by flash chromatography on silica gel.

Table 5. Physical and Biological Properties of Ureas Containing Aryl- and Heteroaryl-Substituted Methyleneamines



no.	R	n	formula[a]	$[\alpha]_D$,[j] deg	mp, °C	IC_{50}, μM[b]	% change TC[c]	CLOGP
9k(±)	Ph	0	$C_{28}H_{35}N_3O$		186–187	0.051	−36*	5.65
9k(+)[k]	Ph	0	$C_{28}H_{55}N_3O$	+23 (1%)	181–182	0.053	−41*	5.65
9k(−)[l]	Ph	0	$C_{28}H_{35}N_3O$	−23 (1%)	180–181	0.033	−29*	5.65
9k′	Ph	1	$C_{29}H_{37}N_3O$		135–138	0.16	−46*	5.47
9l(±)	4-CH_3Ph	0	$C_{29}H_{37}N_3O$		159–162	0.052	−45*	6.15
9m(±)	4-CH_3OPh	0	$C_{29}H_{37}N_3O_2$		145–146	0.048	−54	5.57
9m(−)[m]	4-CH_3OPh	0	$C_{29}H_{37}N_3O_2$	−23 (1%)	143–144	0.039	−45*[e]	5.57
9m(+)[n]	4-CH_3OPh	0	$C_{29}H_{37}N_3O_2$	+21 (1%)	144	0.070	−36*[e]	5.57
9n(−)[o]	4-$(CH_3)_2$NPh	0	$C_{30}H_{40}N_4O$	−17 (1%)	163–164	0.15	−45*	5.85
9n(+)[p]	4-$(Ch_3)_2$NPh	0	$C_{30}H_{40}N_4O$	+19 (1.1%)	160–162	0.060	−56*	5.85
9o(−)	4-$(CH_3)_2NCH_2$Ph	0	$C_{31}H_{42}N_4O$	−20 (1%)	foam	0.17	−57*	5.46
9p(−)	2-CH_3OPh	0	$C_{29}H_{37}N_3O_2$	NA	162–164	0.045	−23*	5.59
9q(−)	2-CF_3Ph	0	$C_{29}H_{34}F_3N_3O{\cdot}0.4H_2O$	−17 (1.1%)	176–178	0.045	−42*	6.53
9r(−)	2-HOPh	0	$C_{28}H_{35}N_3O_2$	−18 (1.1%)	156–157	0.12	−50*	4.98
9s(−)	3-O_2NPh	0	$C_{28}H_{34}N_4O_3$[h]	−12 (1.1%)	166–168	0.045	−32*	5.39
9t(−)	3-$(CH_3)_2NCH_2$-4-HOPh	0	$C_{31}H_{42}N_4O_2$	−9.8 (1.1%)	foam	0.49	−46*	4.80
9u(+)	2-pyridyl	0	$C_{27}H_{34}N_4O{\cdot}0.25H_2O$	+16 (1%)	185–187	0.14	−15	4.17
9v(+)	3-pyridyl	0	$C_{27}H_{34}N_4O$	+0.4 (1%)	148–151	0.37	−26*[e]	4.17
9w(+)	4-pyridyl	0	$C_{27}H_{34}N_4O$[i]	+11 (1.2%)	196–198	1.2	−19*[e]	4.17
9x(−)	2-furanyl	0	$C_{26}H_{33}N_3O_2{\cdot}0.2H_2O$	−29 (1%)	188–190	0.048	−18[e]	4.83
9x(+)	2-furanyl	0	$C_{26}H_{35}N_3O_2$	+25 (1%)	175–178	0.099	−23*	4.83
9y(−)	3-furanyl	0	$C_{28}H_{33}N_3O_2$	−24 (1%)	175–176	0.048	−38*[e]	4.83
9z(+)	2-thienyl	0	$C_{26}H_{33}N_3OS$	+16 (0.6%)	208–210	0.051	−19	5.30

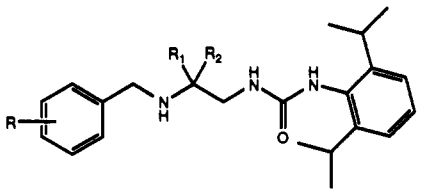
[a–g,*] Refer to footnotes in Tables 1, 2, and 4. [h] Analysis: C: calcd 70.86, found 71.33; H: calcd 7.22, found 7.26; N: calcd, 11.80, found 11.95. [i] C: calcd 75.31, found 75.51; H: calcd 7.96, found 7.50; N: calcd 13.02, found 12.89. [j] Rotations were determined in $CHCl_3$. NA denotes not available. HPLC analysis: [k] t_R = 11.7 min, 100% ee; [l] t_R = 13.5 min, 91% ee; [m] t_R = 18.3 min, 75% ee; [n] t_R = 16.3 min, 100% ee; [o] t_R = 18.2 min, 97% ee; [p] t_R = 16.2 min, 94% ee.

the amines, in general, were less efficacious than the corresponding amides. For example, amine **9u** was equipotent to amide **7u**, in vitro, but was not efficacious in vivo. In the case of the 2-furyl derivative, **7t**, there was a significant 37% decrease in plasma cholesterol in cholesterol-fed rats; however, for the amine there was only a nonsignificant 18% lowering, despite the fact that **9x** was approximately 1 order of magnitude more potent than **7t**. The results of replacing the β-phenyl moiety of **9m** are shown in Table 6. Replacing this phenyl group with some of the substituents found on naturally occurring amino acids led to compounds **31a–d** which were not as efficacious when compared to **9m**; however, **31e** was equiefficacious when compared to **9r**, despite being 3.5-fold less potent.

Two regioisomeric carbamates can exist in which either one of the urea nitrogen atoms can be replaced by an oxygen atom. When the aniline-type nitrogen of the urea was replaced by oxygen, there was no change in activity either in vitro and in vivo. For example, compounds **36a,b** (Table 7) have virtually the same in vitro potencies as their urea counterparts, **7d,e**. The regioisomeric carbamate, i.e., **34b**, was 4-fold less potent than **36b**. This mirrors observations in other urea series.[7,8]

Selected compounds were then evaluated in the chronic cholesterol-fed rat screen. The results are shown in Table 8. As can be seen, compound **2** was ineffective in this model, whereas compound **3** lowers plasma non-HDL cholesterol by 62% and elevates HDL cholesterol by 200%.

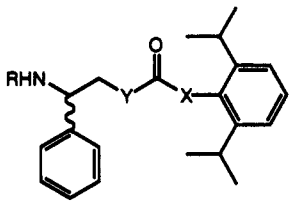
Table 6. Physical and Biological Properties of Ureas Derived from Amino Acids



no.	R	R_1	R_2	formula[a]	$[\alpha]_D$,[j] deg	mp, °C	IC_{50}, μM[b]	% change TC[c]	CLOGP
31a(−)	4-CH_3O	$CH_2CH(CH_3)_2$	H	$C_{27}H_{41}N_3O_2$	−20 (1%)	138–139	0.050	−32*	6.18
31b(+)	4-CH_3O	$(CH_2)_2SCH_3$	H	$C_{26}H_{37}N_3O_2S$	+8 (1%)	96–97	0.49	−31*	4.87
31c(−)	4-CH_3O	$CH(CH_3)_2$	H	$C_{26}H_{37}N_3O_2$	NA	88–90	0.080	−41*	5.65
31d(−)	4-CH_3O	CH_2Ph	H	$C_{30}H_{39}N_3O_2$	−13 (0.7%)	125–126	0.27	−30*[q]	5.57
31e(−)	2-HO	CH_2Ph	H	$C_{29}H_{37}N_3O_2$	−10 (1%)	120–121	0.41	−37*	4.99

[a–c,*] Refer to footnotes in Table 1. [j] Rotations were determined in $CHCl_3$. [q] Dosed at 10 mg/kg.

Table 7. Physical and Biological Properties of Carbamates Containing Amide or Amine Functionalities



no.	R	X	Y	formula[a]	$[\alpha]_D$,[j] deg	mp, °C	IC_{50}, μM[b]	% change TC[c]	CLOGP
32(−)	$[(CH_3)_3C]OCO$	NH	O	$C_{26}H_{36}N_2O_4 \cdot 0.2H_2O$	−24 (0.7%)	170–172	2.5	NT[r]	6.08
34a(+)	$CH_3(CH_2)_5CO$	NH	O	$C_{28}H_{40}N_2O_3$	+37 (1%)	140–142	5.1	NT	6.81
34a(−)	$CH_3(CH_2)_5CO$	NH	O	$C_{28}H_{40}N_2O_3$	−37 (1.1%)	137–139	0.57	−2	6.81
34b(−)	$CH_3(CH_2)_{10}CO$	NH	O	$C_{33}H_{50}N_2O_3$	−23 (0.5%)	105–106	0.20	−16[e]	9.46
34c(−)	4-$(CH_3)_2NCH_2Ph$	NH	O	$C_{30}H_{39}N_3O_2 \cdot 2HCl$	−24 (1.1%)	175 dec	0.96	−23*	6.34
35(−)	$[(CH_3)_3C]OCO$	O	NH	$C_{26}H_{36}N_2O_4$	−55 (1%)	199–200	0.43	−20*	6.79
36a(±)	$CH_3(CH_2)_8CO$	O	NH	$C_{31}H_{46}N_2O_3$		189–190	0.76	−25*	9.11
36b(−)	$CH_3(CH_2)_{10}CO$	O	NH	$C_{33}H_{50}N_2O_3 \cdot 0.1H_2O$	−59 (1%)	144–146	0.051	−25*[e]	10.17

[a–e,*] Refer to footnotes in Tables 1 and 2. [j] Rotations were determined in $CHCl_3$. [r] NT = not tested.

Table 8. Efficacy Data for Selected Compounds in the Chronic Cholesterol-Fed Rat Model

no.	dose, mg/kg	% change in HDL	% change in non-HDL
2	50	−12	−7
3	50	+200*	−62*
7v	50	+70*	−31*
9e	50	+29	+27
9e′	50	N/C	+15
9n(−)	50	+256[s]*	−47*
9n(+)	50	+350[t]*	−57*
9r(−)	50	+40*	+3

[s] Dosed as the HCl salt. [t] Body-weight gain was less than controls. For the experimental protocol, see ref 12. * Denotes significantly different from control, $p < 0.05$ using analysis of variance followed by Fisher's multiple range test.

The most efficacious amide (see Table 2), **7v**, in the acute rat screen was also effective in the chronic rat model, lowering non-HDL cholesterol by 31% and elevating HDL by 70%. In the alkylamine series (see Table 4), both compounds evaluated, **9e** and **9e′**, two of the most potent compounds in the acute rat screen (APCC), were inactive in this screen. However, some of the benzylamines (see Table 5) evaluated showed excellent efficacy in this model. The most efficacious compound identified in this screen, **9n**(−), lowered plasma non-HDL cholesterol by 47% and elevated HDL by 256%. Interestingly, the (+) enantiomer of this compound was comparable in efficacy to **3** and even more effective than the (−) enantiomer at elevating plasma HDL cholesterol; however, it must be noted that the body-weight gain in the animals that were dosed with this compound was less than that observed for the control animals, which could contribute to the dramatic increase in plasma HDL cholesterol.

Conclusions

The object of this SAR study was to modify compounds of the structural type exemplified by compound **2**, in order to improve efficacy in chronic models of preestablished hypercholesterolemia regardless of vehicle choice. In the preceding paper of this series, an investigation into substituent effects on the β-phenyl moiety of **2** yielded **3**, a compound which showed good efficacy in the chronic model.[1] This paper describes an alternative strategy for the modification of **2**, namely replacement of the spirocyclopentyl moiety by various amide and amine groups. Several conclusions can be formed from the various structure–activity relationships discussed in the previous section.

(i) Replacement of the spirocyclopentyl moiety with a variety of alkyl amides and alkylamines gave compounds which were not as potent as **2** in vitro. However, some amines were significantly more efficacious in vivo (e.g., **9a**,**e**, **9e′**). In general, the amines were more potent and efficacious than the amides in the acute rat model of hypercholesterolemia. A weak parabolic relationship of in vitro potency with CLOGP was demonstrated for the previously reported aralkylurea series.[8] A similar trend was obtained for this related series, especially with respect to the rapid falloff of potency, and in most cases, efficacy, as the CLOGP fell much below 6. Specific structural features, such as amine vs amide or α vs β attachment of the amine-containing group, play a more significant role in modulating the in vitro potency level. The best balance between potency and efficacy appears to fall in the CLOGP range between about 5.5 and 7.

(ii) Replacement of the spirocyclopentyl moiety with a variety of aryl and heteroaryl amides and aryl- and heteroarylamines gave compounds which, in general, were much more efficacious than the alkylamines previously discussed. The amines of these series of compounds obeyed the general relationship between lipophilicity and in vitro potency; however, the potency of the amides seemed to be largely controlled by other, less well defined factors.

(iii) In this study, the presence of a secondary amine is necessary for in vitro potency; the tertiary amines were poor ACAT inhibitors. This suggests that there is a role for a hydrogen atom in this region (the amides examined also have this hydrogen atom) either for inter- or intramolecular hydrogen bonding. It is worth noting in this connection that the heterocyclic amides, which are more active than expected (e.g., **7r,u,v**, but not **7s** or **7w**), all have ortho heteroatoms or substituents capable of acting as intramolecular H-bond acceptors to the adjacent amide NH. This may cause the CLOGP to be considerably underestimated for these compounds, since corrections for this are not part of the CLOGP algorithm employed. Alternatively, more favorable conformations of H-bonding potentialities may be stabilized in this subset of compounds by this feature.

(iv) The presence of a chiral center β to the urea moiety has little effect on the in vitro and in vivo activities.

(v) The preferred position of the phenyl group is β to the urea moiety and not α (compare the activities of **7k** and **13**). Replacement of the β-phenyl by other groups gave less efficacious compounds.

(vi) Carbamates, in which the aniline nitrogen atom of the urea moiety is replaced by oxygen, are as potent and efficacious as the ureas. The regioisomeric carbamates, however, are much less active, thus suggesting that the non-aniline nitrogen atom of the urea moiety is involved in some type of intramolecular hydrogen bonding necessary for potent ACAT inhibition.

In conclusion, we have demonstrated that compounds of type **2** can be modified by the introduction of polar functional groups. The strategy of replacing the spirocyclopentyl moiety of compound **2** by polar functionalities complements the earlier strategy of introducing polar substituents into the β-phenyl of compound **2**.[1] Many of the compounds from either strategy, especially those which may be protonated upon in vivo administration (thus possibly providing some limited absorption), show improved in vivo efficacy.

In this study, one compound, **9n(−)**, was more efficacious than **2**, and comparable to compound **3**, in the chronic cholesterol-fed rat model.

Experimental Section

Unless otherwise noted, starting materials were obtained from commercial suppliers and used without further purification. All organic extracts were dried over $MgSO_4$, except when otherwise noted. Melting points were determined on a Thomas–Hoover melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra were determined on either a Varian EM-390 or a Varian XL-200 spectrometer. Chemical shifts (δ) are expressed in ppm, relative to internal tetramethylsilane. Mass spectra were obtained on a VG Masslab Trio-2A, a VG Analytical 7070E/HF, or a Finnigan 4500 mass spectrometer. Elemental analyses were determined on a Perkin-Elmer 240C elemental analyzer and were within ±0.4% unless otherwise noted. Optical rotations were performed on a Perkin-Elmer 241 polarimeter. Chiral HPLC analyses were performed using a Waters 600E high-performance system equipped with a Lambda-Max 481 spectrophotometer with a detection wavelength of 254 nm, and a Chiralcel OD 5-μM column (Diacel Chem Ind. Ltd.), and a mobile phase of 96% hexane, 2.0% 2-propanol, 1.9% acetonitrile, and 0.1% diethylamine.

(±)-*N*-(Cyanophenylmethyl)benzamide (5k). To a solution of **4** (2 g, 15.1 mmol) and triethylamine (1.5 g, 15.1 mmol) in dry THF (40 mL) was added, dropwise, benzoyl chloride (2.3 g, 16.4 mmol). The suspension was stirred at room temperature for 2 h. The precipitate was filtered and the filtrate diluted with ethyl acetate (40 mL). The solution was washed with aqueous HCl (1 M), NaOH (1 M), and brine. The organic phase was dried and filtered, and the filtrate was concentrated in vacuo. The residue was triturated with hexane and collected by filtration to give **5k** (3.4 g, 94%): mp 145–146 °C; ^{1}H NMR ($CDCl_3$) δ 7.8 (d, 2H), 7.5 (m, 3H), 7.4 (m, 5H), 6.8 (d, 1H), 6.3 (d, 1H) ppm; Cl-MS *m/e* 237 $(M + H)^+$. Anal. ($C_{15}H_{12}N_2O$) C, H, N.

(±)-*N*-(2-Amino-1-phenylethyl)benzamide (6k). A solution of **5k** (3 g, 12.7 mmol) in methanolic ammonia (100 mL) was treated with Raney nickel (1.5 g) and hydrogenated at room temperature under 50 psi overnight. The catalyst was filtered and the filtrate concentrated in vacuo. The crude product was triturated with hexane and collected by filtration to give compound **6k** as the free base (2.9 g, 95%): ^{1}H NMR (DMSO-d_6) δ 8.4 (bs, 1H), 7.8 (m, 2H), 7.5 (m, 4H), 7.4 (m, 4H), 4.8 (bs, 1H), 2.9 (bs, 2H) ppm.

(±)-*N*-[2-[[[[2,6-Bis(1-methylethyl)phenyl]amino]carbonyl]amino]-1-phenylethyl]benzenecarboxamide (7k). To a solution of **6k** (2.8 g, 11.6 mmol) in dry tetrahydrofuran (100 mL) was added 2,6-diisopropylphenyl isocyanate (2.4 g, 11.6 mmol) in one portion. The solution was stirred at room temperature. After stirring for 2 h, the suspension was filtered and the solid washed with hexane to give **7k** (3.4 g, 66%): mp 249–250 °C; ^{1}H NMR (DMSO-d_6) δ 9.0 (bs, 1H), 7.8 (d, 2H), 7.5–7.1 (m, 12H), 6.3 (bs, 1H), 5.1 (bs, 1H), 3.5 (m, 2H), 3.0 (m, 2H), 1.1 (dd, 12H) ppm; Cl-MS *m/e* 444 $(M + H)^+$. Anal. ($C_{28}H_{33}N_3O_2$·0.1EtOAc) C, H, N.

Compounds **7a–j,l–q,s–u,w–x** and **7b′,c′,e′,k′,u′** were synthesized utilizing similar reaction conditions. For heterocyclic analogues, amides were prepared by coupling (±)-2-phenylglycinonitrile with appropriately substituted heteroaryl carboxylic acids, as represented by the following example.

(±)-*N*-[2-[[[[2,6-Bis(1-methylethyl)phenyl]amino]carbonyl]amino]-1-phenylethyl]-2-pyridinylamide (5u). To a tetrahydrofuran (20 mL) suspension of 2-picolinic acid (0.72 g, 5.9 mmol) at room temperature under N_2 was added 1,1′-carbonyldiimidazole (1.1 g, 6.4 mmol), and after 5 min complete dissolution occurred. A THF solution (10 mL) of the free amine of (±)-2-phenylglycinonitrile hydrochloride (1.0 g, 5.9 mmol) was added to the previously prepared solution of 2-picolinic acid and CDI and stirred at room temperature for 24 h. Water was added and the layers were separated. The organic phase was washed with water and brine, dried, and filtered, and the filtrate was concentrated in vacuo. The crude product was recrystallized from ethyl acetate/hexane to give **5u** (0.67 g, 48%): ^{1}H NMR ($CDCl_3$) δ 8.5 (d, 1H), 8.3 (d, 1H), 7.9 (tt, 1H), 7.5 (m, 2H), 7.4 (m, 5H), 6.3 (d, 1H); El-MS *m/e* 237 (M^+). Anal. ($C_{14}H_{11}N_3O$) C, H, N.

The heterocyclic amides **7q–x** were synthesized from **5q–x** by employing the reaction conditions previously described for compounds **6k** and **7k**.

(±)-*N*-[2,6-Bis(1-methylethyl)phenyl]-*N′*-[2-phenyl-2-(benzylamino)ethyl]urea (9k). A solution of **7k** (3.0 g, 6.8 mmol) and sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) (29 mL, 6.8 mmol) in toluene (250 mL) was heated at reflux for 1.5 h, cooled to 0 °C, and then quenched by the dropwise addition of aqueous NaOH (1 M). The product was extracted with ethyl acetate, dried, and filtered. The filtrate was concentrated in vacuo to give a white solid that was triturated with hexane and filtered to give analytically pure **9k** (2.0 g, 68%): mp 186–187 °C; ^{1}H NMR ($CDCl_3$) δ 7.5 (bs, 1H), 7.4–7.1 (m, 15H), 6.2 (bs, 1H), 3.7 (m, 1H), 3.5 (m, 2H), 3.2 (m, 2H), 3.1 (m, 2H), 2.6 (bs, 1H), 1.0 (d, 12H) ppm; El-MS *m/e* 430 (M^+). Anal. ($C_{28}H_{35}N_3O$) C, H, N.

Compounds **9b–g**,l–m, and **9e′,k′** are additional examples synthesized in this manner.

(±)-*N*-[2,6-Bis(1-methylethyl)phenyl]-*N'*-[2-[methyl(phenylmethyl)amino]-2-phenylethyl]urea (10a). To a solution of **9k** (1.0 g, 2.3 mmol) in anhydrous DMF (20 mL) was added sodium hydride (0.22 g, 5.3 mmol) in several portions under an atmosphere of N_2. The solution was stirred at room temperature for 5 min followed by the addition of iodomethane (0.49 g, 3.4 mmol) in one portion. Alkylation was complete after 2 h, at which time water was cautiously added and the product extracted with several portions of ethyl ether. The extracts were combined and washed with brine, dried, filtered, and concentrated in vacuo. The resulting colorless liquid was purified on silica gel (elution with 50% EtOAc/hexane) to yield **10a** (0.5 g, 48%) as a white solid: mp 116–117 °C; ^{1}H NMR ($CDCl_3$) δ 7.4 (t, 1H), 7.4–7.2 (m, 12H), 7.0 (d, 2H), 2.4 (t, 1H), 3.7 (m, 2H), 3.6–3.4 (m, 2H), 3.2 (s, 3H), 2.9 (m, 2H), 1.1 (dd, 12H) ppm; Cl-MS *m/e* 444 $(M + H)^+$. Anal. ($C_{29}H_{37}N_3O$) C, H, N.

Similar conditions were employed in preparing **10b**.

(±)-*N*-[2-(Hexylamino)-2-phenylethyl]-*N'*-[2,6-bis(1-methylethyl)phenyl]urea (9j). Via the general procedure for **9k** only substituting **7j** (1.0 g, 1.9 mmol) for **7k** in a toluene solution (20 mL) containing Red-Al (0.6 mL, 2.0 mmol), target compound **9j** (0.52 g, 54%) was obtained: mp 150–152 °C; ^{1}H NMR (DMSO-d_6) δ 7.5 (bs, 1H), 7.4–7.2 (m, 6H), 7.1 (d, 2H), 6.1 (bs, 1H), 3.6 (bs, 1H), 3.2–3.0 (m, 4H), 2.3 (m, 2H), 2.0 (bs, 1H), 1.4–1.0 (m, 20H), 0.8 (t, 3H) ppm; Cl-MS *m/e* 424 $(M + H)^+$. Anal. ($C_{27}H_{41}N_3O$) C, H, N.

(±)-*N*-(Cyanophenylmethyl)-*N'*-[2,6-bis(1-methylethyl)phenyl]urea (11). To a dichloromethane solution (10 mL) of the HCl salt of **4** (1.0 g, 5.9 mmol) and triethylamine (0.6 g, 5.9 mmol) was added 2,6-diisopropylphenyl isocyanate (1.2 g, 5.9 mmol) in one portion. The solution was stirred at room temperature for 16 h and then washed with water. The organic phase was dried, filtered, and concentrated in vacuo to give a yellow solid. The crude product was recrystallized from hexane/EtOAc affording analytically pure **11** (740 mg, 38%): mp 198–199 °C; ^{1}H NMR (DMSO-d_6) δ 7.6 (bs, 1H), 7.4 (m, 5H), 7.2 (t, 1H), 7.1 (d, 2H), 6.1 (d, 1H), 3.1 (m, 2H), 1.1 (d, 12H); El-MS *m/e* 335 (M^+). Anal. ($C_{21}H_{25}N_3O$) C, H, N.

(±)-*N*-(2-Amino-1-phenylethyl)-*N'*-[2,6-bis(1-methylethyl)phenyl]urea, Sulfate (12). Compound **11** (1.82 g, 5.4 mmol) was hydrogenated in a Parr shaker containing 20% Pd/C (0.5 g) suspended in a solution of H_2SO_4 (0.5 mL) and methanol (100 mL) under 50 psi. After 16 h, the catalyst was removed by filtration and the filtrate concentrated in vacuo. The residue was washed thoroughly with water, triturated with ethyl acetate, and collected by filtration. The solid was dried at 40 °C to give **12** (1.80 g, quant) as a white solid: mp 224–227 °C; ^{1}H NMR (DMSO-d_6) δ 7.7 (s, 1H), 7.3 (s, 5H), 7.2 (t, 1H), 7.1 (d, 2H), 6.9 (bs, 1H), 4.9 (m, 1H), 3.1 (m, 2H), 2.8 (m, 2H), 1.1 (d, 12H) ppm; Cl-MS *m/e* 340 $(M + H)^+$. Anal. ($C_{21}H_{29}N_3O \cdot 1.1H_2SO_4$) C, H, N.

(±)-*N*-[2-[[[[2,6-Bis(1-methylethyl)phenyl]amino]carbonyl]amino]-2-phenylethyl]benzamide (13). To a dichloromethane solution (10 mL) of **12** (1 g, 2.9 mmol) and triethylamine (5.9 g, 5.9 mmol) was added benzoyl chloride (0.41 g, 2.9 mmol) in one portion. After the mixture was stirred for 1 h, a gelatinous precipitate was collected by filtration and washed with methanol to give analytically pure **13** (0.5 g, 39%): mp 224–226 °C; ^{1}H NMR (DMSO-d_6) δ 8.7 (bs, 1H), 7.8 (bs, 2H), 7.5 (m, 5H), 7.3 (m, 4H), 7.1 (m, 3H), 6.7 (bs, 1H), 5.0 (m, 1H), 3.5 (m, 2H), 3.0 (m, 2H), 1.0 (d, 12H); El-MS *m/e* 443 (M^+). Anal. ($C_{28}H_{33}N_3O_2 \cdot H_2O$) C, H, N.

(±)-*N*-[2-[[[[2,6-Bis(1-methylethyl)phenyl]amino]carbonyl]amino]-1-phenylethyl]-2-quinolinamide, *N*-Oxide (7r). To a solution of **7q** (0.66 g, 1.34 mmol) in dichloromethane (30 mL) at room temperature, under N_2, with stirring was added 3-chloroperbenzoic (mCPBA) (0.3 g). The solution was stirred at room temperature for 3 h. An additional 0.31 g of MCPBA was added, and the solution was heated to reflux overnight after which an aqueous sodium bicarbonate solution was added with stirring. The layers were separated, and the organic phase was washed with water and brine and dried, and the filtrate was concentrated in vacuo to give **7r** (0.52 g, 76%): mp 176–181 °C; ^{1}H NMR ($CDCl_3$) δ 8.8 (d, 2H), 7.8 (m, 7H), 7.3 (m, 6H), 7.1 (m, 1H), 5.7 (bs, 1H), 5.1 (m, 1H), 3.8 (m, 2H), 3.2 (m, 2H), 1.1 (s, 12H); Cl-MS *m/e* 511 $(M + H)^+$. Anal. ($C_{31}H_{34}N_4O_3 \cdot H_2O$) C, H, N.

(±)-6-[Bis(2-hydroxyethyl)amino]-*N*-[2-[[[[2,6-bis(1-methylethyl)phenyl]amino]carbonyl]amino]-1-phenylethyl]-hexanamide (8n). To a Parr shaker was added **7j** (1.0 g, 1.94 mmol), diethanolamine (0.51 g, 4.8 mmol), and 2-propanol (20 mL). The solution was agitated for 36 h at 80 °C and cooled to room temperature, and the solvent was concentrated in vacuo leaving a viscous liquid which crystallized upon treatment with water. The solid was collected by filtration and oven-dried to give **8n** (0.85 g, 81%): mp 147–150 °C; ^{1}H NMR ($CDCl_3$) δ 7.8 (bs, 1H), 7.3–7.1 (m, 8H), 6.3 (bs, 1H), 4.8 (bs, 1H), 4.5 (bs, 1H), 3.6 (m, 5H), 3.2 (m, 6H), 2.6 (m, 5H), 2.2 (t, 2H), 1.7–1.4 (m, 6H), 1.1 (bs, 12H) ppm; FAB-MS *m/e* 541 $(M + H)^+$. Anal. ($C_{35}H_{48}N_4O_4 \cdot 0.25H_2O$) C, H, N.

Similar conditions were used in preparing compounds **8k–m** and **8o** in Table 1.

(*R*)-(−)-BOC-phenylglycinol (15). To a dry THF solution (2.1 L) of **14** (100 g, 0.73 mol) was added butyloxycarbonyl (BOC) anhydride (179 g, 0.82 mol) and 4-(dimethylamino)pyridine (91.1 g, 0.74 mol). The solution was stirred at room temperature for 16 h and then concentrated in vacuo. The residue was dissolved in EtOAc (2.5 L) and washed with aqueous HCl (1 M), NaOH (1 M), and brine. The organic phase was dried, filtered, and concentrated to dryness to give a crystalline solid. The product was triturated with hexane and collected by filtration to give **15** (130 g, 75%) as a white solid: mp 135–136 °C; ^{1}H NMR ($CDCl_3$) δ 7.3 (m, 5H), 5.3 (bs, 1H), 4.7 (bs, 1H), 3.8 (bs, 2H), 2.5 (bs, 1H), 1.4 (s, 9H) ppm; El-MS *m/e* 238 (M^+); $[\alpha]_D = -39°$ (*c* = 1.0% in $CHCl_3$). Anal. ($C_{13}H_{19}NO_3$), C, H, N.

(*R*)-(−)-[2-[(Methylsulfonyl)oxy]-1-phenylethyl]carbamic Acid 1,1-Dimethylethyl Ester (16). A solution of **15** (121 g, 0.51 mol) in dichloromethane (4 L) was cooled to 0 °C, followed by the addition of triethylamine (103 g, 1.02 mol). The solution was stirred for 10 min before methanesulfonyl chloride (62.5 g, 0.56 mol) was added dropwise. The solution was stirred for 1.5 h at 0 °C and then washed with brine. The organic phase was dried, filtered, and concentrated in vacuo. The resulting solid was triturated with hexane and collected by filtration to give **16** (163 g, quant): mp 114–115 °C; ^{1}H NMR ($CDCl_3$) δ 7.3 (m, 5H), 5.2 (d, 1H), 5.0 (bs, 1H), 4.4 (m, 2H), 2.8 (s, 3H), 1.4 (s, 9H) ppm; Cl-MS *m/e* 316 $(M + H)^+$; $[\alpha]_D = -21°$ (*c* = 1% in $CHCl_3$). Anal. ($C_{14}H_{21}NO_5S$) C, H, N.

(*R*)-(−)-1-[(Butoxycarbonyl)amino]-1-phenylethyl Azide (17). To a DMF solution (1.6 L) of **16** (162 g, 0.51 mol) was added, in one portion, sodium azide (165.8 g, 2.55 mol). The reaction mixture was stirred for 4 h at 80 °C and then cooled to room temperature and treated with 2 L of water. The product was extracted with several portions of ethyl ether (2 × 1.5 L) which were combined, dried, and filtered. The filtrate was concentrated in vacuo to give a colorless liquid which was purified on silica gel (elution with 25% EtOAc/hexane) to give **17** (103 g, 77%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.3 (m, 5H), 5.2 (d, 1H), 4.9 (bs, 1H), 3.6 (d, 2H), 1.4 (s, 9H) ppm; CI-MS *m/e* 263 $(M + H)^+$; $[\alpha]_D = -8.7°$ (*c* = 1% in $CHCl_3$). Anal. ($C_{13}H_{18}N_4O_2$) C, H, N.

(*R*)-(−)-1-[(Butoxycarbonyl)amino]-1-phenylethylamine (18). A solution of **17** (103 g, 0.39 mol) in THF (1 L) was added dropwise to a chilled (−40 °C) suspension of lithium aluminum hydride (LAH) (21 g, 0.71 mol) in THF (1.6 L). The suspension was stirred for 3 h and allowed to warm to 10 °C. The mixture was furhter cooled to −35 °C and cautiously quenched with aqueous sodium bisulfate ($NaHSO_4$). The suspension was diluted with 2L of EtOAc and filtered through a pad of Celite. The filtrate was dried and filtered, and the filtrate was concentrated in vacuo to give analytically pure **18** (85.8 g, 93%): ^{1}H NMR ($CDCl_3$) δ 7.3 (m, 5H), 5.4 (d, 1H), 4.7 (bs, 1H), 3.0 (d, 2H), 1.4 (s, 9H), 1.3 (t, 2H); CI–MS *m/e* 237 $(M + H)^+$; $[\alpha]_D = -44°$ (c = 1.1% in $CHCl_3$). Anal. ($C_{13}H_{20}N_2O_2$) C, H, N.

(*R*)-(−)-*N*-[2,6-Bis(1-methylethyl)phenyl]-*N'*-[2-[(butoxycarbonyl)amino]-2-phenylethyl]urea (19). To a solution containing **18** (28.2 g, 0.12 mol) in EtOAc (900 mL) was added, in one portion, 2,6-diisoproylphenyl isocyanate (26.6 g, 0.13 mol). The resulting suspension was stirred at room temperature for 4 h and filtered, and the solid was washed with hexane to give **19**

(38.5 g, 73%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 6.9 (m, 8H), 6.8 (d, 2H), 6.7 (bs, 1H), 5.8 (bs, 1H), 4.2 (bs, 1H), 3.1 (m, 2H), 2.8 (m, 2H), 1.0 (s, 9H), 0.8 (d, 12H) ppm; CI-MS *m/e* 440 (M + H)$^+$; $[\alpha]_D$ = −37° (c = 0.5% in $CHCl_3$). Anal. ($C_{26}H_{37}N_3O_3$) H, N; C, calcd 71.02; found 70.50.

(*R*)-(−)-*N*-[2,6-Bis(1-methylethyl)phenyl]-*N'*-[2-[[(4-methoxyphenyl)methyl]amino]-2-phenylethyl]urea (9m). (a) The protected amine **19** (38.5 g, 0.087 mol) was suspended in dichloromethane (1.4 L) and treated with gaseous HCl over 30 min at room temperature. The resulting solution was concentrated to dryness to yield a white solid (35.1 g, quant) characterized as (*R*)-(−)-*N*-[2,6-bis(1-methylethyl)phenyl]-*N'*-[2-amino-2-phenylethyl]urea hydrochloride: ^{1}H NMR (DMSO-d_6) δ 8.7 (bs, 3H), 7.6 (s, 1H), 7.5 (m, 5H), 7.2 (t, 1H), 7.1 (d, 2H), 6.5 (bs, 1H), 4.4 (m, 1H), 3.6 (m, 2H), 3.0 (m, 2H), 1.0 (d, 12H) ppm; EI-MS *m/e* 340 (M$^+$). Anal. ($C_{21}H_{29}N_3O$·1.4HCl) C, H, N.

(b) The amine salt (2.5 g, 6.6 mmol) was dissolved in methanol (100 mL) and treated with anhydrous calcium sulfate (3.1 g, 22 mmol), triethylamine (0.72 g, 7.2 mmol), and 4-anisaldehyde (0.9 g, 6.6 mmol). The reaction mixture was stirred at room temperature under an atmosphere of N_2 overnight, followed by the addition of sodium borohydride (1.5 g, 39.6 mmol) in several portions. The mixture was stirred for 20 min and then poured over ice. To the aqueous suspension was added chloroform, and the layers were separated. The organic phase was dried and filtered, and the filtrate was concentrated to dryness. The residue was dissolved in 50% EtOAc/hexane and purified on silica gel (elution with 50% EtOAc/hexane) to give **9m** (2.5 g, 83%) as a white solid: mp 139–140 °C; ^{1}H NMR ($CDCl_3$) δ 7.3 (m, 9H), 6.9 (d, 2H), 6.7 (d, 2H), 5.8 (s, 1H), 4.7 (m, 1H), 3.8 (s, 3H), 3.7 (m, 1H), 3.3 (m, 2H), 3.2 (m, 2H), 1.2 (d, 12H) ppm; EI-MS *m/e* 460 (M$^+$); $[\alpha]_D$ = −23° (*c* = 1.1% in $CHCl_3$). Anal. ($C_{29}H_{37}N_3O_2$) C, H, N.

Steroisomers **9a,k,m–z** were synthesized in an identical manner.

4-[(Dimethylamino)methyl]benzaldehyde (41) was utilized in the synthesis of **9o**.

(a) 4-(Aminomethyl)benzoic Acid, Methyl Ester, Hydrochloride (38). To a solution of commercially available **37** (20 g, 0.12 mol) in methanol (600 mL) was added concentrated HCl (20 mL) in one portion. The solution was refluxed for 5 h, cooled to room temperature, and concentrated to dryness. The residue was slurried in ethyl ether and collected by filtration to give **38** (24.2 g, 98%) as a white solid: ^{1}H NMR (DMSO-d_6) δ 9.8 (bs, 3H), 7.9 (d, 2H), 7.7 (d, 2H), 4.1 (s, 2H) 3.8 (s, 3H) ppm. The product was used in the next step without further characterization.

(b) 4-[(Dimethylamino)methyl]benzoic Acid, Methyl Ester (39). To an aqueous solution (30 mL) of **38** (5 g, 0.024 mol) was added (88%) formic acid (6.5 g, 0.12 mol) and 36% aqueous formaldehyde (4.5 g). The solution was heated on a steam bath for 4 h, cooled to room temperature, and concentrated in vacuo. The resulting oil solidified upon treatment with THF. The solid was collected by filtration, dissolved, in water, and basified (pH 8–9) with aqueous NaOH (1 M). The aqueous suspension was washed with dichloromethane, the organic phase was dried and filtered, and the filtrate was concentrated in vacuo to give **39** (3.1 g, 64%) as a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 8.0 (d, 2H), 7.4 (d, 2H), 3.9 (s, 1H), 3.4 (s, 2H), 2.2 (s, 6H) ppm.

(c) 4-[(Dimethylamino)methyl]benzyl Alcohol (40). A dichloromethane solution (20 mL) of **39** (1.9 g, 9.7 mmol) was cooled to 0 °C and treated dropwise with DIBAL (1.0 M in dichloromethane, 30 mL, 30 mmol). The ice bath was removed, and the solution was stirred at room temperature for 1.5 h. The solution was recooled to 0 °C and cautiously treated with aqueous sodium hydroxide (30 mL). The mixture was filtered through a pad of Celite, and the phases were separated. The organic phase was dried and filtered, and the filtrate was concentrated in vacuo to give **40** (1.3 g, 82%) as a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 7.2 (s, 4H), 4.7 (bs, 1H), 4.5 (s, 2H), 3.3 (s, 2H), 2.1 (s, 6H) ppm.

The alcohol **40** (1.3 g, 7.8 mmol) was dissolved in toluene (40 mL) containing MnO_2 (6.1 g). The reaction mixture was refluxed for 5 h, cooled to room temperature, and filtered through Celite. The filtrate was concentrated in vacuo to give **41** (1.3 g, quant) as a viscous yellow liquid: ^{1}H NMR ($CDCl_3$) δ 10.0 (s, 1H), 7.8 (d, 2H), 7.4 (d, 2H), 3.5 (s, 2H), 2.3 (s, 6H) ppm. This was used without further purification.

3-[(Dimethylamino)methyl]-4-hydroxybenzaldehyde (44) was utilized in the synthesis of **9t**.

(a) 4-Cyano-3-[(Dimethylamino)methyl]phenol (43). A solution containing 63 mL of 40% dimethylamine (aqueous) and 38.5 mL of 36% formaldehyde (aqueous) was added, at room temperature, to an ethanolic solution (400 mL) of 4-hydroxybenzonitrile (**42**) (59.6 g, 0.50 mol). The solution was stirred overnight at ambient temperature, concentrated, and partitioned between ethyl acetate and dilute aqueous HCl. The aqueous phase was basified and the product extracted with ethyl acetate. The organic solution was washed with brine, dried, and filtered. The filtrate was concentrated in vacuo, and the crude product obtained was purified by distillation (145–150 °C/1 mmHg) to give **43** (12 g, 14%) as a yellow oil which gradually solidified on standing: ^{1}H NMR ($CDCl_3$) δ 7.3 (m, 2H), 6.78 (d, 1H), 3.7 (s, 2H), 2.3 (s, 6H) ppm.

To a solution of **43** (10 g, 0.056 mol) in formic acid (250 mL) warmed to 60 °C was added Raney nickel in several portions. The suspension was stirred for 3 h, cooled to room temperature, and filtered. The filtrate was concentrated, neutralized with saturated sodium bicarbonate (aqueous), saturated with brine, and extracted with several portions of ethyl acetate. The combined ethyl acetate extracts were washed with brine, dried, filtered, and concentrated to provide **44** (6.1 g, 60%): ^{1}H NMR ($CDCl_3$) δ 9.7 (s, 1H), 7.6 (m, 2H), 6.8 (d, 1H), 3.6 (s, 2H), 2.3 (s, 6H) ppm. This was used without further purification.

(±)-*N*-[1-Cyano-1-(2-pyridinyl)ethyl]-4-methoxybenzamide (22e). A solution of sodium cyanide (4 g, 0.082 mol), ammonium chloride (4.9 g, 0.09 mol), and ammonium hydroxide (2.9 g, 0.082 mol) in 22 mL of water and 10 mL methanol was heated to 50 °C and treated with 2-acetylpyridine (10 g, 0.082 mol). The reaction mixture was stirred at 50 °C overnight, cooled, and concentrated in vacuo. The resulting solid was dissolved in dichloromethane (40 mL), washed with water, dried, and filtered. The filtrate was concentrated to dryness to give amine **21e** as a dark red oil. The crude amine was dissolved in methanol and treated with a saturated ethereal HCl solution. Concentration of the solvent yielded a low-melting solid that was dissolved in tetrahydrofuran (50 mL) and treated sequentiallly with triethylamine (13.7 g, 0.13 mol) and *p*-anisoyl chloride (8.4 g, 0.049 mol). The solution was stirred at room temperature for 3 h, diluted with ethyl ether (100 mL), washed with aqueous HCl (1 M) and aqueous NaOH (1 M), and dried. After filtration, the filtrate was concentrated in vacuo to give a solid that was purified by recrystallization from EtOAc/hexane to give analytically pure **22e** (5.2 g, 22%): mp 173 °C; ^{1}H NMR ($CDCl_3$) δ 8.6 (m, 1H), 8.5 (bs, 1H), 7.8 (m, 4H), 7.4 (m, 1H), 6.9 (m, 2H), 3.9 (s, 3H), 2.1 (s, 3H) ppm; EI-MS *m/e* 282 (M$^+$). Anal. ($C_{16}H_{15}N_3O_2$) C, H, N.

(±)-*N*-[2-Amino-1-methyl-1-(2-pyridinyl)ethyl]-4-methoxybenzamide (23e). The nitrile **22e** (4.7 g, 0.016 mol) was dissolved in methanolic ammonia (100 mL) and catalytically hydrogenated at 40 °C using Raney nickel (1.5 g) under 50 psi for 10 h. The catalyst was filtered and the filtrate concentrated in vacuo to give 2.3 g of a pale green oil. The crude product was used in the next step without further purification.

(±)-*N*-[2-[[[[2,6-Bis(1-methylethyl)phenyl]amino]carbonyl]amino]-(1-methyl-1-pyridyl)ethyl]-4-methoxybenzamide, Hydrochloride (24e). To a solution of **23e** (2.3 g, 8 mmol) in ethyl acetate (15 mL) was added 2,6-diisopropylphenyl isocyanate (1.7 g, 8.3 mmol). The mixture was stirred for 2 h at room temperature and then concentrated in vacuo. The resulting solid was dissolved in methanol and treated with a saturated ethereal HCl solution. The solvent was concentrated in vacuo and the solid recrystallized from methanol/ethyl ether to give **26e** as the monohydrochloride salt (2.8 g, 67%): mp 154–158 °C; ^{1}H NMR (DMSO-d_6) δ 9.2 (m, 1H), 8.6 (m, 1H), 8.4 (m, 1H), 7.8 (m, 4H), 6.9 (m, 7H), 3.8 (s, 3H), 3.7 (m, 2H), 2.5 (m, 2H), 1.9 (s, 3H), 1.0 (bs, 12H) ppm; EI-MS *m/e* 489 (M$^+$). Anal. ($C_{29}H_{36}N_4O_3$·0.33H_2O·HCl) C, H, N.

Compounds **24a–d** in Table 3 were synthesized in an identical manner.

(*S*)-(−)-1,1-Dimethylethyl [1-(Hydroxymethyl)-3-methylbutyl]carbamate (26a). BOC-protected leucine methyl ester

(3.0 g, 12.2 mmol) was dissolved in tetrahydrofuran (15 mL) and added dropwise to LAH (0.65 g, 17.1 mmol) suspended in tetrahydrofuran (60 mL), cooled to 0 °C. The reaction mixture was gradually warmed to room temperature and was stirred overnight. The suspension was cooled to −40 °C and cautiously quenched with saturated sodium bisulfate (aqueous). The gelatinous suspension was diluted with ethyl acetate and filtered through a pad of Celite. The filtrate was dried, filtered, and concentrated to dryness to give 2.2 g of a viscous liquid. The crude product was purified on silica gel (elution with ethyl ether) to give **26a** (1.9 g, 72%): ^{1}H NMR ($CDCl_3$) δ 4.7 (d, 1H), 3.7 (m, 1H), 3.6 (m, 2H), 3.1 (m, 1H), 1.4 (s, 9H), 1.2 (m, 2H), 0.9 (d, 6H) ppm.

(*S*)-(−)-1,1-Dimethylethyl [3-Methyl-1-[[(methylsulfonyl)oxy]methyl]butyl]carbamate (27a). To a dichloromethane (70 mL) solution of **26a** (1.9 g, 8.7 mmol) cooled to 0 °C was added triethylamine (1.0 g, 9.5 mmol) in one portion. Methanesulfonyl chloride (1.7 g, 17.4 mmol) was added dropwise at such a rate so as to maintain a reaction temperature of 0 °C. The solution was stirred for 45 min and then treated with brine. The organic phase was separated, dried, filtered, and concentrated in vacuo. The residue was triturated with hexane and filtered to give analytically pure **27a** (2.0 g, 77%) as a crystalline solid: $[\alpha]_D$ = −38° (*c* = 1% in $CHCl_3$). Anal. ($C_{12}H_{25}NO_5S$) C, H, N.

(*S*)-(−)-1,1-Dimethylethyl [1-(Azidomethyl)-3-methylbutyl]carbamate (28a). The mesylate **27a** (1.9 g, 6.4 mmol) was dissolved in DMF (20 mL) and treated with sodium azide (2.0 g, 32 mmol). The reaction mixture was stirred at 80 °C for 4 h, cooled to room temperature, and diluted with water (40 mL). The product was extracted with several portions of ethyl ether, and the extracts were combined, dried, and filtered. The filtrate was concentrated in vacuo. The crude product was purified using silica gel (elution with ethyl ether) to give **28a** (1.2 g, 76%) as a white solid: $[\alpha]_D$ = −50° (*c* = 1% in $CHCl_3$). Anal. ($C_{11}H_{22}N_4O_2$) C, H, N.

(*S*)-(−)-1,1-Dimethylethyl [1-(Aminomethyl)-3-methylbutyl]carbamate (29a). LAH (1.1 g, 4.6 mmol) was suspended in dry tetrahydrofuran (20 mL) and cooled to 0 °C. The suspension was treated dropwise with a solution of **28a** (1.1 g, 4.6 mmol) in dry tetrahydrofuran (10 mL). The reaction mixture was stirred at 0 °C for 2 h and then further cooled to −30 °C before the dropwise addition of saturated sodium bisulfate (aqueous). The gelatinous suspension was diluted with ethyl acetate (50 mL) and filtered through Celite. The filtrate was dried, filtered, and concentrated in vacuo to give crude **29a** as a colorless liquid (1.0 g, quant), which was used in the next step without further characterization.

(*S*)-(−)-1,1-Dimethylethyl [3-Methyl-1-[[[[[2,6-bis(1-methylethyl)phenyl]amino]carbonyl]amino]methyl]butyl]carbamate (30a). The crude amine **29a** (1.0 g, 4.6 mmol) was dissolved in ethyl acetate (25 mL) and treated with 2,6-diisopropylphenyl isocyanate (1.0 g, 5.0 mmol) in one portion. Precipitation occurred after 5 min of stirring at room temperature. The mixture was stirred for an additional hour, and the resulting solid was collected by filtration and washed with hexane to yield **30a** (1.2 g, 63%) as a white solid: ^{1}H NMR (DMSO-d_6) δ 7.2 (m, 3H), 3.6 (m, 1H), 3.2 (m, 4H), 1.6 (m, 2H), 1.4 (s, 9H), 1.2 (d, 12H), 0.9 (d, 6H) ppm; FAB-MS *m/e* 420 $(M + H)^+$. Anal. ($C_{24}H_{41}N_3O_3$) C, H, N.

(*S*)-(−)-*N*-[2-Amino-4-methylpentyl]-*N'*-[2,6-bis(1-methylethyl)phenyl]urea (31a). (a) To a solution of **30a** (1.0 g, 2.3 mmol) in dichloromethane (125 mL) was added gaseous HCl in a continuous stream for over 30 min. The solution was concentrated in vacuo to leave a white foam. The HCl salt was triturated with hexane and collected by filtration to give 0.85 g of a white solid. The salt was dissolved in ethyl acetate (25 mL)/methanol (2 mL) and treated with triethylamine (0.24 g, 2.4 mmol) in one portion. The solution was stirred for 10 min, followed by the addition of water. The layers were separated, and the organic phase was dried, filtered, and concentrated in vacuo to give 0.7 g (quant) of the amine as a white solid.

(b) The amine (0.7 g) was dissolved in methanol (50 mL) and stirred over anhydrous sodium sulfate (2.2 g) for 10 min. To the methanolic solution was added 4-anisaldehyde (0.24 g, 2.1 mmol) with stirring at room temperature for 24 h. The insoluble material was filtered, and the filtrate was treated with sodium borohydride (0.39 g, 10.3 mmol). The mixture was stirred for 30 min at room temperature, followed by the addition of 50 mL of water. The methanol was concentrated in vacuo and the aqueous suspension washed with several portions of chloroform. The combined organic extracts were dried over Na_2SO_4 and filtered, and the filtrate was concentrated to dryness, leaving a white foam. The crude product was crystallized from EtOAc/hexane to give **31a** (0.54 g, 56%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 8.0 (s, 1H), 7.4 (d, 2H), 7.2 (t, 1H), 7.1 (d, 2H), 6.8 (d, 2H), 6.0 (bs, 1H), 4.4 (bs, 1H), 3.6 (s, 3H), 3.5 (m, 1H), 3.2 (m, 4H), 1.4 (m, 2H), 1.3 (m, 2H), 1.2 (bs, 12H), 0.9 (dd, 6H) ppm; EI-MS *m/e* 438 (M^+); $[\alpha]_D$ = −20° (*c* = 1.0% in $CHCl_3$). Anal. ($C_{27}H_{41}N_3O_2$) C, H, N.

Compounds **31b–e** (Table 6) were also synthesized by this method.

(*R*)-(−)-[2-[[[[2,6-Bis(1-methylethyl)phenyl]amino]carbonyl]oxy]-1-phenylethyl]carbamic Acid, 1,1-Dimethylethyl Ester (32). Alcohol **15** (9.5 g, 40 mmol) was dissolved in dichloromethane (100 mL) containing triethylamine (4.4 g, 44 mmol). To this solution was added in one portion 2,6-diisopropylphenyl isocyanate (8.9 g, 44 mmol). The solution was stirred at room temperature for 72 h and then concentrated in vacuo to give a white solid. The product was triturated with hexane and collected by filtration to give **32** (16.5 g, 93%): ^{1}H NMR (DMSO-d_6) δ 8.7 (s, 1H), 7.5 (d, 1H), 7.4 (d, 3H), 7.3 (m, 3H), 7.1 (d, 2H), 4.9 (m, 1H), 4.2 (m, 2H), 3.1 (m, 2H), 1.4 (s, 9H), 1.1 (d, 12H) ppm; EI-MS *m/e* 440 (M^+). Anal. ($C_{26}H_{36}N_2O_4$) C, H, N.

(*R*)-(−)-[2,6-Bis(1-methylethyl)phenyl]carbamic Acid, 2-Amino-2-phenylethyl Ester, Hydrochloride (33). The carbamate **32** (16 g, 36 mmol) was dissolved in dichloromethane (575 mL) and treated with gaseous HCl in a continuous stream for over 30 min. The solution was concentrated in vacuo and the resulting residue triturated with hexane. The solid was collected by filtration to give the amine hydrochloride **33** (13.2 g, 97%): ^{1}H NMR (DMSO-d_6) δ 8.9 (bs, 3H), 8.6 (s, 1H), 7.6 (d, 2H), 7.5 (d, 3H), 7.2 (m, 1H), 7.1 (d, 2H), 4.5 (m, 1H), 4.4 (m, 2H), 3.0 (m, 2H), 1.1 (d, 12H) ppm; CI-MS *m/e* 341 $(M + H)^+$. Anal. ($C_{21}H_{28}N_2O_2 \cdot 1.1HCl \cdot 0.3C_6H_{14}$) C, H, N.

(*R*)-(−)-[2,6-Bis(1-methylethyl)phenyl]carbamic Acid, 2-[(1-Oxododecyl)amino]-2-phenylethyl Ester (34b). The amine salt **33** (2 g, 5.3 mmol) was dissolved in a solution containing triethylamine (1.0 g, 10 mmol) in THF (40 mL), and the suspension was stirred at room temperature for 5 min. The suspension was filtered, and the filtrate was treated dropwise with lauroyl chloride (1.1 g, 5.3 mmol). The reaction mixture was stirred at room temperature for 15 min and then filtered. The filtrate was diluted with ethyl acetate and washed with 1 M HCl (aqueous), 1 M NaOH (aqueous), and brine. The organic phase was dried, filtered, and concentrated to dryness leaving a wax-like solid. The crude product was recrystallized from EtOAc/hexane to give **34b** (1.7 g, 62%): mp 105–106 °C; ^{1}H NMR ($CDCl_3$) δ 7.4 (m, 6H), 7.2 (d, 2H), 6.7 (d, 1H), 6.1 (s, 1H), 5.3 (m, 1H), 4.6–4.3 (m, 2H), 3.1 (m, 2H), 2.1 (m, 2H), 1.6 (m, 2H), 1.3 (s, 16H), 1.1 (dd, 12H), 0.9 (t, 3H) ppm; CI-MS *m/e* 523 $(M + H)^+$. Anal. ($C_{33}H_{50}N_2O_3$) C, H, N.

The stereoisomers of **34a** were also synthesized in this manner.

(*R*)-(−)-[2,6-Bis(1-methylethyl)phenyl]carbamic Acid, 2-[[[4-(dimethylamino)phenyl]methyl]amino]-2-phenylethyl ester, dihydrochloride (34c). To a methanolic solution (100 mL) of **33** (1.5 g, 3.9 mmol) was added anhydrous calcium sulfate (1.8 g) and triethylamine (0.44 g, 4.3 mmol). The mixture was stirred for 10 min at room temperature before adding *p*-(dimethylamino)benzaldehyde (0.6 g, 3.9 mmol) in one portion. The reaction mixture was stirred under an inert atmosphere (N_2) overnight, after which sodium borohydride (0.73 g, 19.2 mmol) was added. The suspension was stirred at room temperature for 30 min, and concentrated to dryness, and the residue was partitioned between ethyl acetate and water. The layers were separated, the organic phase was dried and filtered, and the filtrate was concentrated in vacuo. The crude product was dissolved in ethyl ether and precipitated as the HCl salt upon treatment with gaseous HCl. The solid was collected by filtration to give **34c** (0.8 g, 40%) as the dihydrochloride salt: mp 175 °C dec; ^{1}H NMR (DMSO-d_6) δ 8.7 (s, 1H), 7.7 (m, 2H), 7.5 (m, 5H), 7.2 (m, 2H), 7.1 (m, 3H), 4.7 (m, 1H), 4.6 (m, 2H), 4.0 (m, 2H), 3.1 (s, 1H),

3.0 (s, 6H), 2.9 (m, 2H), 1.1 (d, 12H); CI-MS *m/e* 472 $(M + H)^+$; $[\alpha]_D = -24°$ (*c* = 1.1% in $CHCl_3$). Anal. ($C_{30}H_{39}N_3O_2 \cdot 2HCl$) C, H, N.

(±)-[2-[(1-Oxodecyl)amino]-2-phenylethyl]carbamic Acid, 2,6-Bis(1-methylethyl)phenyl Ester (36a). To a solution of **6d** (0.74 g, 2.5 mmol) in dry THF (10 mL) were added dropwise triethylamine (0.25 g, 2.5 mmol) and 2,6-diisopropylphenylchloromate (1.0 g, 2.5 mmol). The reaction mixture was vigorously stirred for 1 h and filtered, and the filtrate was concentrated to dryness. The solid obtained was triturated with hexane and filtered to give **36a** (0.9 g, 75%) as a white solid: mp 189–190 °C; ^1H NMR ($CDCl_3$) δ 8.2 (d, 1H), 7.8 (t, 1H), 7.3–7.1 (m, 8H), 5.0 (m, 1H), 3.3 (m, 2H), 2.8 (m, 2H), 2.0 (t, 2H), 1.4 (bs, 2H), 1.2 (s, 14H), 1.0 (dd, 12H), 0.8 (t, 3H) ppm; FAB-MS *m/e* 495 $(M + H)^+$. Anal. ($C_{31}H_{46}N_2O_3$) C, H, N.

***(R)*-(−)-*N*-[2-[[[2,6-Bis(1-methylethyl)phenoxy]carbonyl]amino]-1-phenylethyl]carbamic Acid, 1,1-Dimethylethyl Ester (35).** To a THF solution (35 mL) of **18** (2.5 g, 10.5 mmol) and triethylamine (1.74 g, 17.2 mmol) was added, dropwise, 2,6-diisopropylphenyl chloroformate (4.16 g, 10.7 mmol). The reaction mixture was stirred at room temperature for 1 h, and the resulting precipitate was removed by filtration. The filtrate was concentrated in vacuo, and the resulting solid was triturated with hexane and filtered to give **35** (3.9 g, 84%) as a white solid: mp 199–200 °C; $[\alpha]_D = -55°$ (*c* = 1% in $CHCl_3$). Anal. ($C_{26}H_{36}N_2O_4$) C, H, N.

***(R)*-(−)-[2-[(1-Oxododecyl)amino]-2-phenylethyl]carbamic Acid, 2,6-Bis(1-methylethyl)phenyl Ester (36b).** The BOC-protected amine **35** (3.1 g, 7 mmol) was slurried in dichloromethane (150 mL), with dissolution occurring upon treatment with gaseous HCl. The amine salt gradually precipitated from the saturated acidic solution and was collected by filtration (2.1 g) after stirring at room temperature for 30 min. A portion of the amine salt (1.0 g, 2.9 mmol) was slurried in dry THF (25 mL) and treated with triethylamine (0.6 g, 6.1 mmol). The mixture was stirred for 30 min and filtered, and to the filtrate was added, dropwise, lauroyl chloride (0.69 g, 3.2 mmol). After the mixture was stirred for 1 h at room temperature, the precipitate was removed by filtration and the filtrate was diluted with ethyl ether (25 mL). The solution was washed with 1 M HCl (aqueous), 1 M NaOH (aqueous), and brine and dried. Filtration followed by concentration of the solvent in vacuo gave **36b** (1.36 g, 90%) as a white solid: mp 144–146 °C; ^1H NMR ($CDCl_3$) δ 7.3 (m, 5H), 7.1 (m, 3H), 6.8 (d, 1H), 5.5 (t, 1H), 5.1 (q, 1H), 3.6 (m, 2H), 2.9 (m, 2H), 2.2 (m, 2H), 1.6 (m, 2H), 1.3 (s, 16H), 1.2 (dd, 12H), 0.9 (t, 3H) ppm; EI-MS 523 (M^+); $[\alpha]_D = -59°$ (*c* = 1% in $CHCl_3$). Anal. ($C_{33}H_{50}N_2O_3 \cdot 0.1H_2O$) C, H, N.

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