Orally Active β-Lactam Inhibitors of Human Leukocyte Elastase. 3.[1] Stereospecific Synthesis and Structure–Activity Relationships for 3,3-Dialkylazetidin-2-ones

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The stereospecific synthesis of several 4-[(4-carboxyphenyl)oxy]-3,3-dialkyl-1-[[(1-phenylalkyl)-amino]carbonyl]azetidin-2-ones **3** is described in which the C-3 alkyl groups were varied from methyl to butyl as well as allyl, benzyl and methoxymethyl. The structure–activity relations for these compounds are discussed in terms of the hydrolytic stability of the β-lactam ring, their *in vitro* inhibitory potency for human leukocyte elastase (HLE), and their *in vivo* oral efficacy in an HLE-mediated hamster lung hemorrhage assay. Further alkyl substitution on the benzylic urea moiety, especially in the *R* configuration, afforded enhanced HLE inhibition and *in vivo* efficacy. The stereochemical assignments for (3*R*,4*S*)-4-[(4-carboxyphenyl)oxy]-3-ethyl-3-methyl-1-[[((*R*)-1-phenylpropyl)amino]carbonyl]azetidin-2-one (**42a**) (k_{obs}/[I] = 91 000 M^{-1} s^{-1}) were confirmed with an X-ray structure determination, which was also utilized to develop an HLE inhibition model.

The use of a β-lactam structure to provide time-dependent, mechanism-based inhibition of human leukocyte elastase (HLE, EC 3.4.21.37), a serine protease, was initiated in these laboratories[2] and has now been investigated by other groups as well.[3,4] In addition, several other classes of low molecular weight inhibitory agents, both competitive and/or mechanism-based, are being actively studied and have recently been reviewed.[5,6] HLE is stored in the azurophilic granules of polymorphonuclear leukocytes (PMNs), and on release its proteolytic activity is normally tightly regulated by endogenous antiproteases, such as α_1-protease inhibitor (α_1-PI). However, excessive HLE release or the impairment of its regulatory processes has been implicated as a causative factor in several degenerative diseases of the lung[7] and other connective tissues.[8] In certain disease states, such as chronic bronchitis and especially cystic fibrosis, free elastase has been detected in the lung fluid.[9] Thus, the aim of these studies has been to mitigate the adverse effects of any unregulated extracellular HLE activity with the additional inhibitory potential of a low molecular weight therapeutic agent.

Our use of a β-lactam nucleus to give mechanism-based inhibition of HLE was based on the knowledge that some of the bacterial β-lactamases are also serine-utilizing proteases.[2] Our initial studies were directed toward the use of substituted cephalosporin esters and amides which afforded potent, time-dependent inhibitors of HLE; however, they were not orally active. Subsequently, investigation of the inhibitory mechanism by means of X-ray structure determinations on the related serine protease porcine pancreatic elastase (PPE) indicated that acylation of the serine by the β-lactam carbonyl had occurred, and evidence for a putative "second hit" involving the active site histidine was demonstrated.[10] The cephalosporin work ultimately resulted in the selection of **1a** (L-658,758) as a topical aerosol for possible use in lung diseases.[11] A detailed biochemical study of its time-dependent inhibition has been reported with additional refinements in the proposed mechanism.[12] The utility of a cephalosporin nucleus, with further modification of the C-4 carboxyl, has now been more extensively studied by others as well.[3b] Recently, we also reported on our concurrent studies employing the penem[13] (**1b**) and penicillin[14] (**1c**) nuclei as well as the use of monocyclic β-lactams[15] as topical agents. However, our experience with these modified, traditional antibiotic β-lactam structures has been that, while excellent topical activity could be achieved for treatment of lung diseases, the unexpectedly poor hydrolytic stability of these compounds precluded their use as orally active therapeutic agents.[12–15]

Improved stability was achieved in the monocyclic series with further modification of the *N*-acyl and C-4 leaving group,[16] and the structure–activity relationships (SAR) were still in agreement with the previous bicyclic stereochemical results,[17] the *trans*-3α,4β stereochemistry of **2** having the best HLE inhibitory activity of the four possible isomers. *In vitro* blood stability ($t_{1/2}$ < 6 h) and oral absorption in the marmoset were also demonstrated.[17] We then reasoned that a second 3β-alkyl group as in **3** might further enhance the β-lactam stability and thus improve the oral absorption and pharmacokinetic properties. Herein we report in detail the development, stereoselective synthesis, and unexpected stereochemical requirements of 3,3-dialkylazetidin-2-one derivatives as stable, orally active HLE inhibitors. Subsequent extensive SAR investigations of the phenoxy[1] and urea[18] moieties provided further

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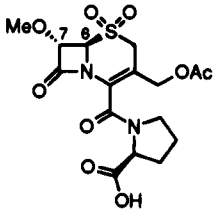
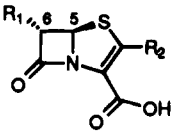
enhancements to both *in vitro* and *in vivo* activities as already reported. Alkyl substitution on the benzylic urea methylene as indicated in **3** was also found to give enhanced HLE inhibitory potency and improved *in vivo* efficacy. The combination and optimization of all these results ultimately lead to the selection of **4** as a development candidate.[19]



1a



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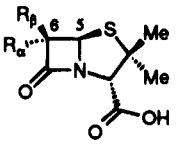

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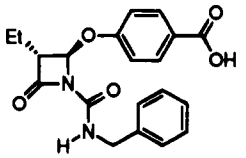

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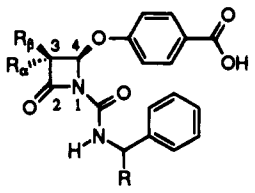

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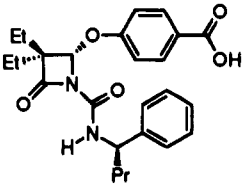


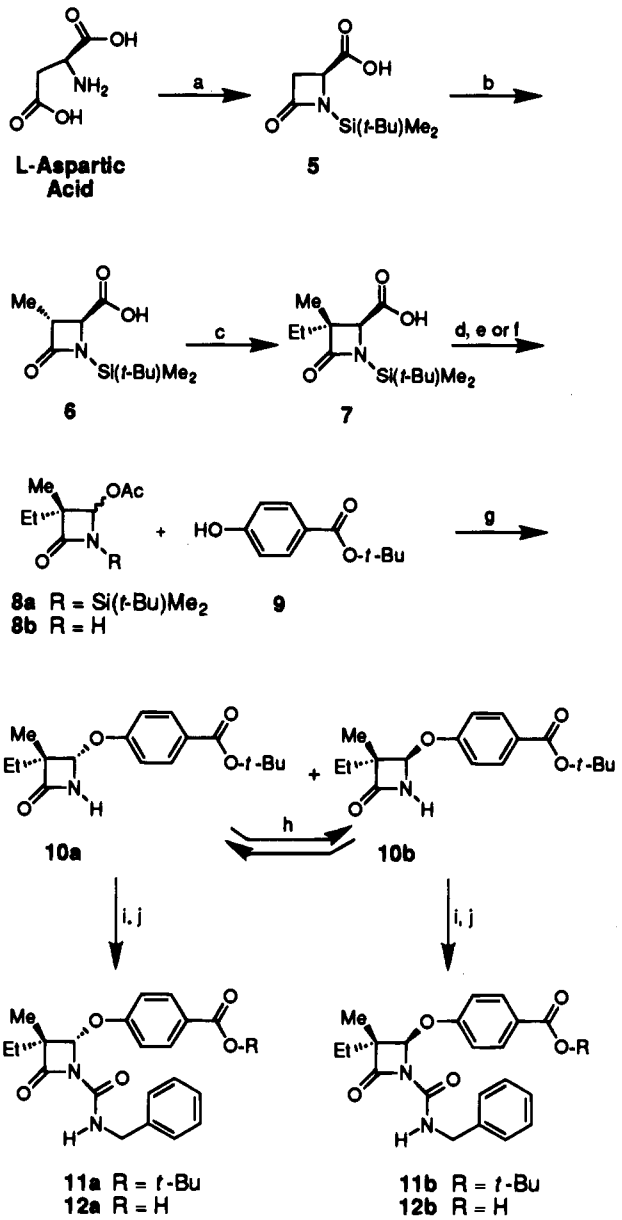
4

Chemistry

On the basis of our previous cephalosporin[11] and penicillin[14] work, we reasoned that the second 3β-alkyl group should be small for optimal activity while the size of the 3α-group might be varied to maximize HLE inhibition. Thus, the stereospecific introduction of the two alkyl groups was critical. Research on the synthesis of thienamycin had shown that alkylation of the dianion derived from (*S*)-4-carboxyazetidin-2-one (**5**) stereoselectively afforded the 3,4-*trans* product,[20,21] and this methodology was employed in the stereospecific synthesis of the four stereoisomers of **2**.[17] A second alkylation with a different group should provide chiral 3,3-dialkyl derivatives of known stereochemistry at C-3, which could then be used to direct the stereochemistry at C-4 during subsequent conversion to the desired 3,3-disubstituted derivatives of **2**.

Scheme 1 shows a representative synthesis of the two 3α-ethyl-3β-methyl derivatives **12a,b**. Deprotonation of **5**, prepared from L-aspartic acid,[20,21a,22] with 2 equiv of lithium diisopropylamide (LDA) followed by alkylation with methyl iodide at −70 °C afforded selectively the 3α-methyl product **6** in 88% yield. The second alkylation with ethyl iodide selectively introduced an ethyl group *trans* to the carboxyl to afford **7** in 79% yield. Once the C-3 stereochemistry had been set, on the basis of the known chirality of the C-4 carboxylic acid, the C-3 stereochemistry was then used to differentiate the subsequent functionalization at C-4. Lead tetraacetate oxidation of the carboxylic acid[20] afforded the 4-acetoxy

Scheme 1[a]

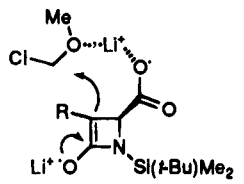


[a] Reagents: (a) see ref 21; (b) LDA (2 equiv), THF, −70−(−20) °C, then MeI, −20−0 °C; (c) LDA (2 equiv), THF, −70−(−20) °C, then EtI, −20−0 °C; (d) $PbOAc_4$, DMF, HOAc, 50 °C, 0.5 h; (e) THF, 2 N HCl; (f) $PbOAc_4$, DMF, HOAc, 50 °C, 3 h, then 25 °C, 16 h; (g) acetone, then 1.5 equiv of **9** and 1.35 equiv of 2 N NaOH in H_2O; (h) acetone, then 0.5 equiv of **9** and 0.35 equiv of 2 N NaOH in H_2O; (i) $PhCH_2NCO$, TEA, DMAP, CH_2Cl_2; (j) TFA, anisole, 0 °C.

derivative **8a** as a mixture of C-4 isomers, and the *tert*-butyldimethylsilyl N-protecting group was removed with 2 N HCl in tetrahydrofuran at room temperature to give **8b**. More conveniently, since the silyl group of **8a** was not stable to either the reaction conditions or purification by silica gel chromatography, prolonged reaction with the acetic acid in the oxidation step gave the deprotected N-H azetidinone **8b** in 88% yield after a short silica gel column chromatography. The crude **8b** could also be used directly in the next step. Displacement of the acetoxy with the preformed sodium salt of *tert*-butyl 4-hydroxybenzoate (**9**) afforded predominantly **10b**, the product derived from preferential attack from the least hindered side (initial ratio of **10a** to **10b** was <1:6). In the presence of an excess of the sodium

salt of **9** and after an extended reaction time (24 h), a 1:2 equilibrium mixture of **10a,b** was obtained which could be separated by chromatography in 26% and 45% yields, respectively. Additional evidence that the reaction first gives a kinetic product followed later by equilibration was demonstrated in a separate reaction in which isolated, pure major isomer **10b** and a catalytic amount of the phenoxide afforded the same 1:2 mixture of **10a**:**10b.** Each isomer was individually acylated with phenylmethylisocyanate to afford the ureas **11a,b**, respectively. Final conversion to the desired products **12a,b** was achieved by trifluoroacetic acid (TFA) removal of the *tert*-butyl ester. Alternatively, the same products could have been prepared starting with D-aspartic acid and reversing the order of the alkylations.

As shown in Scheme 2 and Table 1, a variety of alkyl substitutions were prepared from either L- or D-aspartic acid (via **5** or **13**, respectively). The simple alkyl derivatives were prepared from the iodides and ranged in size from methyl to *sec*-butyl, while the allyl and benzyl alkylations were done with the respective bromides. For the preparation of the spiropentane derivative **21**, 1-bromo-4-chlorobutane was used in a single step with an additional 1 equiv of LDA. In the preparation of ether analogues (e.g., **30a**, R_α = Et, R_β = CH_2-OMe), the corresponding chloroalkyl ethers were used in the second alkylation step and were the only cases where complete selectivity was not observed. While these reactions gave variable results, the products were separable by chromatography and readily identified by ^{1}H-NMR as described below. Apparently, a complex can form between the lithium carboxylate and the ether oxygen, which could then direct the alkylation from the same side as the carboxyl rather than from the less hindered side as occurred with the simple alkyl groups.



The oxidation of **14** to the acetoxy intermediates and displacement with **9** afforded the NH compounds **15** without incident. The resulting diastereomers were separated by chromatography and identified by proton NMR analysis. Each was then individually acylated and deblocked to give the desired derivatives **16**–**32**. For those compounds with the same R_α and R_β groups (**16, 20, 21,** and **23**), while the acid intermediates **14a,b** were chiral, racemization at C-4 occurred during the oxidation and phenol displacement steps and the final compounds were racemic. The carbamate derivative **33** was also prepared by acylation of **15a** (R_α = Me, R_β = *n*-Pr) with benzyl chloroformate and TFA deesterification.

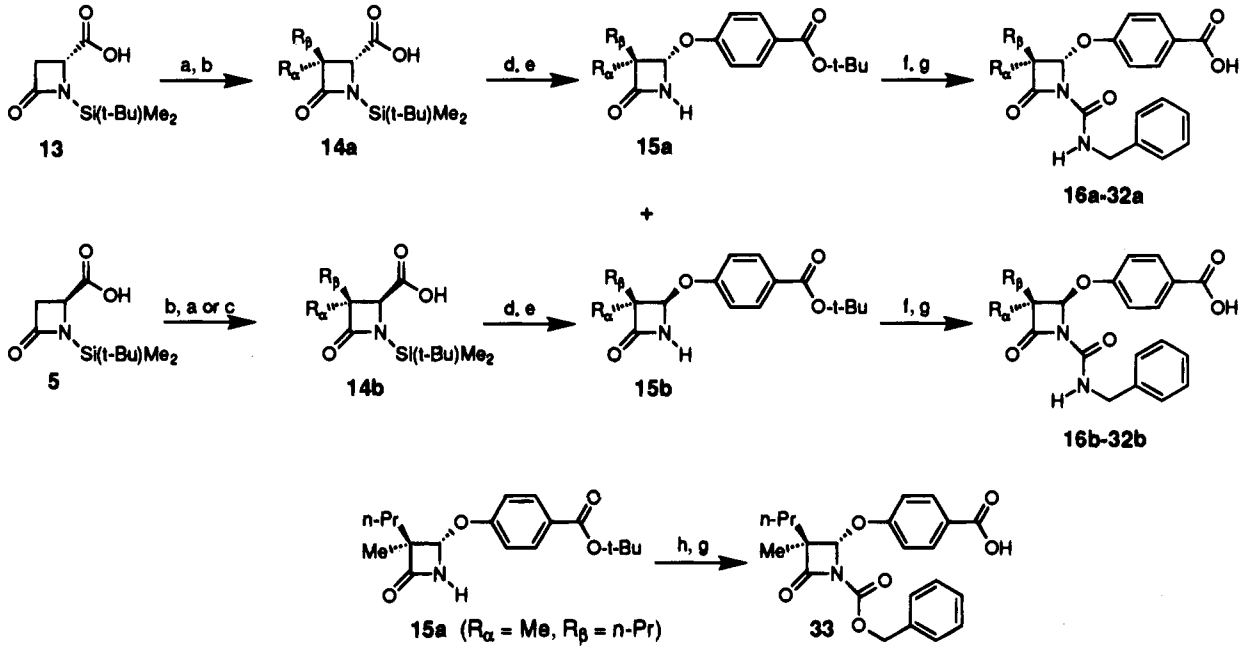
The assignment of the stereocenter at C-4 for **10a,b** was based on the following comparisons to the previous preparation of **2** and its isomers.[17] (1) The displacement should occur from the less hindered side based on the C-3 substituents (the 3:4 *trans* relation in **2** was evident from the H3:H4 coupling constants). (2) The methylene hydrogens of the 3-ethyl moiety appear as a simple quartet in the ^{1}H-NMR (δ 1.84, J = 7.5 Hz) when *trans* to the ether as in **10b**. However, when the methylene is *cis* to the ether, as in **10a**, the ethyl has more restricted rotation and the methylene hydrogens are clearly diastereotopic in the ^{1}H-NMR and give an AB pattern centered at δ 1.68 and 1.93 (J = 15 Hz). When further split by the three methyl hydrogens (J = 7.5 Hz), each hydrogen appears as a skewed hextet (due to the 2:1 ratio of the coupling constants). (3) The C-3 methyl is shifted downfield to δ 1.46 for **10a** when *trans* to the ether compared to δ 1.34 for **10b.** (4) The C-4 hydrogen for **10b** was shifted downfield compared to that for **10a** (δ 5.44 vs 5.37). The above differences in chemical shifts were easily used to determine the diastereomeric purities following the chromatographic separations of **15a,b**, especially the difference in the C-4 hydrogens. These chemical shift differences were also evident in the acylated products **16**–**32** and to a lesser extent in the carboxylic acid intermediates **14a,b**.

Once the preferred stereochemistry at C-3 and C-4 of the β-lactam had been established chemically as above and biologically (see below), the last possible stereocenter of the original lead structure **2** to be investigated was the benzylic methylene of the urea. Alkyl substitution at this position had previously been shown[23] to improve the activity of **2**; therefore, this effect was also investigated with the chiral compounds **12a,b** and **24a**. This was accomplished as shown in Scheme 3 by acylation of **10a,b** and **38a** with the readily available chiral (*R*)- or (*S*)-1-phenylalkyl isocyanates. Both (*R*)- and (*S*)-1-phenylethyl isocyanate were commercially available, while the 1-phenylpropyl isocyanates **35** were prepared from the available amines **34** by reaction with phosgene. (*R*)-1-Phenylbutyl isocyanate (**37**) was prepared by Curtius rearrangement[24] of (*R*)-2-phenylpentanoic acid (**36**) after resolution with (*R*)-α-methylbenzylamine.[25] The acylation products **39**–**46** (*tert*-butyl esters) now contained an additional chiral center at the benzylic position, and the resulting diastereomers were readily separable on TLC. Thus, acylation of intermediates **15** with a chiral isocyanate provided a useful method for determining the enantiomeric purity at C-3/C-4 and also a means for removal of any undesired stereochemical contamination. The excellent enantiomeric purity of the alkylations at C-3 was now apparent by TLC analysis of the crude acylation products which generally indicated only a trace of the diastereomer.

As described below, the stereochemical assignments were also confirmed in the case of **42a** with a low-resolution X-ray structure determination. With all three stereocenters definitively known, a complete SAR for chemical stability, HLE inhibition, and *in vivo* biological activity for this class of compounds could now be evaluated.

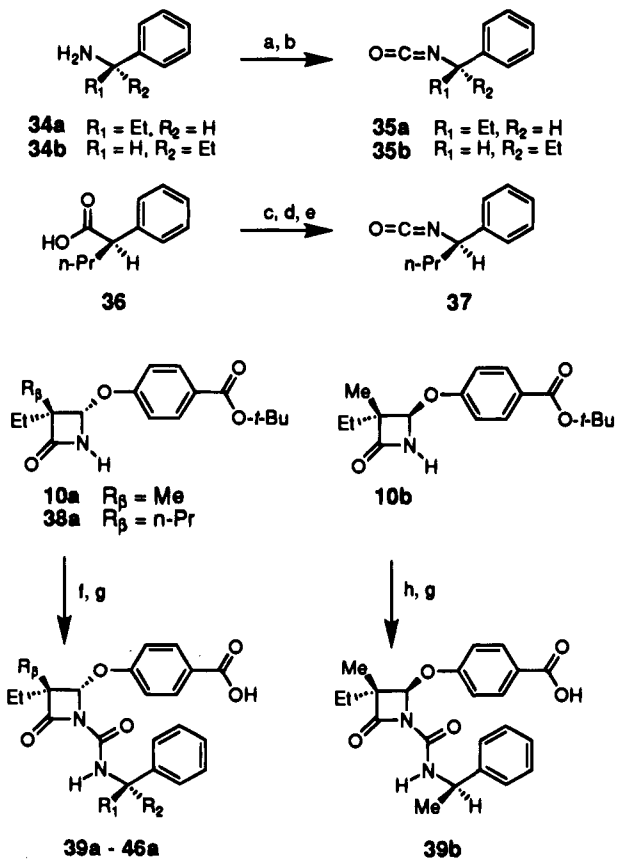
Previously, the stability of the cephalosporins had been determined by incubation in 0.5 M MOPS buffer at pH 8 at 25 °C and had given half-lives in the 1–24 h range.[11] With the increased stability observed with the monoalkyl structures such as **2,** a stronger nucleophile, 6-aminocaproic acid (0.5 M in 0.5 M MOPS buffer adjusted to pH 7.4), was required to obtain useful half-lives.[16,17] Under these conditions, **2** had exhibited a $t_{1/2}$ = 48 h. With the additional alkyl group at C-3, indeed, a further dramatic increase in stability was observed with less than 10% of **12a** or **12b** being degraded after incubation with 6-aminocaproic acid for more than 300

Scheme 2[a]



[a] Reagents: (a) LDA (2 equiv), THF, −70−(−20) °C, then $R_\alpha X$, −20−0 °C; (b) LDA (2 equiv), THF, −70−(−20) °C, then $R_\beta X$, −20−0 °C; (c) LDA (2 equiv), THF, −70−(−20) °C, then −70 °C, LDA (1 equiv), $Br(CH_2)_4Cl$, then −70−0 °C; (d) $PbOAc_4$, DMF, HOAc, 50 °C, 3 h, then 25 °C, 16 h; (e) acetone, then 1.5 equiv of **9** and 1.35 equiv of 2 N NaOH in H_2O; (f) $PhCH_2NCO$, TEA, DMAP, CH_2Cl_2; (g) TFA, anisole, 0 °C; (h) $PhCH_2COCl$, TEA, DMAP, CH_2Cl_2.

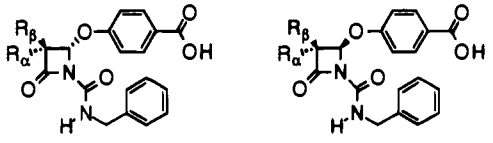
Scheme 3[a]



[a] Reagents: (a) EtOAc, PhMe, $COCl_2$; (b) 80 °C; (c) CH_2Cl_2, DMF, $(CO)_2Cl_2$; (d) acetone, H_2O, NaN_3; (e) PhH, 80 °C; (f) (*R*)- or (*S*)-1-phenylethyl isocyanate, **35a**, **35b**, or **37**, TEA, DMAP, CH_2Cl_2; (g) TFA, anisole, 0 °C; (h) (*R*)-1-phenylethyl isocyanate, TEA, DMAP, CH_2Cl_2.

h. Thus, an even stronger nucleophile, *N*-acetyl-L-cysteine, was employed to again obtain experimentally measurable half-lives as indicated in Table 1. In practice, 1 mg/mL solutions of representative compounds were incubated at 37 °C in 0.5 M MOPS buffer containing 0.25 M *N*-acetyl-L-cysteine (adjusted to pH 7.5 with 2 N sodium hydroxide). Aliquots (50 μL) were removed at regular intervals, quenched into 2% trifluoroacetic acid, and analyzed by C-18 reverse phase HPLC. The disappearance of compound was monitored for at least 1−2 half-lives, and the results fit to a first-order decay curve from which the reported $t_{1/2}$ values were derived. In general, the stability was directly related to the bulk of the two C-3 groups as evident in the 3α-ethyl series **2**, **12a**, **20**, and **24a** ($t_{1/2}$ = <0.3, 1.80, 7.70, and 7.66 h, respectively). Little difference was observed whether the larger group was α or β (compare **12a** and **19a**, $t_{1/2}$ = 1.80 and 1.89 h) or between the two C-4 configurations (compare **12a** with **12b**, $t_{1/2}$ = 1.80 and 1.89 h). Thus, the relative order for hydrolytic stability was hydrogen ≪ methyl < ethyl = *n*-propyl < isopropyl. In keeping with these findings was the decreased stability of the spiropentane compound **21** (0.58 vs 7.70 h for diethyl **20**) in which the steric hindrance would be minimized due to the ring restriction. In the case of the ethers, a 4-fold decrease in the $t_{1/2}$ value was seen for the methoxymethyl derivative **30a** compared to the *n*-propyl compound **24a** ($t_{1/2}$ = 1.81 vs 7.66 h, respectively), probably due to a lower steric requirement for an oxygen vs a methylene and/or some inductive activation of the β-lactam by the ether oxygen. The dramatic effect of the urea moiety on the hydrolysis rate was again shown in the case of **17a** ($t_{1/2}$ = 1.77 h) vs its carbamate derivative **33** ($t_{1/2}$ = <0.25 h). This result precluded any consideration of this class of compounds for oral use. Finally, there was no further enhancement in the stability of the substituted urea derivatives (**42a**, $t_{1/2}$ = 1.38 h).[26]

Table 1. Chemical Structure, Hydrolytic Stability, and Biochemical and Biological Data for 3,3-Dialkylazetidin-2-ones



a b

compd	R_α	R_β	$t_{1/2}$,[b] h (SD)[g]	k_{obs}/[I],[c] M^{-1} s^{-1} (SD)[h]	lung hemorrhage activity: % inhibition[a] screen,[d] 30 mpk 30 min (SD)[i]	titration,[e] 30/10/3 mpk, 30 min[j]	duration,[f] 30 mpk, 0.25/0.5/1/2 h[j]
3[k]	Et	H	<0.3	3800 (70)	nd[l]		
12a	Et	Me	1.80 (0.14)	2000 (150)	70 (16)	70/46/33[m]	70/70/69/32
12b	Et	Me	1.94 (0.14)	220 (15)	nd		
16[n]	Me	Me	nd	280 (20)	nd		
17a	*n*-Pr	Me	1.77 (0.35)	1900 (300)	49[o]		
17b	*n*-Pr	Me	1.82 (0.15)	K_i = 51 μM (2)[p]	nd		
18a	*i*-Pr	Me	2.43 (0.07)	21 (2)	nd		
19a	Me	Et	1.89 (0.02)	160 (10)	nd		
19b	Me	Et	nd	200 (60)	nd		
20[n,q]	Et	Et	7.70 (0.17)	1500 (170)	59 (11)	59/23/20	69/59/68/nd
21[n]	-$CH_2CH_2CH_2CH_2$-		0.58 (0.02)	1900 (150)	8 (8)		
22a	*n*-Pr	Et	nd	3300 (70)	52 (33)		
23[n]	*n*-Pr	*n*-Pr	5.96 (0.2)	2500 (200)	56 (10)	56/24/10	62/56/55/nd
24a	Et	*n*-Pr	7.66 (0.33)	5200 (700)	78 (14)	59/51/22[m]	59/78/50/nd
25a	Et	*i*-Pr	nd	10 (1.4)	13 (33)		
26a	Et	*n*-Bu	nd	4400 (300)	36 (22)		
27a	Et	*s*-Bu	nd	1200 (120)	23 (16)		
28a	allyl	Et	nd	2000 (40)	51 (14)		
29a	Et	allyl	4.20 (0.26)	2800 (70)	56 (14)		40/56/40/nd
30a	Et	$MeOCH_2$	1.81 (0.06)	1900 (130)	46 (14)		
31a	Bn	Et	12.2 (0.3)	90 (10)	−15 (27)		
32a	Et	Bn	nd	84 (20)	nd		

[a] See the Biochemistry and Biology section and refs 18 and 28 for methodology. [b] See the Experimental Section for methodology. [c] See ref 27 for methodology. [d] The compounds were usually screened in three animals dosing po at 30 mpk 30 min prior to IT instillation of HLE. The percent inhibition is the average of all determinations at the stated dose and time point. [e] The dose titrations were done as in the screen but using 30, 10, and 3 mpk. [f] The duration studies were done as for the screen, but administration of the HLE was after 0.25, 0.5, 1, and 2 h. [g] Standard deviation of experimental points from the calculated first-order decay curve. [h] Average of two or more determinations at different inhibitor concentrations. [i] Average of three animals at each dose and time. [j] Similar errors were obtained for the titration and duration experiments. [k] Structure **b**. See ref 17. [l] Not determined. [m] Determined with a 15 min dosing time. [n] Racemic. [o] Determined at 100 mpk and with a 15 min dosing time. [p] No time-dependent inhibition was observed. [q] See ref 18.

Biochemistry and Biology

The *in vitro* HLE inhibition (k_{obs}/[I], M^{-1} s^{-1})[27] and oral potency in a hamster lung hemorrhage assay[18,28] for these inhibitors are listed in Table 1. The k_{obs}/[I] is the second-order rate constant for the time-dependent inactivation of HLE by these inhibitors and under these conditions is ≥90% of K_{inact}/K_i.[27] In some cases no time dependence was observed and the apparent initial K_i is reported. The hamster lung hemorrhage assay was described previously[28] and was used as the primary screening model to determine if the compounds, when now orally administered, were effective inhibitors of HLE-induced damage. In the routine screening protocol, 30 mg/kg (mpk) of test compound as a suspension in Methocel (Dow) was given orally 30 min prior to intratracheal (IT) instillation of 50 units of HLE/animal. Three hours later the animals were sacrificed, the lungs were lavaged with saline, and the amount of hemoglobin in the fluid was measured spectrophotometrically at 414 nm. The percent inhibition was calculated as the ratio of hemorrhage in drug-treated animals compared to vehicle-treated animals. For those compounds with good activity at the screening dose, a dose−response curve was obtained at 30, 10, 3, and 1 mpk and the 50% effective dose (ED_{50}) at the 30 min predose time point was determined. This assay was also used as a pharmacokinetic tool by administering selected compounds at 30 mpk at 15, 30, 60, 120, 180, and 240 min prior to HLE instillation. The time at which 50% inhibition (T_{50}) was still achieved was thereby determined and used as a measure of the effective duration of the compound in the lung environment.

Discussion

Our work with the cephalosporin nucleus had indicated that α-monosubstitution at C-7 and the natural β stereochemistry of the sulfur at C-6 (S *trans* to the 7α-group as in **1a**) afforded optimal HLE inhibition. The initial monoalkyl azetidinone work also seemed to confirm this hypothesis in that structure **2** was found to be the most potent of the four possible stereoisomers, although weak time-dependent inhibition was also seen for the *cis*-3β,4β and *trans*-3β,4α isomers.[17] The penicillin work[14] had shown a somewhat expanded SAR in that larger 3α-substituents (e.g., the trifluoroacetamido moiety) were optimal and even α,β-disubstitution was tolerated, albeit with a significant reduction in activity. We believed that the monocyclic derivative **2** had shown some oral absorption and measurable blood stability[17] due to its increased hydrolytic stability over the bicyclic compounds. Therefore, we decided to investigate the possible use of a second alkyl group at the 3β-position as in **3** to further improve the chemical stability and thus enhance the oral absorption and blood half-life.

Further modification of the N-1 acyl and/or the C-4 leaving group was expected to be necessary to augment any concomitant loss in HLE activity from the 3β-substitution.

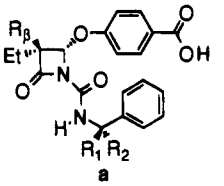
As shown in Table 1, a wide variety of 3,3-dialkyl derivatives were prepared to determine the most active configuration and optimal steric bulk at C-3 for achieving both *in vitro* HLE inhibitory activity and hydrolytic stability as well as *in vivo* efficacy. It was known from peptide mapping[29] that valine was the preferred P-1 residue and, from our previous β-lactam inhibitors,[11,13,14] that small alkyl or alkoxy groups at C-3 were required for good inhibition (methoxy, ethyl, or propyl being best but not methyl). Our previous work had also shown that the substituents on the carbon next to the β-lactam carbonyl could fit into the S-1 specificity pocket of HLE[11,18] and that the serine hydroxyl should attack the carbonyl from the α face.[18,30] Therefore, it seemed reasonable that a small, second alkyl group in the β orientation might only minimally affect the inhibitory activity, while a dramatic increase in stability should be obtained. The first targets for synthesis were the 3β-methyl, 3α-ethyl, and propyl derivatives of **2**.

As desired, the hydrolytic stabilities of **12a,b** were much improved compared to that of **2** ($t_{1/2} \gg 300$ h vs 48 h using 6-aminocaproic acid and $t_{1/2} = 1.80$ and 1.94 h vs <20 min using *N*-acetyl-L-cysteine). The activity of **12b**, which based on previous experience[17] was expected to be the more active isomer, was disappointingly poor ($k_{obs}/[I] = 220$ M^{-1} s^{-1}). Surprisingly, the 4*S* isomer **12a** was found to have a $k_{obs}/[I] = 2000$ M^{-1} s^{-1}, being within a factor of 2 to both **3**[17] ($k_{obs}/[I] = 3800$ M^{-1} s^{-1}) and **1a**[11] ($k_{obs}/[I] = 3800$ M^{-1} s^{-1}). This is especially noteworthy since the *cis*-3α,4α diastereomer of **2** had not shown any time-dependent inhibition.[17] In the penem series[13] there had been the implication that the most active penem isomer might have the 5α,6α configuration, although the absolute stereochemistry was never definitively proven. Also, in the monoalkyl compounds,[17] the *trans*-3β,4α derivative of **2** had shown some activity ($k_{obs}/[I] = 425$ M^{-1} s^{-1}). Even more encouraging was the finding that upon oral administration of **12a** in the hamster lung hemorrhage assay, a 95% inhibition of the hemorrhage was obtained at 100 mpk. While the *tert*-butyl esters were actually more active on HLE *in vitro* than the acids[31] (i.e., $k_{obs}/[I] = 8900$ vs 1200 M^{-1} s^{-1} for **17a**), the esters were not considered viable oral agents for water insolubility and metabolic instability reasons.

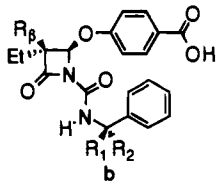
To determine the optimal substitution at the 3-position, the sizes of both the α and β-groups were varied between methyl and *sec*-butyl as well as allyl, benzyl, and straight chain ethers. Table 1 shows the HLE inhibitory activity as the $k_{obs}/[I]$ for several selected compounds. The need for a 3α-substituent larger than methyl to obtain potent inhibitors was again seen with the dimethyl compound **16** ($k_{obs}/[I] = 280$ M^{-1} s^{-1}) and the reversed C-3 stereochemistry of **12a** as in **19a** ($k_{obs}/[I] = 160$ M^{-1} s^{-1}). The 4*R* isomers always gave poor inhibition for any of the 3,3-dialkyl derivatives as evident with **12b**, **17b**, **19b** ($k_{obs}/[I] = 220$ M^{-1} s^{-1}, $K_i = 51$ μM, $k_{obs}/[I] = 200$ M^{-1} s^{-1}, respectively), and others.[31] A decrease in activity was also evident with a 3α-group larger than ethyl as seen with the *n*-propyl (**17a**, $k_{obs}/[I] = 1200$ M^{-1} s^{-1}) and isopropyl (**18a**, $k_{obs}/[I] = 21$ M^{-1} s^{-1}) compounds. Fortunately, incorporation of a 3β-group larger than methyl not only improved the hydrolytic stability by another 4-fold but was clearly advantageous for HLE inhibition as well. The 3β-ethyl (**20**, racemic, $k_{obs}/[I] = 1500$ M^{-1} s^{-1}) and *n*-propyl (**24a**, $k_{obs}/[I] = 5200$ M^{-1} s^{-1}) derivatives showed improved activity, although this again diminished with the *n*-butyl and *sec*-butyl compounds **26a** and **27a** ($k_{obs}/[I] = 4400$ and 1200 M^{-1} s^{-1}, respectively). The isopropyl compound **25a** was inactive ($k_{obs}/[I] = 10$ M^{-1} s^{-1}). A 3α-ethyl was still optimal with the larger 3β-groups as seen in the series **19a**, **20**, **22a**, and **23** ($k_{obs}/[I] = 160$, 1500 (racemic), 3300, and 2500 (racemic) M^{-1} s^{-1}, respectively). Use of substituents other than simple alkyl was investigated with allyl, benzyl, and ether derivatives (i.e., **30a**, $k_{obs}/[I] = 1900$ M^{-1} s^{-1}). These were all less active against HLE and/or less stable than the isosteric alkyl compounds as shown in Table 1.[31] While the spiropentane **21** displayed equivalent *in vitro* activity to diethyl **20** (both racemic, $k_{obs}/[I] = 1900$ vs 1500 M^{-1} s^{-1}, respectively), **20** was 10-fold less stable (0.58 vs 7.70 h). Thus, the optimal 3α group was again found to be ethyl, and the best 3β was *n*-propyl as seen with **24a** ($k_{obs}/[I] = 5200$ M^{-1} s^{-1}). This result was completely unexpected on the basis of our previous investigations of the bicyclic and monoalkyl monocyclic compounds. However, the diethyl substitution was chosen for extensive SAR work[1,18] for several reasons. (1) The hydrolytic stability of **20** was equivalent to that of **24a**, and **20** was shown to be completely stable in human or rat blood for over 12 h at 37 °C.[18] (2) There was only a slight loss in activity on HLE when correcting for **20** being racemic. (3) The increase in the *in vivo* potency for the propyl derivatives was not as large as expected from the increase in the *in vitro* enzyme assay, probably due to greater protein binding (see below). (4) Racemic 4-acetoxy-3,3-diethylazetidin-2-one was much more readily available through an alternate synthesis[18] which allowed the extensive SAR work to be more rapidly pursued.

Since the monoalkyl compounds had shown a large enhancement in HLE activity with substitution on the urea benzyl carbon,[23] this was again investigated in the chiral 3α-ethyl-3β-methyl series. Acylation of **10a** or **10b** with either (R)- or (*S*)-α-alkylbenzyl isocyanates afforded all four possible diastereomers. In the case of methyl substitution, both 4*S* diastereomers gave enhanced activity with that of **40a** being double that of **12a** ($k_{obs}/[I] = 4800$ vs 2000 M^{-1} s^{-1}) and **39a** showing a 7–8-fold increase ($k_{obs}/[I] = 15\,200$ M^{-1} s^{-1}). The 4*R*, α-R diastereomer **39b** remained inactive ($k_{obs}/[I] = 400$ M^{-1} s^{-1}), and the 4*R*, α-S diastereomer (data not shown) was also inactive. Thus, the requirement for *S* stereochemistry at C-4 was maintained. An even more dramatic effect was seen with the *R*-ethyl (**42a**) and *R*-*n*-propyl (**45a**) substitutions with their $k_{obs}/[I]$ values increasing to 91 000 and 152 000 M^{-1} s^{-1}, respectively. The *S*-ethyl diastereomer **43a** remained unchanged at 4700 M^{-1} s^{-1}. However, this effect was not as pronounced in the 3α-ethyl-3β-propyl series with **41a** being comparable to **24a** ($k_{obs}/[I] = 4500$ and 5200 M^{-1} s^{-1}) and **44a** and **46a** ($k_{obs}/[I] = 35\,500$ and 60 000 M^{-1} s^{-1}) having less than one-half the activity of the 3β-methyl series. Using the HLE[32] and **42a** crystal structures, molecular modeling afforded a rational for these enhancements as discussed below.

Table 2. Chemical Structure and Biochemical and Biological Data for the 3,3-Dialkylazetidin-2-ones Having an Alkyl-Substituted Urea



a



b

compd	R_β	R_1	R_2	k_{obs}/[I],[b] M^{-1} s^{-1} (SD)[f]	lung hemorrhage activity: % inhibition[a] screen,[c] 30 mpk, 30 min (SD)[g]	titration,[d] 30/10/3/1/0.3 mpk, 30 min[h]	duration,[e] 30 mpk, 0.5/1/2/3/4/5 h[h]
39a	Me	Me	H	15 200 (1200)	82 (13)	82/51/9/nd[i]/nd	82/87/nd/nd/nd
39b	Me	Me	H	400 (100)	nd		
40a	Me	H	Me	4800 (100)	13 (34)		
41a	*n*-Pr	Me	H	4500 (950)	61 (11)		
42a	Me	Et	H	91 000 (7000)	98 (2)	98/91/58/18/nd $ED_{50} = 3.7$	87/87/73/75/66/51 ($T_{50} = 5$ h)
43a	Me	H	Et	4700 (16)	22 (17)		
44a	*n*-Pr	Et	H	35 500 (400)	52 (20)		
45a	Me	*n*-Pr	H	152 000 (1000)	94 (6)	nd/99/75/38/40 $ED_{50} = 1.5$	
46a	*n*-Pr	*n*-Pr	H	60 000 (1000)	53 (10)		

[a] See the Biochemistry and Biology section and refs 18 and 28 for methodology. [b] See ref 27 for methodology. [c] The compounds were usually screened in three animals dosing po at 30 mpk 30 min prior to IT instillation of HLE. The percent inhibition is the average of all assays run at this dose and time. [d] The dose titrations were done as in the screen but using 30, 10, 3, 1, and 0.3 mpk. On repeated assaying, an ED_{50} could be determined. [e] The duration studies were done as for the screen, but administration of the HLE was after 0.25, 0.5, 1, and 2 h and a $t_{1/2}$ was estimated. [f] Average of two or more determinations at different inhibitor concentrations. [g] Average of three animals at each dose and time. [h] Similar errors were obtained for the titration and duration experiments. [i] Not determined.

Once the enhanced stability and good HLE potency of **12a** had been demonstrated, the hamster lung hemorrhage assay[18,28] was used to screen for possible systemic activity. Upon oral administration of 100 mpk **12a** 15 min prior to IT instillation of 50 units of HLE and allowing the hemorrhage to develop for 3 h, a 95% inhibition of the hemorrhage was obtained. Titration of the dose to lower levels (30, 10, and 3 mpk gave 68%, 46%, and 33% inhibition, respectively) and extension of the predosing time to 30 min to allow for full absorption gave reproducible inhibition in the 60–75% range after a 30 mpk dose. Thus, this protocol became our standard *in vivo* efficacy screen. In a duration assay, the activity at 30 mpk was shown to last for up to 2 h (71%, 67%, 69%, and 32% inhibition after 15, 30, 60, and 120 min, respectively) indicating that good blood stability had also been achieved.

Concurrently with the above *in vitro* SAR work, selected compounds were also evaluated in the above 30 mpk standard screen with the results shown in Table 1. Compounds showing greater than 50% inhibition were also evaluated with a dose–response and/or duration protocol. For good hemorrhage inhibition, both the chemical stability and the HLE inhibitory potency of the compound had to be at least those of **12a**. From the initial work, it was seen that compounds having either less stability (**21**) or lower *in vitro* potency (**12b**, **17a**, **25a**, **27a**, **31a**, and **32a**) than **12a** gave poor results, while this minimal stability, combined with equivalent or better potency, gave comparable (**22a**, **28a**, **29a**, and **30a**) or slightly better (**20** (racemic), **23** (racemic), and **24a**) *in vivo* results. The dramatically increased HLE activity obtained with the alkyl substitutions in the urea also translated into enhanced *in vivo* potency. In the 3α-ethyl-3β-methyl series, **12a**, **39a**, **42a**, and **45a** afforded ED_{50}s of ~25, 10, 2, and 1.5 mpk, respectively, when administered 30 min prior to elastase instillation. The poorer than expected enhancement in the hemorrhage assay (about 20-fold for **45a**) as compared to the k_{obs}/[I] values (75-fold increase for **45a**) is probably attributable to the increased protein binding observed with these more lipophilic derivatives, **12a** exhibiting 86%; **39a**, 88%; **42a**, 96%; and **45a**, nearly 100% protein binding.[33] This was also true with the larger 3β-alkyl moieties with **12a** showing 86%; **20**, 88%; and **24a**, 98% protein binding and is probably the reason for the moderate results with the larger R_β substitutions (i.e., **24a** and **26a**). The combined protein-binding effects at both positions also explains the very poor results in the 3α-ethyl-3β-propyl series **24a**, **41a**, **44a**, and **46a**, giving only 78%, 55%, 52%, and 53% inhibition of hemorrhage at 30 mpk, respectively. Thus, the 3,3-diethyl substitution seemed to possess the optimal balance of stability, inhibitory potency, and *in vivo* efficacy.

With the availability of an X-ray crystal structure of HLE[32] and our previous modeling experience with the cephalosporins,[11] it was of interest to also model these compounds to gain insight into any possible further enhancement of the HLE inhibitory activity and to understand the reversed affinities for the C-4 isomers compared to **2** and the large increase in activity from the urea substitution. Fortunately, **42a** was found to be a crystalline solid amenable for a low-resolution X-ray structure determination[34] which was then utilized as a beginning conformation for the modeling work. This structure also confirmed the stereochemical assignments at the C-3, C-4, and urea positions that had been made by other arguments. Figure 1 shows a schematic model[35] of **42a** fit into the active site of HLE with the hydroxyl of Ser195 covalently bound to the β-lactam carbonyl from the α face in the tetrahedral transition state. The transition state is stabilized by the "oxyanion" pocket formed by hydrogen bonds to the Gly193 and Ser195 backbone NHs. The 3α-ethyl again occupies the S-1 site, and the 3α-methyl can be accommodated with only an apparently small rotation of the β-lactam ring

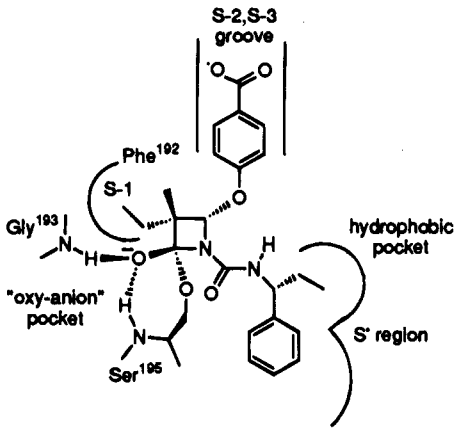


Figure 1. Schematic drawing of **42a** in the active site of HLE.

about the C-2–C-4 axis in order minimize interaction with Phe192, which caps the opening of the S-1 pocket. The *S* configuration at C-4 allows the phenoxy moiety to optimally lie in the S-2–S-3 grove, while the *R* configuration is not able to adopt this orientation and would extend the phenoxy into the solvent. It was also noted that the benzyl of the urea optimally lies along a hydrophilic surface in the prime region and that the potency-enhancing *R* substituents project into a small hydrophobic pocket. The *S* orientation is pointing toward solvent and therefore would not affect the binding as was observed. Surprisingly, upon comparing the X-ray structure with the final minimized bound structure in the HLE model, it was observed that they were nearly identical, the only difference being the conformation of the terminal methyl in the urea.

Conclusion

The placement of a second alkyl group at the C-3 position of monocyclic β-lactam HLE inhibitors has provided the level of chemical stability sufficient for oral absorption and the necessary blood stability for *in vivo* efficacy. The stereospecific synthesis of several 3,3-dialkyl monocyclic derivatives allowed the determination of the optimal binding requirements at the S-1 site of HLE as well as the unanticipated reversal of the configuration of the phenoxy moiety at C-4. Incorporation of *R*-alkyl substituents into the urea was also shown to give a dramatic enhancement in HLE inhibitory potency. These modifications have translated into highly potent, orally active entities as demonstrated in a hamster lung hemorrhage model. With the identification of the 3,3-diethyl substitution as being optimal, an extensive exploration of the phenol-leaving group[1] and substitution on the urea phenyl[18] was pursued. Further optimization of the *R* substitution on the benzylic urea position and incorporation of all the best features from the above studies will be detailed in a subsequent manuscript.[36] Extensive studies of the basic hydrolysis[37] and HLE inhibitory mechanism[38] for this class of compounds and a summary of the chemical development and biological activity of the very potent, orally active HLE inhibitor **4** have also been published.[19]

Experimental Section

General Procedures. Proton NMR spectra were recorded on a Varian XL-200 instrument with tetramethylsilane as internal standard (δ scale) and in the given solvent. Elemental analyses were conducted by the Micro-Analytical Laboratory of Merck and Co. or by Robertson Microlit Laboratories, Inc., and are within 0.4% of the calculated values except as noted. Analytical thin layer chromatography (TLC) was carried out on Analtech, Inc. silica gel GF 250 μm plates (visualized with UV light or ceric sulfate), and preparative TLC was done with Analtech, Inc., silica gel GF 1000 and 2000 μm plates. Flash chromatography was performed with EM silica gel 60 (230–400 mesh) and the given solvent. Preparative liquid chromatography (prep LC) was preformed with a Waters Prep LC500 instrument using silica gel (Prep Pak) columns eluted with the given solvent. Extractions were routinely carried out twice with the given solvent, and each extract was washed with a portion of water and/or sodium bicarbonate ($NaHCO_3$) solution followed by a portion of brine. The organic layers were then combined, dried over sodium sulfate (Na_2SO_4), and concentrated *in vacuo* on a rotary evaporator. Proton NMR spectra were obtained for all intermediates and new compounds and are consistent with the assigned structures. The reported yields are generally the result of a single experiment and are not optimized.

(3*R*,4*S*)-1-[(1,1-Dimethylethyl)dimethylsilyl]-3-methyl-2-oxoazetidine-4-carboxylic Acid (6). To a solution of diisopropylamine (27.5 mL, 200 mmol) in tetrahydrofuran (THF) (150 mL) at −20 °C was added 2.4 M *n*-butyllithium in hexanes (73.5 mL, 175 mmol). After 15 min, the solution was cooled to −70 °C and a solution of (4*S*)-1-[(1,1-dimethylethyl)-dimethylsilyl]-2-oxoazetidine-4-carboxylic acid[20,21a,22] (**5**) (20 g, 87 mmol, $[\alpha]_D = -73.1°$ (EtOH, c = 1), lit.[20] $[\alpha]_D = -74°$ ($CHCl_3$, c = 1)) in THF (75 mL) was added over 5 min via a cannula. The solution was warmed to −20 °C for 15 min before a solution of methyl iodide (13.5 mL, 217 mmol) in THF (20 mL) was added. The reaction mixture was kept between −20 and 0 °C for 30 min and then diluted with ether (300 mL) and poured into a mixture of ice and 1 N HCl (400 mL). The layers were separated, and the aqueous layer was extracted with ether. The ether layers were each washed with brine, combined, dried over Na_2SO_4, and evaporated. The residue was crystallized from hexanes to give 16.7 g (79%) of **6**, $[\alpha]_D = -36.8°$ (EtOH, c = 1.15). An additional 2.0 g (9%) was obtained from the mother liquors after prep LC and crystallization from hexanes. NMR ($CDCl_3$): δ 0.14 (s, 3H, SiMe), 0.32 (s, 3H, SiMe), 0.91 (d, *J* = 7 Hz, 3H, 3-Me), 0.98 (s, 9H, Si-*t*-Bu), 3.34 (dq, *J* = 7 and 4 Hz, 1H, 3-H), 3.71 (d, *J* = 4 Hz, 1H, 4-H). Anal. ($C_{11}H_{21}NO_3Si$) C, H, N.

(3*R*,4*S*)-1-[(1,1-Dimethylethyl)dimethylsilyl]-3-ethyl-3-methyl-2-oxoazetidine-4-carboxylic Acid (7). To a solution of diisopropylamine (13 mL, 93 mmol) in THF (75 mL) at −20 °C was added 2.4 M *n*-butyllithium in hexanes (35 mL, 84 mmol). After 15 min, the solution was cooled to −70 °C and a solution of **6** (10 g, 41 mmol) in THF (50 mL) was added. The solution was warmed to −20 °C for 15 min, and a solution of ethyl iodide (6.7 mL, 84 mmol) in THF (10 mL) was added. After 30 min at −20–0 °C, the reaction mixture was diluted with ether and poured into a mixture of ice and 1 N HCl (200 mL). The layers were separated, and the aqueous layer was reextracted with ether. The ether layers were each washed with brine, dried over Na_2SO_4, combined, and evaporated. The residue was crystallized from a minimum amount of hexanes to give 8.8 g (79%) of **7**, $[\alpha]_D = -66.8°$ (EtOH, c = 0.8). NMR ($CDCl_3$): δ 0.15 (s, 3H, SiMe), 0.31 (s, 3H, SiMe), 0.98 (s, 9H, Si-*t*-Bu), 1.04 (t, *J* = 7 Hz, 3H, 3-CH_2CH_3), 1.22 (s, 3H, 3-Me), 1.78 (q, *J* = 7 Hz, 2H, 3-CH_2CH_3), 3.94 (s, 1H, 4-H). Anal. ($C_{13}H_{25}NO_3Si$) C, H, N.

(3*R*,4*S*)- and (3*R*,4*R*)-4-Acetoxy-3-ethyl-3-methylazetidin-2-one (8b). To a solution of **7** (4.5 g, 16.6 mmol) in dimethylformamide (DMF; 50 mL) and acetic acid (HOAc, 10 mL) under N_2 was added lead tetraacetate (8.1 g, 18.3 mmol). The reaction mixture was heated at 45-50 °C for 3 h and then stirred at room temperature for 16 h before it was poured into ice water and extracted with two portions of ethyl acetate (EtOAc). The EtOAc layers were each washed with water, sodium bicarbonate solution, and brine, combined, dried over Na_2SO_4, and evaporated. The residue was partially purified by elution (0–20% EtOAc/hexanes) through a short silica gel column and gave 2.5 g (88%) of **8b** as an oil and a 3:1 mixture of C-4 isomers. NMR ($CDCl_3$): δ 0.93 and 0.95 (2 s, 3H, 3-Me),

1.02 and 1.04 (2 t, J = 7 Hz, 3H, CH_2CH_3), 1.5–1.8 (m, 2H, CH_2CH_3), 2.08 and 2.12 (2 s, 3H, OAc), 5.53 and 5.60 (2 s, 1H, 4-H), 6.65 (br s, 1H, NH).

(3*R*,4*S*)- and (3*R*,4*R*)-4-[[4-[(1,1-Dimethylethoxy)carbonyl]phenyl]oxy]-3-ethyl-3-methylazetidin-2-one (10a,b). To a solution of **8b** (3.0 g, 17.5 mmol) in acetone (30 mL) was slowly added a solution of 1,1-dimethylethyl 4-hydroxybenzoate[18] (**9**) (5.1 g, 26 mmol) in acetone (20 mL), H_2O (15 mL), and 2 N sodium hydroxide (12 mL, 24 mmol). The reaction mixture was stirred at room temperature for 64 h and then diluted with water and extracted with two portions of EtOAc. The EtOAc layers were each washed with brine and then combined, dried over Na_2SO_4, and evaporated to give 7 g of oil. This was purified using prep LC eluting first with 15–20% EtOAc/hexanes to give recovered phenol and then 2.4 g (45%) of the higher R_f isomer **10b**, $[\alpha]_D$ = +33.3° (EtOH, c = 1). NMR ($CDCl_3$): δ 1.10 (t, 3H, 3-CH_2CH_3), 1.34 (s, 3H, 3-Me), 1.60 (s, 9H, *t*-Bu), 1.84 (q, J = 7.5 Hz, 2H, 3-CH_2CH_3), 5.44 (s, 1H, 4-H), 6.4 (br s, 1H, NH), 6.87 (d, J = 9 Hz, 2H, 2,6-ArH), 7.97 (d, J = 9 Hz, 2H, 3,5-ArH). Anal. ($C_{17}H_{23}NO_4$) C, H, N.

Further elution with 25% EtOAc/hexanes afforded 1.4 g (26%) of the lower R_f isomer **10a**, $[\alpha]_D$ = −39.6° (EtOH, c = 1). NMR ($CDCl_3$): δ 1.06 (t, J = 7.5 Hz, 3H, 3-CH_2CH_3), 1.46 (s, 3H, 3-Me), 1.54 (s, 9H, *t*-Bu), 1.68 (dq, J = 15 and 7.5 Hz, 1H, 3-CH_2CH_3), 1.93 (dq, J = 15 and 7.5 Hz, 1H, 3-CH_2CH_3), 5.37 (s, 1H, 4-H), 6.7 (br s, 1H, NH), 6.87 (d, J = 9 Hz, 2H, 2,6-ArH), 7.97 (d, J = 9 Hz, 2H, 3,5-ArH). Anal. ($C_{17}H_{23}NO_4$) C, H, N.

Equilibration of 10a,b. To a solution of **10b** (4.0 g, 13.1 mmol) in acetone (25 mL) was added a solution of 1,1-dimethylethyl 4-hydroxybenzoate (1.3 g, 6.6 mmol) in acetone (25 mL) and 2 N sodium hydroxide (2.5 mL, 5 mmol). The reaction mixture was stirred at room temperature for 24 h and then diluted with water and extracted with two portions of EtOAc. The EtOAc layers were each washed with brine and then combined, dried over Na_2SO_4, and evaporated. Purification as above afforded 2.4 g (60%) of recovered higher R_f isomer **10b** and 1.4 g (35%) of the desired lower R_f isomer **10a**.

(3*R*,4*S*)-4-[[4-[(1,1-Dimethylethoxy)carbonyl]phenyl]oxy]-3-ethyl-3-methyl-1-[[(phenylmethyl)amino]carbonyl]azetidin-2-one (11a). To a solution of **10a** (1.5 g, 4.9 mmol) in methylene chloride (CH_2Cl_2, 25 mL) were added phenylmethyl isocyanate (1.2 mL, 9.8 mmol), triethylamine (1.4 mL, 9.8 mmol), and 4-(dimethylamino)pyridine (DMAP) (10 mg, catalytic). The reaction mixture was stirred at room temperature for 16 h and then evaporated. The residue was purified by flash chromatography eluting with 10–25% EtOAc/hexanes to give 2.1 g of **11a** as an oil. NMR ($CDCl_3$): δ 1.07 (t, J = 7.5 Hz, 3H, 3-CH_2CH_3), 1.46 (s, 3H, 3-Me), 1.60 (s, 9H, *t*-Bu), 1.68 (dq, J = 15 and 7.5 Hz, 1H, 3-CH_2CH_3), 1.97 (dq, J = 15 and 7.5 Hz, 1H, 3-CH_2CH_3), 4.51 (d, J = 6 Hz, 2H, NCH_2), 5.73 (s, 1H, 4-H), 6.8 (br t, J = 6 Hz, 1H, NH), 7.16 (d, J = 9 Hz, 2H, 2,6-ArH), 7.35 (m, 5H, C_6H_5), 7.99 (d, J = 9 Hz, 2H, 3,5-ArH). Anal. ($C_{25}H_{30}N_2O_5$) C, H, N.

(3*R*,4*S*)-4-[(4-Carboxyphenyl)oxy]-3-ethyl-3-methyl-1-[[(phenylmethyl)amino]carbonyl]azetidin-2-one (12a). To **11a** (2.1 g) in an ice bath under N_2 were added anisole (5 mL) and then precooled trifluoroacetic acid (TFA; 25 mL). After 1.5 h at 0 °C, the volatiles were removed *in vacuo* without heating and the residue was purified by flash chromatography using hexanes, 15% EtOAc/hexanes, and then 1% HOAc in 15% EtOAc/hexanes to give, after ether trituration, 1.8 g of **12a** as a white solid, $[\alpha]_D$ = +6.4° (EtOH, c = 1.3). NMR ($CDCl_3$): δ 1.07 (t, J = 7.5 Hz, 3H, 3-CH_2CH_3), 1.49 (s, 3H, 3-Me), 1.70 (dq, J = 15 and 7.5 Hz, 1H, 3-CH_2CH_3), 1.98 (dq, J = 15 and 7.5 Hz, 1H, 3-CH_2CH_3), 4.53 (d, J = 6 Hz, 2H, NCH_2), 5.79 (s, 1H, 4-H), 6.95 (br t, J = 6 Hz, 1H, NH), 7.14 (d, J = 9 Hz, 2H, 2,6-ArH), 7.35 (m, 5H, C_6H_5), 8.03 (d, J = 9 Hz, 2H, 3,5-ArH). Anal. ($C_{21}H_{22}N_2O_5$) C, H, N.

(3*R*,4*R*)-4-[[4-[(1,1-Dimethylethoxy)carbonyl]phenyl]oxy]-3-ethyl-3-methyl-1-[[(phenylmethyl)amino]carbonyl]azetidin-2-one (11b). Acylation of **10b** (130 mg, 0.43 mmol) with phenylmethyl isocyanate, the same as for **10a**, afforded **11b** (175 mg, 94%). NMR ($CDCl_3$): δ 1.04 (t, J = 7.5 Hz, 3H, 3-CH_2CH_3), 1.34 (s, 3H, 3-Me), 1.60 (s, 9H, *t*-Bu), 1.83 (q, J = 7.5 Hz, 2H, 3-CH_2CH_3), 4.49 (d, J = 6 Hz, 2H, NCH_2), 5.78 (s, 1H, 4-H), 6.87 (br t, J = 6 Hz, 1H, NH), 7.16 (d, J = 9 Hz, 2H, 2,6-ArH), 7.35 (m, 5H, C_6H_5), 7.98 (d, J = 9 Hz, 2H, 3,5-ArH). Anal. ($C_{25}H_{30}N_2O_5$) C, H, N.

(3*R*,4*R*)-4-[(4-Carboxyphenyl)oxy]-3-ethyl-3-methyl-1-[[(phenylmethyl)amino]carbonyl]azetidin-2-one (12b). Deesterification of **11b** (165 mg, 0.38 mmol) was done with TFA, the same as with **11a**, to give **12b** (140 mg, 97%) as a white solid, $[\alpha]_D$ = +0.5° (EtOH, c = 1). NMR ($CDCl_3$): δ 1.05 (t, J = 7.5 Hz, 3H, 3-CH_2CH_3), 1.33 (s, 3H, 3-Me), 1.84 (q, J = 7.5 Hz, 2H, 3-CH_2CH_3), 4.49 (d, J = 6 Hz, 2H, NCH_2), 5.79 (s, 1H, 4-H), 6.87 (br t, J = 6 Hz, 1H, NH), 7.14 (d, J = 9 Hz, 2H, 2,6-ArH), 7.35 (m, 5H, C_6H_5), 8.03 (d, J = 9 Hz, 2H, 3,5-ArH). Anal. ($C_{25}H_{30}N_2O_5$) C, H, N.

Preparation of (3*R*,4*S*)- and (3*S*,4*S*)-3,3-Dialkyl-1-[(1,1-dimethylethyl)dimethylsilyl]-2-oxoazetidine-4-carboxylic Acids (14b). The following intermediate 4*S* acids were derived from L-aspartic acid through alkylation of **5** as described for **7**. The products were generally solids from hexanes or purified by chromatography eluting with EtOAc/hexanes mixtures containing 1% HOAc.

(3*R*,4*S*)-1-[(1,1-Dimethylethyl)dimethylsilyl]-3-methyl-2-oxo-3-propylazetidine-4-carboxylic acid (14b, R_α = *n*-Pr, R_β = Me): NMR ($CDCl_3$) δ 0.13 (s, 3H, SiMe), 0.30 (s, 3H, SiMe), 0.98 (t, J = 7 Hz, 3H, 3-$CH_2CH_2CH_3$), 0.99 (s, 9H, Si-*t*-Bu), 1.21 (s, 3H, 3-Me), 1.1–1.5 (m, 3H, 3-CH_2CH_2), 1.5–1.7 (m, 1H, 3-CH_2), 3.94 (s, 1H, 4-H).

(4*S*)-1-[(1,1-Dimethylethyl)dimethylsilyl]-2-oxo-3,3-dipropylazetidine-4-carboxylic acid (14b, R_α = R_β = *n*-Pr): NMR ($CDCl_3$) δ 0.13 (s, 3H, SiMe), 0.31 (s, 3H, SiMe), 0.8–1.05 (m, 6H, 3-$CH_2CH_2CH_3$), 0.99 (s, 9H, Si-*t*-Bu), 1.2–2.0 (m, 8H, 3-CH_2CH_2), 3.92 (s, 1H, 4-H).

(3*S*,4*S*)-1-[(1,1-Dimethylethyl)dimethylsilyl]-3-ethyl-3-methyl-2-oxoazetidine-4-carboxylic acid (14b, R_α = Me, R_β = Et): NMR ($CDCl_3$) δ 0.12 (s, 3H, SiMe), 0.32 (s, 3H, SiMe), 0.98 (s, 9H, Si-*t*-Bu), 0.99 (t, J = 7.5 Hz, 3H, 3-CH_2CH_3), 1.44 (s, 3H, 3-Me), 1.60 (dq, J = 7.5 and 15 Hz, 1H, 2-CH_2CH_3), 1.76 (dq, J = 7.5 and 15 Hz, 1H, 2-CH_2CH_3), 3.86 (s, 1H, 4-H).

(3*R*,4*S*)-1-[(1,1-Dimethylethyl)dimethylsilyl]-3-ethyl-2-oxo-3-propylazetidine-4-carboxylic acid (14b, R_α = *n*-Pr, R_β = Et): NMR ($CDCl_3$) δ 0.13 (s, 3H, SiMe), 0.30 (s, 3H, SiMe), 0.98 (m, 15H, Si-*t*-Bu, 3-CH_2CH_3, 3-$CH_2CH_2CH_3$), 1.5–2.0 (2 m, 6H, 3-CH_2CH_3, 3-CH_2CH_2), 3.95 (s, 1H, 4-H).

(3*R*,4*S*)-1-[(1,1-Dimethylethyl)dimethylsilyl]-3-ethyl-2-oxo-3-[1-(2-propenyl)]azetidine-4-carboxylic acid (14b, R_α = allyl, R_β = Et): NMR ($CDCl_3$) δ 0.13 (s, 3H, SiMe), 0.31 (s, 3H, SiMe), 0.98 (t, J = 7 Hz, 3H, 3-CH_2CH_3), 0.99 (s, 9H, Si-*t*-Bu), 1.5–2.0 (m, 2H, 3-CH_2), 2.45 (br d, J = 8 Hz, 2H, 3-CH_2CH), 3.94 (s, 1H, 4-H), 5.14 (br d, J = 12 Hz, 1H, 3-CH_2CHCH_2), 5.23 (br s, 1H, 3-CH_2CHCH_2), 5.4–6.0 (m, 1H, 3-CH_2CHCH_2).

(3*R*,4*S*)-1-[(1,1-Dimethylethyl)dimethylsilyl]-3-ethyl-2-oxo-3-(phenylmethyl)azetidine-4-carboxylic acid (14b, R_α = Bn, R_β = Et): NMR ($CDCl_3$) δ −0.09 (s, 3H, SiMe), 0.07 (s, 3H, SiMe), 0.75 (s, 9H, Si-*t*-Bu), 1.12 (t, J = 7.5 Hz, 3H, 3-CH_2CH_3), 1.6–2.0 (m (overlapping q of an ABq), 2H, 2-CH_2CH_3), 2.77 (d, J = 14 Hz, 1H, 3-CH_2Ar), 3.22 (d, J = 14 Hz, 1H, 3-CH_2Ar), 3.92 (s, 1H, 4-H), 7.29 (br s, 5H, C_6H_5).

(3*R*,4*S*)-1-[(1,1-Dimethylethyl)dimethylsilyl]-3-methyl-2-oxo-3-[1-(1-methylethyl)]-2-oxoazetidine-4-carboxylic acid (14b, R_α = *i*-Pr, R_β = Me): NMR ($CDCl_3$) δ 0.16 (s, 3H, SiMe), 0.31 (s, 3H, SiMe), 0.99 (s, 9H, Si-*t*-Bu), 1.04 and 1.06 (2 d, J = 7 Hz, 6H, $CH(CH_3)_2$), 1.22 (s, 3H, 3-Me), 2.0 (heptet, 1H, 3-CH), 3.97 (s, 1H, 4-H).

(4*S*)-1-[(1,1-Dimethylethyl)dimethylsilyl]-2-oxospiro-[cyclopentane-1,3′-azetidine]-4-carboxylic Acid (14b, R_α, R_β = -$(CH_2)_4$-). To a solution of diisopropylamine (7.6 mL, 54.5 mmol) in THF (100 mL) at −20 °C was added 2.3 M *n*-butyllithium in hexanes (21 mL, 48 mmol). After 15 min, the solution was cooled to −70 °C and a solution of **5** (5.0 g, 21.8 mmol) in THF (50 mL) was added over 5 min via a cannula. The solution was warmed to −20 °C for 30 min before being recooled to −70 °C. Another 1 equiv of LDA (prepared as above from diisopropylamine (3.8 mL, 27.3 mmol) in THF (50 mL) and 2.3 M *n*-butyllithium in hexanes (10.5 mL, 24.2 mmol)) was added followed immediately by addition of 1-bromo-4-chlorobutane (5.0 mL, 43.6 mmol) in THF (20 mL). The

reaction mixture was warmed to between −20 and 0 °C for 30 min and then diluted with ether and poured into a mixture of ice and 1 N HCl (200 mL). The layers were separated, and the aqueous layer was extracted with ether. The ether layers were each washed with brine, combined, dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (0−30% EtOAc/hexanes) to give 3.3 g (53%) of **14b** (R_α, R_β = -$(CH_2)_4$-): NMR ($CDCl_3$): δ 0.11 (s, 3H, SiMe), 0.32 (s, 3H, SiMe), 0.97 (s, 9H, Si-*t*-Bu), 1.6−2.2 (3 m, 8H, 3,3-$(CH_2)_4$), 3.97 (s, 1H, 4-H).

Preparation of (3*R*,4*R*) and (3*S*,4*R*)-3,3-Dialkyl-1-[(1,1-dimethylethyl)dimethylsilyl]-2-oxoazetidine-4-carboxylic Acids 14a. The following intermediate 4*R* acids were derived from D-aspartic acid through alkylation of **13** as described for **7**. The products were generally solids from hexanes or purified by chromatography eluting with EtOAc/hexanes mixtures containing 1% HOAc.

(4*R*)-1-[(1,1-Dimethylethyl)dimethylsilyl]-3,3-dimethyl-2-oxoazetidine-4-carboxylic acid (14a, R_α = R_β = Me): NMR ($CDCl_3$) δ 0.14 (s, 3H, SiMe), 0.33 (s, 3H, SiMe), 0.98 (s, 9H, Si-*t*-Bu), 1.22 and 1.46 (2 s, 6H, 3-Me), 3.86 (s, 1H, 4-H).

(3*S*,4*R*)-1-[(1,1-Dimethylethyl)dimethylsilyl]-3-ethyl-3-[1-(2-propenyl)]-2-oxoazetidine-4-carboxylic acid (14a, R_α = Et, R_β = allyl): NMR ($CDCl_3$) δ 0.13 (s, 3H, SiMe), 0.30 (s, 3H, SiMe), 0.97 (t, *J* = 7 Hz, 3H, 3-CH_2CH_3), 0.99 (s, 9H, Si-*t*-Bu), 1.5−2.0 (m, 2H, 3-CH_2CH_3), 2.45 (br d, *J* = 8 Hz, 2H, 3-CH_2CH), 3.93 (s, 1H, 4-H), 5.13 (br d, *J* = 12 Hz, 1H, 3-CH_2-CHCH_2), 5.23 (br s, 1H, 3-CH_2CHCH_2), 5.4−6.0 (m, 1H, 3-CH_2CHCH_2).

(3*S*,4*R*)-1-[(1,1-Dimethylethyl)dimethylsilyl]-3-ethyl-2-oxo-3-propylazetidine-4-carboxylic acid (14a, R_α = Et, R_β = *n*-Pr): NMR ($CDCl_3$) δ 0.13 (s, 3H, SiMe), 0.30 (s, 3H, SiMe), 0.98 (m, 15H, Si-*t*-Bu, 3-CH_2CH_3, 3-$CH_2CH_2CH_3$), 1.5−2.0 (2 m, 6H, 3-CH_2CH_3, 3-CH_2CH_2), 3.95 (s, 1H, 4-H).

(3*S*,4*R*)-1-[(1,1-Dimethylethyl)dimethylsilyl]-3-ethyl-2-oxo-3-(phenylmethyl)azetidine-4-carboxylic acid (14a, R_α = Et, R_β = Bn): NMR ($CDCl_3$) δ −0.09 (s, 3H, SiMe), 0.07 (s, 3H, SiMe), 0.75 (s, 9H, Si-*t*-Bu), 1.12 (t, *J* = 7.5 Hz, 3H, 3-CH_2CH_3), 1.6−2.0 (m (overlapping q of an ABq), 2H, 2-CH_2-CH_3), 2.77 (d, *J* = 14 Hz, 1H, 3-CH_2Ar), 3.22 (d, *J* = 14 Hz, 1H, 3-CH_2Ar), 3.92 (s, 1H, 4-H), 7.29 (br s, 5H, C_6H_5).

(3*S*,4*R*)-1-[(1,1-Dimethylethyl)dimethylsilyl]-3-ethyl-3-[1-(1-methylethyl)]-2-oxoazetidine-4-carboxylic acid (14a, R_α = Et, R_β = *i*-Pr): NMR ($CDCl_3$) δ 0.16 (s, 3H, SiMe), 0.28 (s, 3H, SiMe), 0.99 (m, 9H, Si-*t*-Bu), 0.95−1.1 (m, 9H, 3-CH_2CH_3, 3-CH$(CH_3)_2$), 1.74 (m, 2H, 3-CH_2CH_3), 2.18 (heptet, 1H, 3-CH), 4.00 (s, 1H, 4-H).

(3*S*,4*R*)-1-[(1,1-Dimethylethyl)dimethylsilyl]-3-ethyl-3-[1-(2-methylpropyl)]-2-oxoazetidine-4-carboxylic acid (14a, R_α = Et, R_β = *s*-Bu): NMR ($CDCl_3$) δ 0.13 (s, 3H, SiMe), 0.34 (s, 3H, SiMe), 0.98 (s, 9H, Si-*t*-Bu), 1.14 (m, 9H, CH$(CH_3)_2$, 3-CH_2CH_3), 1.4−2.1 (4 m, 5H, 3-CH_2CH_3, 3-CH_2CH), 3.99 (s, 1H, 4-H).

(3*S*,4*R*)-1-[(1,1-Dimethylethyl)dimethylsilyl]-3-ethyl-3-butyl-2-oxoazetidine-4-carboxylic acid (14a, R_α = Et, R_β = *n*-Bu): NMR ($CDCl_3$) δ 0.13 (s, 3H, SiMe), 0.31 (s, 3H, SiMe), 0.98 (s, 9H, Si-*t*-Bu), 0.95−1.05 (m, 6H, 3-$(CH_2)_3(CH_3)$, 3-CH_2CH_3), 1.3−2.0 (2 m, 8H, 3-CH_2CH_3, 3-$(CH_2)_3$), 3.94 (s, 1H, 4-H).

(3*S*,4*R*)-1-[(1,1-Dimethylethyl)dimethylsilyl]-3-ethyl-3-(methoxymethyl)-2-oxoazetidine-4-carboxylic acid (14a, R_α = Et, R_β = CH_2OMe): NMR ($CDCl_3$) δ 0.14 (s, 3H, SiMe), 0.32 (s, 3H, SiMe), 0.98 (s, 9H, Si-*t*-Bu), 1.07 (t, *J* = 7 Hz, 3H, 3-CH_2CH_3), 1.6−2.0 (m (overlapping q of an ABq), 2H, 3-CH_2-CH_3), 3.40 (s, 3H, OMe), 3.60 (ABq, *J* = 9 and 27 Hz, 2H, 3-CH_2O), 4.27 (s, 1H, 4-H).

Preparation of 4-[[4-[(1,1-Dimethylethoxy)carbonyl]-phenyl]oxy]-3,3-dialkylazetidin-2-ones 15a,b. The following intermediate NH compounds **15a** were derived from the acid intermediates **14a** or **14b** via lead tetraacetate oxidation in acetic acid and simultaneous desilylation followed by displacement of the acetoxy with excess sodium salt of **9** as described for **10a,b**. When diastereomers were formed, they were separated by chromatography using EtOAc/hexanes mixtures, and their relative R_f values are noted.

(3*R*,4*R*)-4-[[4-[(1,1-Dimethylethoxy)carbonyl]phenyl]-oxy]-3-methyl-3-propylazetidin-2-one (15b, R_α = *n*-Pr, R_β = Me): higher R_f major isomer derived from **14b** (R_α = *n*-Pr, R_β = Me); NMR ($CDCl_3$) δ 0.98 (t, 3H, 3-$CH_2CH_2CH_3$), 1.32 (s, 3H, 3-Me), 1.60 (s, 9H, *t*-Bu), 1.4−1.9 (m, 4H, 3-CH_2CH_2), 5.42 (s, 1H, 4-H), 6.50 (br s, 1H, NH), 6.84 (d, *J* = 9 Hz, 2H, 2,6-ArH), 7.96 (d, *J* = 9 Hz, 2H, 3,5-ArH).

(3*R*,4*S*)-4-[[4-[(1,1-Dimethylethoxy)carbonyl]phenyl]-oxy]-3-methyl-3-propylazetidin-2-one (15a, R_α = *n*-Pr, R_β = Me): lower R_f minor isomer derived from **14b** (R_α = *n*-Pr, R_β = Me); NMR ($CDCl_3$): δ 0.93 (t, 3H, *J* = 7.5 Hz, 3-CH_2-CH_2CH_3), 1.44 (s, 3H, 3-Me), 1.60 (s, 9H, *t*-Bu), 1.2−1.9 (m, 4H, 3-CH_2CH_2), 5.32 (s, 1H, 4-H), 6.85 (d, *J* = 9 Hz, 2H, 2,6-ArH), 7.1 (br s, 1H, NH), 7.96 (d, *J* = 9 Hz, 2H, 3,5-ArH).

(*R*,*S*)-4-[[4-[(1,1-Dimethylethoxy)carbonyl]phenyl]oxy]-3,3-dipropylazetidin-2-one (15a,b, R_α = R_β = *n*-Pr): racemic, derived from **14b** (R_α = R_β = *n*-Pr); NMR ($CDCl_3$) δ 0.98 (t, 6H, *J* = 7.5 Hz, 3-$CH_2CH_2CH_3$), 1.60 (s, 9H, *t*-Bu), 1.2−1.9 (m, 8H, 3-CH_2CH_2), 5.40 (s, 1H, 4-H), 6.85 (d, *J* = 9 Hz, 2H, 2,6-ArH), 7.14 (br s, 1H, NH), 7.95 (d, *J* = 9 Hz, 2H, 3,5-ArH).

(3*S*,4*S*)-4-[[4-[(1,1-Dimethylethoxy)carbonyl]phenyl]-oxy]-3-methyl-3-ethylazetidin-2-one (15a, R_α = Me, R_β = Et): higher R_f major isomer derived from **14b** (R_α = Me, R_β = Et); NMR ($CDCl_3$) δ 1.07 (t, *J* = 7.5 Hz, 3H, 3-CH_2CH_3), 1.32 (s, 3H, 3-Me), 1.60 (s, 9H, *t*-Bu), 1.82 (q, *J* = 7.5 Hz, 2H, 3-CH_2), 5.43 (s, 1H, 4-H), 6.70 (br s, 1H, NH), 6.85 (d, *J* = 9 Hz, 2H, 2,6-ArH), 7.96 (d, *J* = 9 Hz, 2H, 3,5-ArH).

(3*S*,4*R*)-4-[[4-[(1,1-Dimethylethoxy)carbonyl]phenyl]-oxy]-3-ethyl-3-methylazetidin-2-one (15b, R_α = Me, R_β = Et): lower R_f minor isomer derived from **14b** (R_α = Me, R_β = Et); NMR ($CDCl_3$) δ 1.06 (t, 3H, *J* = 7.5 Hz, 3-CH_2CH_3), 1.44 (s, 3H, 3-Me), 1.60 (s, 9H, *t*-Bu), 1.68 (dq, *J* = 15 and 7.5 Hz, 1H, 3-CH_2CH_3), 1.93 (dq, *J* = 15 and 7.5 Hz, 1H, 3-CH_2CH_3), 5.37 (s, 1H, 4-H), 6.50 (br s, 1H, NH), 6.85 (d, *J* = 9 Hz, 2H, 2,6-ArH), 7.97 (d, *J* = 9 Hz, 2H, 3,5-ArH).

(3*S*,4*S*)-4-[[4-[(1,1-Dimethylethoxy)carbonyl]phenyl]-oxy]-3-ethyl-3-[1-(2-propenyl)]azetidin-2-one (15a, R_α = Et, R_β = allyl): higher R_f major isomer derived from **14a** (R_α = Et, R_β = allyl); NMR ($CDCl_3$) δ 1.08 (t, 3H, *J* = 7.5 Hz, 3-CH_2CH_3), 1.60 (s, 9H, *t*-Bu), 1.5−2.1 (m, 2H, 3-CH_2CH_3), 2.50 (br d, *J* = 8 Hz, 2H, 3-CH_2CH), 5.10 (br s, 1H, 3-CH_2CHCH_2), 5.22 (br d, *J* = 5 Hz, 1H, 3-CH_2CHCH_2), 5.40 (s, 1H, 4-H), 5.5−6.0 (m, 1H, 3-CH_2CHCH$_2$), 6.85 (d, *J* = 9 Hz, 2H, 2,6-ArH), 7.1 (br s, 1H, NH), 7.97 (d, *J* = 9 Hz, 2H, 3,5-ArH).

(3*S*,4*S*)-4-[[4-[(1,1-Dimethylethoxy)carbonyl]phenyl]-oxy]-3-ethyl-3-propylazetidin-2-one (15a, R_α = Et, R_β = *n*-Pr): higher R_f major isomer derived from **14a** (R_α = Et, R_β = *n*-Pr); NMR ($CDCl_3$) δ 1.00 and 1.07 (2 t, 6H, *J* = 7.5 Hz, 3-CH_2CH_3, 3-$CH_2CH_2CH_3$), 1.60 (s, 9H, *t*-Bu), 1.2−1.8 (m, 5H, 3-CH_2CH_2, 3-$CH_2CH_2CH_3$), 1.96 (dq, *J* = 7.5 and 15 Hz, 1H, 3-CH_2CH_3), 5.44 (s, 1H, 4-H), 6.50 (br s, 1H, NH), 6.86 (d, *J* = 9 Hz, 2H, 2,6-ArH), 7.96 (d, *J* = 9 Hz, 2H, 3,5-ArH).

(3*R*,4*S*)-4-[[4-[(1,1-Dimethylethoxy)carbonyl]phenyl]-oxy]-3-ethyl-3-propylazetidin-2-one (15a, R_α = *n*-Pr, R_β = Et): lower R_f minor isomer derived from **14b** (R_α = Et, R_β = *n*-Pr); NMR ($CDCl_3$) δ 0.96 and 1.07 (2 t, 6H, *J* = 7.5 Hz, 3-CH_2CH_3, 3-$CH_2CH_2CH_3$), 1.60 (s, 9H, *t*-Bu), 1.2−1.8 (m, 5H, 3-CH_2CH_2, 3-$CH_2CH_2CH_3$), 1.83 (br q, *J* = 7.5, 1H, 3-CH_2CH_2-CH_3), 5.44 (s, 1H, 4-H), 6.40 (br s, 1H, NH), 6.87 (d, *J* = 9 Hz, 2H, 2,6-ArH), 7.97 (d, *J* = 9 Hz, 2H, 3,5-ArH).

(3*R*,4*S*)-4-[[4-[(1,1-Dimethylethoxy)carbonyl]phenyl]-oxy]-3-ethyl-3-[1-(2-propenyl)]azetidin-2-one (15a, R_α = allyl, R_β = Et): lower R_f minor isomer derived from **14b** (R_α = Et, R_β = allyl); NMR ($CDCl_3$) δ 1.07 (t, 3H, *J* = 7.5 Hz, 3-CH_2CH_3), 1.60 (s, 9H, *t*-Bu), 1.80 (q, *J* = 7.5 Hz, 2H, 3-CH_2-CH_3), 2.58 (dABq, *J* = 8, 14, and 28 Hz, 2H, 3-CH_2CH), 5.05−5.2 (3 br s, 2H, 3-CH_2CHCH_2), 5.46 (s, 1H, 4-H), 5.90 (m, 1H, 3-CH_2CHCH$_2$), 6.65 (br s, 1H, NH), 6.85 (d, *J* = 9 Hz, 2H, 2,6-ArH), 7.97 (d, *J* = 9 Hz, 2H, 3,5-ArH).

(3*R*,4*S*)-4-[[4-[(1,1-Dimethylethoxy)carbonyl]phenyl]-oxy]-3-ethyl-3-(phenylmethyl)azetidin-2-one (15a, R_α = Bn, R_β = Et): lower R_f minor isomer derived from **14b** (R_α = Et, R_β = Bn); NMR ($CDCl_3$) δ 1.02 (t, 3H, *J* = 7.5 Hz, 3-CH_2CH_3), 1.60 (s, 9H, *t*-Bu), 1.5−1.9 (m, 2H, 3-CH_2CH_3), 3.20 (ABq, *J* = 14 and 25 Hz, 2H, CH_2Ar), 5.52 (s, 1H, 4-H), 6.85

(br s, 1H, NH), 6.93 (d, J = 9 Hz, 2H, 2,6-ArH), 7.2–7.4 (m, 5H, C_6H_5), 8.01 (d, J = 9 Hz, 2H, 3,5-ArH).

(3*S*,4*S*)-4-[[4-[(1,1-Dimethylethoxy)carbonyl]phenyl]oxy]-3-ethyl-3-(phenylmethyl)azetidin-2-one (15a, R_α = Et, R_β = Bn): higher R_f major isomer derived from **14a** (R_α = Et, R_β = Bn); NMR ($CDCl_3$) δ 1.18 (t, 3H, J = 7.5 Hz, 3-CH_2CH_3), 1.60 (s, 9H, t-Bu), 1.78 (dq, J = 15 and 7.5 Hz, 1H, 3-CH_2CH_3), 2.03 (dq, J = 15 and 7.5 Hz, 1H, 3-CH_2CH_3), 3.09 (ABq, J = 14 and 58 Hz, 2H, CH_2Ar), 5.34 (s, 1H, 4-H), 6.38 (br s, 1H, NH), 6.75 (d, J = 9 Hz, 2H, 2,6-ArH), 7.2–7.4 (m, 5H, C_6H_5), 7.93 (d, J = 9 Hz, 2H, 3,5-ArH).

(*R*,*S*)-4-[[4-[(1,1-Dimethylethoxy)carbonyl]phenyl]oxy]-spiro[cyclopentane-1,3′-azetidin]-2-one (15a,b, R_α, R_β = -$(CH_2)_4$-): racemic derived from **14b** (R_α, R_β = -$(CH_2)_4$-); NMR ($CDCl_3$) δ 1.60 (s, 9H, t-Bu), 1.5–2.2 (2 m, 8H, 3,3-$(CH_2)_4$), 5.45 (s, 1H, 4-H), 6.50 (br s, 1H, NH), 6.86 (d, J = 9 Hz, 2H, 2,6-ArH), 7.97 (d, J = 9 Hz, 2H, 3,5-ArH).

(3*R*,4*S*)-4-[[4-[(1,1-Dimethylethoxy)carbonyl]phenyl]oxy]-3-methyl-3-[1-(1-methylethyl)]-2-oxoazetidine-4-carboxylic acid (15a, R_α = *i*-Pr, R_β = Me): lower R_f minor isomer derived from **14b** (R_α = i-Pr, R_β = Me); NMR ($CDCl_3$) δ 0.99 and 1.14 (2 d, J = 7 Hz, 6H, $CH(CH_3)_2$), 1.35 (s, 3H, 3-Me), 1.62 (s, 9H, t-Bu), 2.45 (heptet, 1H, 3-C*H*), 5.37 (s, 1H, 4-H), 6.65 (br s, 1H, NH), 6.88 (d, J = 9 Hz, 2H, 2,6-ArH), 7.97 (d, J = 9 Hz, 2H, 3,5-ArH).

(3*S*,4*S*)-4-[[4-[(1,1-Dimethylethoxy)carbonyl]phenyl]oxy]-3-ethyl-3-[1-(1-methylethyl)]-2-oxoazetidine-4-carboxylic acid (15a, R_α = Et, R_β = *i*-Pr): higher R_f major isomer derived from **14a** (R_α = Et, R_β = i-Pr); NMR ($CDCl_3$) δ 1.04 and 1.06 (2 d, J = 7 Hz, 6H, $CH(CH_3)_2$), 1.14 (t, 3H, 3-CH_2CH_3), 1.62 (s, 9H, t-Bu), 1.82 (dq, J = 15 and 7.5 Hz, 1H, 3-CH_2CH_3), 2.03 (dq, J = 15 and 7.5 Hz, 1H, 3-CH_2CH_3), 2.15 (heptet, 1H, 3-C*H*), 5.48 (s, 1H, 4-H), 6.50 (br s, 1H, NH), 6.89 (d, J = 9 Hz, 2H, 2,6-ArH), 7.97 (d, J = 9 Hz, 2H, 3,5-ArH).

(3*S*,4*S*)-4-[[4-[(1,1-Dimethylethoxy)carbonyl]phenyl]oxy]-3-ethyl-3-[1-(2-methylpropyl)]-2-oxoazetidine-4-carboxylic acid (15a, R_α = Et, R_β = *s*-Bu): higher R_f major isomer derived from **14a** (R_α = Et, R_β = s-Bu); NMR ($CDCl_3$) δ 0.92 and 1.02 (2 d, J = 7 Hz, 6H, $CH(CH_3)_2$), 1.12 (t, 3H, 3-CH_2CH_3), 1.60 (s, 9H, t-Bu), 1.4–2.1 (m, 5H, 3-CH_2CH_3, 3-CH_2CH), 5.46 (s, 1H, 4-H), 6.50 (br s, 1H, NH), 6.88 (d, J = 9 Hz, 2H, 2,6-ArH), 7.97 (d, J = 9 Hz, 2H, 3,5-ArH).

(3*S*,4*S*)-4-[[4-[(1,1-Dimethylethoxy)carbonyl]phenyl]oxy]-3-ethyl-3-butyl-2-oxoazetidine-4-carboxylic acid (15a, R_α = Et, R_β = *n*-Bu): higher R_f major isomer derived from **14a** (R_α = Et, R_β = n-Bu); NMR ($CDCl_3$) δ 0.95 (t, J = 7 Hz, 3H, 3-$(CH_2)_3CH_3$), 1.06 (t, 3H, 3-CH_2CH_3), 1.58 (s, 9H, t-Bu), 1.2–1.8 (2 m, 7H, 3-CH_2CH_3, 3-$(CH_2)_3$), 1.94 (dq, J = 15 and 7.5 Hz, 1H, 3-CH_2CH_3), 5.44 (s, 1H, 4-H), 6.60 (br s, 1H, NH), 6.87 (d, J = 9 Hz, 2H, 2,6-ArH), 7.97 (d, J = 9 Hz, 2H, 3,5-ArH).

(3*S*,4*S*)-4-[[4-[(1,1-Dimethylethoxy)carbonyl]phenyl]oxy]-3-ethyl-3-(methoxymethyl)-2-oxoazetidine-4-carboxylic acid (15a, R_α = Et, R_β = CH_2OMe): lower R_f isomer derived from **14a** (R_α = Et, R_β = CH_2OMe); NMR ($CDCl_3$) δ 1.08 (t, J = 7 Hz, 3H, 3-CH_2CH_3), 1.60 (s, 9H, t-Bu), 1.89 (dq, J = 15 and 7.5 Hz, 1H, 3-CH_2CH_3), 1.94 (dq, J = 15 and 7.5 Hz, 1H, 3-CH_2CH_3), 3.45 (s, 3H, OMe), 3.67 (ABq, J = 10 and 15 Hz, 2H, 3-CH_2O), 5.73 (s, 1H, 4-H), 6.60 (br s, 1H, NH), 6.93 (d, J = 9 Hz, 2H, 2,6-ArH), 7.97 (d, J = 9 Hz, 2H, 3,5-ArH).

Preparation of 4-[(4-Carboxyphenyl)oxy]-3,3-dialkyl-1-[[(phenylmethyl)amino]carbonyl]azetidin-2-ones 16–32. The following compounds as listed in Table 1 were prepared from the above intermediate NH compounds **15a** or **15b** by acylation with phenylmethyl isocyanate and deesterification with TFA as described above for **12a**. The compounds were usually purified by preparative TLC using 1% HOAc in EtOAc/hexanes mixtures and/or precipitation from ether/hexanes.

(4*R*,*S*)-4-[(4-Carboxyphenyl)oxy]-3,3-dimethyl-1-[[(phenylmethyl)amino]carbonyl]azetidin-2-one (16): derived from racemic **15a,b** (R_α = R_β = Me); NMR ($CDCl_3$) δ 1.34 and 1.51 (2 s, 6H, 3-Me_2), 4.52 (d, J = 6 Hz, 2H, NCH_2), 5.77 (s, 1H, 4-H), 6.88 (br t, J = 6 Hz, 1H, NH), 7.10 (d, J = 9 Hz, 2H, 2,6-ArH), 7.34 (s, 5H, C_6H_5), 8.03 (d, J = 9 Hz, 2H, 3,5-ArH); no analysis available.

(3*R*,4*S*)-4-[(4-Carboxyphenyl)oxy]-3-methyl-3-propyl-1-[[(phenylmethyl)amino]carbonyl]azetidin-2-one (17a): derived from the lower R_f isomer **15a** (R_α = n-Pr, R_β = Me); NMR ($CDCl_3$) δ 0.94 (t, 3H, 3-$CH_2CH_2CH_3$), 1.49 (s, 3H, 3-Me), 1.2–1.7 (2 m, 3H, 3-CH_2CH_2), 1.85 (br q, J = 7.5 Hz, 1H, 3-CH_2), 4.53 (d, J = 6 Hz, 2H, NCH_2), 5.76 (s, 1H, 4-H), 6.92 (br t, J = 6 Hz, 1H, NH), 7.15 (d, J = 9 Hz, 2H, 2,6-ArH), 7.36 (s, 5H, C_6H_5), 8.04 (d, J = 9 Hz, 2H, 3,5-ArH). Anal. ($C_{22}H_{24}N_2O_5$) C, H, N.

(3*R*,4*R*)-4-[(4-Carboxyphenyl)oxy]-3-methyl-3-propyl-1-[[(phenylmethyl)amino]carbonyl]azetidin-2-one (17b): derived from the higher R_f isomer **15b** (R_α = n-Pr, R_β = Me); NMR ($CDCl_3$) δ 0.99 (t, 3H, 3-$CH_2CH_2CH_3$), 1.34 (s, 3H, 3-Me), 1.2–1.9 (2 m, 4H, 3-CH_2CH_2), 4.51 (d, J = 6 Hz, 2H, NCH_2), 5.81 (s, 1H, 4-H), 6.90 (br t, J = 6 Hz, 1H, NH), 7.16 (d, J = 9 Hz, 2H, 2,6-ArH), 7.36 (s, 5H, C_6H_5), 8.04 (d, J = 9 Hz, 2H, 3,5-ArH). Anal. ($C_{22}H_{24}N_2O_5$) C, H, N.

(3*R*,4*S*)-4-[(4-Carboxyphenyl)oxy]-3-methyl-3-[1-(1-methylethyl)]-1-[[(phenylmethyl)amino]carbonyl]-azetidin-2-one (18a): derived from the lower R_f minor isomer **15a** (R_α = i-Pr, R_β = Me); NMR ($CDCl_3$) δ 0.96 and 1.14 (2 d, J = 7 Hz, 6H, $CH(CH_3)_2$), 1.37 (s, 3H, 3-Me), 2.51 (heptet, 1H, 3-C*H*), 4.50 (d, J = 6 Hz, NCH_2), 5.76 (s, 1H, 4-H), 6.94 (br t, J = 6 Hz, 1H, NH), 7.29 (d, J = 9 Hz, 2H, 2,6-ArH), 7.33 (s, 5H, C_6H_5), 8.08 (d, J = 9 Hz, 2H, 3,5-ArH). Anal. ($C_{22}H_{24}N_2O_5$) C, H, N.

(3*S*,4*S*)-4-[(4-Carboxyphenyl)oxy]-3-ethyl-3-methyl-1-[[(phenylmethyl)amino]carbonyl]azetidin-2-one (19a): derived from the major isomer **15a** (R_α = Me, R_β = Et); NMR ($CDCl_3$) δ 1.05 (t, J = 7.5 Hz, 3H, 3-CH_2CH_3), 1.33 (s, 3H, 3-Me), 1.85 (q, J = 7.5 Hz, 2H, 3-CH_2CH_3), 4.51 (d, J = 6 Hz, 2H, NCH_2), 5.83 (s, 1H, 4-H), 6.90 (br t, J = 6 Hz, 1H, NH), 7.16 (d, J = 9 Hz, 2H, 2,6-ArH), 7.35 (m, 5H, C_6H_5), 8.05 (d, J = 9 Hz, 2H, 3,5-ArH). Anal. ($C_{21}H_{22}N_2O_5$) C, H, N.

(3*S*,4*R*)-4-[(4-Carboxyphenyl)oxy]-3-ethyl-3-methyl-1-[[(phenylmethyl)amino]carbonyl]azetidin-2-one (19b): derived from the lower R_f minor isomer **15b** (R_α = Me, R_β = Et); NMR ($CDCl_3$) δ 1.07 (t, J = 7.5 Hz, 3H, 3-CH_2CH_3), 1.49 (s, 3H, 3-Me), 1.68 (dq, J = 15 and 7.5 Hz, 1H, 3-CH_2CH_3), 1.98 (dq, J = 15 and 7.5 Hz, 1H, 3-CH_2CH_3), 4.52 (d, J = 6 Hz, 2H, NCH_2), 5.78 (s, 1H, 4-H), 6.92 (br t, J = 6 Hz, 1H, NH), 7.14 (d, J = 9 Hz, 2H, 2,6-ArH), 7.35 (m, 5H, C_6H_5), 8.04 (d, J = 9 Hz, 2H, 3,5-ArH). Anal. ($C_{21}H_{22}N_2O_5$) C, H, N.

(4*R*,*S*)-4-[(4-Carboxyphenyl)oxy]-1-[[(phenylmethyl)amino]carbonyl]spiro[cyclopentane-1,3′-azetidin]-2-one (21): derived from racemic **15a,b** (R_α, R_β = -$(CH_2)_4$-); NMR (acetone-d_6) δ 1.5–2.4 (4 m, 8H, 3,3-$(CH_2)_4$), 4.44 (d, J = 6 Hz, 2H, NCH_2), 6.05 (s, 1H, 4-H), 7.15 (br t, 1H, NH), 7.26 (d, J = 9 Hz, 2H, 2,6-ArH), 7.1–7.3 (m, 5H, C_6H_5), 7.97 (d, J = 9 Hz, 2H, 3,5-ArH). Anal. ($C_{22}H_{22}N_2O_5$) C, H, N.

(3*R*,4*S*)-4-[(4-Carboxyphenyl)oxy]-3-ethyl-3-propyl-1-[[(phenylmethyl)amino]carbonyl]azetidin-2-one (22a): derived from the lower R_f minor isomer **15a** (R_α = n-Pr, R_β = Et); NMR ($CDCl_3$) δ 0.97 and 1.09 (2 t, 6H, J = 7.5 Hz, 3-CH_2CH_3, 3-$CH_2CH_2CH_3$), 1.2–1.9 (m, 5H, 3-CH_2CH_3, 3-$CH_2CH_2CH_3$), 1.98 (br q, J = 7.5 Hz, 1H, 3-$CH_2CH_2CH_3$), 4.50 (d, J = 6 Hz, 2H, NCH_2), 5.81 (s, 1H, 4-H), 6.92 (br t, J = 6 Hz, 1H, NH), 7.24 (d, J = 9 Hz, 2H, 2,6-ArH), 7.33 (m, 5H, C_6H_5), 8.06 (d, J = 9 Hz, 2H, 3,5-ArH). Anal. ($C_{21}H_{22}N_2O_5$) C, H, N.

(4*R*,*S*)-4-[(4-Carboxyphenyl)oxy]-3,3-dipropyl-1-[[(phenylmethyl)amino]carbonyl]azetidin-2-one (23): derived from racemic **15a,b** (R_α = R_β = n-Pr); NMR ($CDCl_3$) δ 0.98 (t, 6H, 3-$CH_2CH_2CH_3$), 1.1–2.0 (2 m, 8H, 3-CH_2CH_2), 4.52 (d, J = 6 Hz, 2H, NCH_2), 5.82 (s, 1H, 4-H), 6.93 (br t, J = 6 Hz, 1H, NH), 7.16 (d, J = 9 Hz, 2H, 2,6-ArH), 7.36 (m, 5H, C_6H_5), 8.08 (d, J = 9 Hz, 2H, 3,5-ArH). Anal. ($C_{24}H_{28}N_2O_5$) C, H, N.

(3*S*,4*S*)-4-[(4-Carboxyphenyl)oxy]-3-ethyl-3-propyl-1-[[(phenylmethyl)amino]carbonyl]azetidin-2-one (24a): derived from the higher R_f major isomer **15a** (R_α = Et, R_β = n-Pr); NMR ($CDCl_3$) δ 0.99 and 1.07 (2 t, 6H, J = 7.5 Hz, 3-CH_2CH_3, 3-$CH_2CH_2CH_3$), 1.2–1.9 (m, 5H, 3-CH_2CH_3, 3-$CH_2CH_2CH_3$), 1.98 (dq, J = 7.5 and 15 Hz, 1H, 3-CH_2CH_3),

4.51 (d, J = 6 Hz, 2H, NCH_2), 5.82 (s, 1H, 4-H), 6.90 (br t, J = 6 Hz, 1H, NH), 7.26 (d, J = 9 Hz, 2H, 2,6-ArH), 7.33 (m, 5H, C_6H_5), 8.06 (d, J = 9 Hz, 2H, 3,5-ArH). Anal. ($C_{23}H_{26}N_2O_5$) C, H, N.

(3*S*,4*S*)-4-[(4-Carboxyphenyl)oxy]-3-ethyl-3-[1-(1-methylethyl)]-1-[[(phenylmethyl)]amino]carbonyl]azetidin-2-one (25a): derived from the higher R_f major isomer **15a** (R_α = Et, R_β = *i*-Pr); NMR ($CDCl_3$) δ 1.02 and 1.03 (2 d, J = 7 Hz, 6H, $CH(CH_3)_2$), 1.13 (t, 3H, 3-CH_2CH_3), 1.82 (dq, J = 7.5 and 15 Hz, 1H, 3-CH_2CH_3), 2.04 (dq, J = 7.5 and 15 Hz, 1H, 3-CH_2CH_3), 2.25 (heptet, 1H, 3-CH), 4.50 (d, J = 6 Hz, NCH_2), 5.83 (s, 1H, 4-H), 6.92 (br t, J = 6 Hz, 1H, NH), 7.32 (s, 5H, C_6H_5), 7.35 (d, J = 9 Hz, 2H, 2,6-ArH), 8.07 (d, J = 9 Hz, 2H, 3,5-ArH). Anal. ($C_{23}H_{26}N_2O_5$) C, H, N.

(3*S*,4*S*)-4-[(4-Carboxyphenyl)oxy]-3-ethyl-3-butyl-1-[[(phenylmethyl)amino]carbonyl]azetidin-2-one (26a): derived from the higher R_f major isomer **15a** (R_α = Et, R_β = *n*-Bu); NMR ($CDCl_3$) δ 0.94 (t, J = 7 Hz, 3H, 3-$(CH_2)_3CH_3$), 1.07 (t, 3H, 3-CH_2CH_3), 1.1–1.8 (2 m, 7H, 3-$(CH_2)_3CH_3$, 3-CH_2CH_3), 1.99 (dq, J = 7.5 and 15 Hz, 1H, 3-CH_2CH_3), 4.52 (d, J = 6 Hz, 2H, NCH_2), 5.82 (s, 1H, 4-H), 6.95 (br t, 1H, NH), 7.26 (d, J = 9 Hz, 2H, 2,6-ArH), 7.32 (s, 5H, C_6H_5), 8.08 (d, J = 9 Hz, 2H, 3,5-ArH). Anal. ($C_{24}H_{28}N_2O_5$) C, H, N.

(3*S*,4*S*)-4-[(4-Carboxyphenyl)oxy]-3-ethyl-3-[1-(2-methylpropyl)-1-[[(phenylmethyl)amino]carbonyl]azetidin-2-one (27a): derived from the higher R_f major isomer **15a** (R_α = Et, R_β = *s*-Bu); NMR ($CDCl_3$) δ 0.92 and 0.98 (2 d, J = 7 Hz, 6H, $CH(CH_3)_2$), 1.12 (t, 3H, 3-CH_2CH_3), 1.4–2.0 (2 m, 4H, 3-CH_2CH_3, 3-CH_2CH), 2.07 (dq, J = 7.5 and 15 Hz, 1H, 3-CH_2CH_3), 4.50 (d, J = 6 Hz, 2H, NCH_2), 5.87 (s, 1H, 4-H), 6.95 (br t, 1H, NH), 7.2–7.4 (m, 7H, C_6H_5, 2,6-ArH), 8.07 (d, J = 9 Hz, 2H, 3,5-ArH).

(3*R*,4*S*)-4-[(4-Carboxyphenyl)oxy]-3-ethyl-3-[1-(2-propenyl)]-1-[[(phenylmethyl)amino]carbonyl]azetidin-2-one (28a): derived from the lower R_f minor isomer **15a** (R_α = allyl, R_β = Et); NMR (acetone-d_6) δ 0.97 (t, 3H, J = 7.5 Hz, 3-CH_2CH_3), 1.84 (q, J = 7.5 Hz, 2H, 3-CH_2CH_3), 2.53 (d, ABq, J = 7, 14, and 28 Hz, 2H, 3-CH_2CH), 4.44 (d, J = 6 Hz, 2H, NCH_2), 5.07, 5.09, 5.15 (3 br s, 2H, 3-CH_2CHCH_2), 5.5–6.0 (m, 1H, 3-CH_2CHCH_2), 5.99 (s, 1H, 4-H), 7.1–7.4 (m, 8H, NH, 2,6-ArH, C_6H_5), 7.97 (d, J = 9 Hz, 2H, 3,5-ArH). Anal. ($C_{23}H_{24}N_2O_5$) C, H, N.

(3*S*,4*S*)-4-[(4-Carboxyphenyl)oxy]-3-ethyl-3-[1-(2-propenyl)]-1-[[(phenylmethyl)amino]carbonyl]azetidin-2-one (29a): derived from the higher R_f major isomer **15a** (R_α = Et, R_β = allyl); NMR ($CDCl_3$) δ 1.08 (t, 3H, J = 7.5 Hz, 3-CH_2CH_3), 1.5–2.1 (m, 2H, 3-CH_2CH_3), 2.50 (br d, J = 8 Hz, 2H, 3-CH_2CH), 4.43 (d, J = 6 Hz, 2H, NCH_2), 5.10 (br s, 1H, 3-CH_2CHCH_2), 5.22 (br d, J = 5 Hz, 3-CH_2CHCH_2), 5.5–6.0 (m, 1H, 3-CH_2CHCH_2), 5.83 (s, 1H, 4-H), 6.8 (t, J = 6 Hz, 1H, NH), 7.13 (d, J = 9 Hz, 2H, 2,6-ArH), 7.35 (m, 5H, C_6H_5), 8.00 (d, J = 9 Hz, 2H, 3,5-ArH). Anal. ($C_{23}H_{24}N_2O_5$) C, H, N.

(3*S*,4*S*)-4-[(4-Carboxyphenyl)oxy]-3-ethyl-3-(methoxymethyl)-1-[[(phenylmethyl)amino]carbonyl]azetidin-2-one (30a): derived from the lower R_f isomer **15a** (R_α = Et, R_β = CH_2OMe); NMR (acetone-d_6) δ 1.06 (t, 3H, J = 7.5 Hz, 3-CH_2CH_3), 1.72 (dq, J = 7.5 and 15 Hz, 1H, 3-CH_2CH_3), 1.82 (dq, J = 7.5 and 15 Hz, 1H, 3-CH_2CH_3), 3.40 (s, 3H, OMe), 3.78 (s, 2H, 3-OCH_2), 4.50 (d, J = 6 Hz, 2H, NCH_2), 6.14 (s, 1H, 4-H), 7.2–7.4 (m, 8H, NH, 2,6-ArH, C_6H_5), 8.00 (v br s, 2H, 3,5-ArH). Anal. ($C_{22}H_{24}N_2O_6$) C, H, N.

(3*R*,4*S*)-4-[(4-Carboxyphenyl)oxy]-3-ethyl-3-(phenylmethyl)-1-[[(phenylmethyl)amino]carbonyl]azetidin-2-one (31a): derived from the lower R_f minor isomer **15a** (R_α = Bn, R_β = Et); NMR ($CDCl_3$) δ 1.02 (t, 3H, J = 7.5 Hz, 3-CH_2CH_3), 1.5–1.9 (m, 2H, 3-CH_2CH_3), 3.22 (ABq, J = 14 and 58 Hz, 2H, CH_2Ar), 4.52 (d, J = 6 Hz, 2H, NCH_2), 5.97 (s, 1H, 4-H), 7.00 (br t, 1H, NH), 7.2–7.4 (m, 12H, 3-$CH_2C_6H_5$, $NCH_2C_6H_5$, 2,6-ArH), 8.11 (d, J = 9 Hz, 2H, 3,5-ArH). Anal. ($C_{27}H_{26}N_2O_5 \cdot 0.25H_2O$) C, H, N.

(3*S*,4*S*)-4-[(4-Carboxyphenyl)oxy]-3-ethyl-3-(phenylmethyl)-1-[[(phenylmethyl)amino]carbonyl]azetidin-2-one (32a): derived from the higher R_f major isomer **15a** (R_α = Et, R_β = Bn); NMR ($CDCl_3$) δ 1.18 (t, 3H, J = 7.5 Hz, 3-CH_2CH_3), 1.78 (dq, J = 15 and 7.5 Hz, 1H, 3-CH_2CH_3), 2.03 (dq, J = 15 and 7.5 Hz, 1H, 3-CH_2CH_3), 3.12 (ABq, J = 14 and 38 Hz, 2H, CH_2Ar), 4.44 (dABq, J = 6, 14, and 26 Hz, 2H, NCH_2), 5.80 (s, 1H, 4-H), 6.85 (br t, 1H, NH), 7.00 (d, J = 9 Hz, 2H, 2,6-ArH), 7.2–7.4 (m, 10H, 3-$CH_2C_6H_5$, $NCH_2C_6H_5$), 7.98 (d, J = 9 Hz, 2H, 3,5-ArH). Anal. ($C_{27}H_{26}N_2O_5$) C, H, N.

(3*S*,4*S*)-4-[(4-Carboxyphenyl)oxy]-3-propyl-3-methyl-1-[[(phenylmethyl)oxy]carbonyl]azetidin-2-one (33). To a solution of (3*S*,4*S*)-4-[[4-[(1,1-dimethylethoxy)carbonyl]phenyl]-oxy]-3-propyl-3-methylazetidin-2-one (**14a**, R_α = Me, R_β = *n*-Pr) (150 mg, 0.47 mmol, prepared the same as **14a** (R_α = Me, R_β = Et)) in CH_2Cl_2 (5 mL) at 0 °C were added triethylamine (0.135 mL, 0.94 mmol), DMAP (catalytic), and phenylmethyl isocyanate (0.135 mL, 0.94 mmol). The reaction mixture was allowed to warm to room temperature for 6 h. The reaction mixture was concentrated, and the residue was purified by prep TLC (30% EtOAc/hexanes) to afford 170 mg (80%) of (3*S*,4*S*)-4-[[4-[(1,1-dimethylethoxy)carbonyl]phenyl]oxy]-3-propyl-3-methyl-1-[[(phenylmethyl)oxy]carbonyl]azetidin-2-one. Deesterification of 150 mg with TFA (3 mL) and anisole (1 mL) as above for **12a** gave, after prep TLC (1% HOAc in 20% EtOAc/hexanes), 120 mg (91%) of **33** as a white solid. NMR ($CDCl_3$): δ 0.98 (t, 3H, J = 7.5 Hz, 3-$CH_2CH_2CH_3$), 1.35 (s, 3H, 3-CH_3), 1.2–1.9 (2 m, 4H, 3-CH_2CH_2), 5.23 (s, 2H, OCH_2), 5.74 (s, 1H, 4-H), 7.05 (d, J = 9 Hz, 2H, 2,6-ArH), 7.33 (s, 5H, C_6H_5), 8.04 (d, J = 9 Hz, 2H, 3,5-ArH). Anal. ($C_{22}H_{23}N_2O_6$) C, H, N.

(*R*)- and (*S*)-1-Phenylpropyl Isocyanate (35a,b).[39] A saturated solution of phosgene in EtOAc (70 mL) was prepared in a three-necked flask by bubbling through phosgene gas for 10 min. A solution of (*S*)-1-phenylpropylamine (**34b**) (423 mg, 3.13 mmol) in EtOAc (10 mL) was added dropwise over 10 min, and phosgene was bubbled through for another 45 min. The reaction mixture was then heated to 45 °C for 1 h when a clear solution had been attained. The reaction mixture was concentrated by distillation to 5 mL to give a solution of **35b** which was used directly in the acylation reaction. IR ($CHCl_3$): 2280 cm^{-1}. Similarly, **35a** was prepared from **34a**.

(*R*)-1-Phenylbutyl Isocyanate (37). To a solution of (*R*)-2-phenylpentanoic acid (**36**)[25] ($[\alpha]_D$ = −40.1° (EtOH, c = 1)) (0.8 g, 4.5 mmol) in CH_2Cl_2 (15 mL) were added a drop of DMF (catalytic) and oxalyl chloride (1 mL) at room temperature. The reaction mixture was stirred for 30 min, at which time the gas evolution had stopped, and then concentrated *in vacuo* to dryness. The residue was taken up in acetone (15 mL) and cooled in an ice bath. A solution of sodium azide (0.7 g, 11 mmol) in H_2O (10 mL) was added, and the reaction mixture was stirred for 30 min at <5 °C and then poured into a mixture of ice water, ether, and hexanes (1:1). The layers were separated, and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* without heating to 5 mL. IR: 2140 cm^{-1}. (Note: the acyl azide can violently decompose when heated or concentrated to dryness and should be used immediately.) The concentrated solution of acyl azide was taken up in chloroform (5 mL) and added dropwise to another 10 mL of chloroform at 80 °C. After a further 30 min at reflux, the solution was concentrated *in vacuo* to give 0.8 g (100%) of crude **37** which was used directly in the acylation. IR ($CHCl_3$): 2260 cm^{-1}.

(3*R*,4*S*)-4-[[4-[(1,1-Dimethylethoxy)carbonyl]phenyl]-oxy]-3-ethyl-3-methyl-1-[[[(*R*)-1-(1-phenylpropyl)]amino]-carbonyl]azetidin-2-one (42a, *tert*-butyl ester). To a solution of **10a** (3.26 g, 10.7 mmol) in CH_2Cl_2 (15 mL) were added triethylamine (3.1 mL, 21.4 mmol), DMAP (50 mg, catalytic) and (*R*)-1-phenylpropyl isocyanate (**35a**) (2.15 g, 13.4 mmol). The reaction mixture was heated at 50 °C for 1.5 h and then stirred at room temperature for 16 h. TLC (20% EtOAc/hexanes) at this time indicated some remaining **10a**, so an additional portion of **35a** (0.5 g, 3.1 mmol) was added and the reaction mixture heated again at 50 °C for 2 h to complete the reaction. TLC now indicated complete conversion to the product and indicated only a trace of any lower diastereomer. The solution was poured into aqueous $NaHCO_3$ and extracted twice with CH_2Cl_2. The CH_2Cl_2 layers were washed with H_2O, 1.2 N HCl, and brine, dried over Na_2SO_4, combined, and evaporated. The residue was purified by prep LC with a gradient of 10–20% EtOAc/hexanes to obtain **42a** (*t*-Bu ester) as a thick oil (5.0 g, 100%). NMR ($CDCl_3$): δ 0.95

(t, J = 7.5 Hz, 3H, NCHCH$_2$CH_3), 1.10 (t, J = 7.5 Hz, 3H, 3-CH$_2$CH_3), 1.44 (s, 3H, 3-Me), 1.60 (s, 9H, t-Bu), 1.6–2.1 (m, 4H, CH_2CH$_3$, NCHCH_2), 4.93 (q, J = 7.5 Hz, 1H, NCH), 5.87 (s, 1H, 4-H), 6.95 (br d, J = 7.5 Hz, 1H, NH), 7.19 (d, J = 9 Hz, 2H, 2,6-ArH), 7.35 (m, 5H, C$_6$H$_5$), 7.98 (d, J = 9 Hz, 2H, 3,5-ArH).

(3*R*,4*S*)-4-[(4-Carboxyphenyl)oxy]-3-ethyl-3-methyl-1-[[[(*R*)-1-(1-phenylpropyl)amino]carbonyl]azetidin-2-one (42a). To a solution of **42a** (*t*-Bu ester) (2.61 g, 5.71 mmol) in anisole (1.5 mL) was added precooled TFA (15 mL), and the reaction mixture was stirred for 1 h. The volatiles were removed *in vacuo*, and then a portion of CH_2Cl_2 (5 mL) was evaporated to remove most of the TFA. The solid residue was triturated with hexanes and further purified by prep LC (20% EtOAc/hexanes and then 1% HOAc) to afford **42a** (2.07 g, 88%) as a white solid from EtOAc/hexanes: NMR ($CDCl_3$): δ 0.92 (t, J = 7.5 Hz, 3H, NCHCH$_2$CH_3), 1.07 (t, J = 7.5 Hz, 3H, 3-CH$_2$CH_3), 1.43 (s, 3H, 3-Me), 1.6–2.1 (m, 4H, CH_2CH$_3$, NCHCH_2), 4.80 (q, J = 7.5 Hz, 1H, NCH), 5.68 (s, 1H, 4-H), 6.95 (br d, J = 7.5 Hz, 1H, NH), 7.16 (d, J = 9 Hz, 2H, 2,6-ArH), 7.35 (m, 5H, C$_6$H$_5$), 8.03 (d, J = 9 Hz, 2H, 3,5-ArH). Anal. (C$_{23}$H$_{26}$N$_2$O$_5$) C, H, N.

Preparation of 39–41 and 43–46. Using essentially the same procedures as for the preparation of **42a**, the following compounds as listed in Table 2 were prepared from **10a**, **10b**, or **38a** (R_β = *n*-Pr).

(3*R*,4*S*)-4-[(4-Carboxyphenyl)oxy]-3-ethyl-3-methyl-1-[[[(*R*)-1-(1-phenylethyl)amino]carbonyl]azetidin-2-one (39a): derived from **10a** and (*R*)-1-phenylethyl isocyanate; NMR (acetone-d_6) δ 0.98 (t, J = 7.5 Hz, 3H, 3-CH$_2$CH_3), 1.42 (s, 3H, 3-Me), 1.47 (d, J = 7.5 Hz, 3H, NCHCH_3), 1.67 (m, J = 7.5 Hz, 1H, CH_2CH$_3$), 1.86 (m, J = 7 Hz, 1H, CH_2CH$_3$), 4.95 (p, J = 7.5 Hz, 1H, NCHCH$_3$), 5.87 (s, 1H, 4-H), 6.95 (br d, J = 7.5 Hz, 1H, NH), 7.22 (d, J = 9 Hz, 2H, 2,6-ArH), 7.34 (m, 5H, C$_6$H$_5$), 7.98 (d, J = 9 Hz, 2H, 3,5-ArH). Anal. (C$_{22}$H$_{24}$N$_2$O$_5$·0.26TFA) C, H, N.

(3*R*,4*R*)-4-[(4-Carboxyphenyl)oxy]-3-ethyl-3-methyl-1-[[[(*R*)-1-(1-phenylethyl)]amino]carbonyl]azetidin-2-one (39b): derived from **10b** and (*R*)-1-phenylethyl isocyanate; NMR (acetone-d_6) δ 0.98 (t, J = 7.5 Hz, 3H, 3-CH$_2$*C*H3), 1.44 (s, 3H, 3-Me), 1.46 (d, J = 7.5 Hz, 3H, NCHCH_3), 1.62 (m, J = 7.5 Hz, 1H, CH_2CH$_3$), 1.85 (m, J = 7 Hz, 1H, CH_2CH$_3$), 4.90 (p, J = 7.5 Hz, 1H, NCHCH$_3$), 5.95 (s, 1H, 4-H), 6.95 (br d, J = 7.5 Hz, 1H, NH), 7.20 (d, J = 9 Hz, 2H, 2,6-ArH), 7.34 (m, 5H, C$_6$H$_5$), 7.95 (d, J = 9 Hz, 2H, 3,5-ArH); presence of ethyl acetate confirmed by NMR. Anal. (C$_{22}$H$_{24}$N$_2$O$_5$·0.57C$_4$H$_8$O$_2$) C, H, N.

(3*R*,4*S*)-4-[(4-Carboxyphenyl)oxy]-3-ethyl-3-methyl-1-[[[(*S*)-1-(1-phenylethyl)]amino]carbonyl]azetidin-2-one (40a): derived from **10a** and (*S*)-1-phenylethyl isocyanate; NMR ($CDCl_3$) δ 1.02 (t, J = 7.5 Hz, 3H, 3-CH$_2$CH_3), 1.47 (s, 3H, 3-Me), 1.54 (d, J = 7.5 Hz, 3H, NCHCH_3), 1.64 (m, J = 7.5 Hz, 1H, CH_2CH$_3$), 1.90 (m, J = 7 Hz, 1H, CH_2CH$_3$), 5.06 (p, J = 7.5 Hz, 1H, NCHCH$_3$), 5.75 (s, 1H, 4-H), 6.90 (br d, J = 7.5 Hz, 1H, NH), 7.06 (d, J = 9 Hz, 2H, 2,6-ArH), 7.34 (m, 5H, C$_6$H$_5$), 7.96 (d, J = 9 Hz, 2H, 3,5-ArH). Anal. (C$_{22}$H$_{24}$N$_2$O$_5$) C, H, N.

(3*S*,4*S*)-4-[(4-Carboxyphenyl)oxy]-3-ethyl-3-propyl-1-[[[(*R*)-1-(1-phenylethyl)]amino]carbonyl]azetidin-2-one (41a): derived from **38a** (R_β = *n*-Pr) and (*R*)-1-phenylethyl isocyanate; NMR (acetone-d_6) δ 0.90 (t, J = 7.5 Hz, 3H, 3-CH$_2$CH$_2$CH_3), 0.98 (t, J = 7.5 Hz, 3H, 3-CH$_2$CH_3), 1.2–1.65 (2 m, 2H, CH$_2$CH_2CH$_3$), 1.47 (d, J = 7.5, 3H, NCHCH_3), 1.65–2.0 (m, 4 H, 3-CH_2CH$_3$, 3-CH_2CH$_2$CH$_3$), 4.93 (p, J = 7.5 Hz, 1H, NCHCH$_3$), 5.96 (s, 1H, 4-H), 6.95 (br d, J = 7.5 Hz, 1H, NH), 7.2–7.4 (m, 7H, 2,6-ArH, C$_6$H$_5$), 7.94 (d, J = 9 Hz, 2H, 3,5-ArH). Anal. (C$_{24}$H$_{26}$N$_2$O$_5$) C, H, N.

(3*R*,4*S*)-4-[(4-Carboxyphenyl)oxy]-3-ethyl-3-methyl-1-[[[(*S*)-1-(1-phenylpropyl)]amino]carbonyl]azetidin-2-one (43a): derived from **10a** and (*S*)-1-phenylpropyl isocyanate; NMR (acetone-d_6) δ 0.87 (t, J = 7.5 Hz, 3H, NCHCH$_2$CH_3), 0.99 (t, J = 7.5 Hz, 3H, 3-CH$_2$CH_3), 1.47 (s, 3H, 3-Me), 1.65 (m, J = 7.5 Hz, 1H, CH_2CH$_3$), 1.75–1.95 (m, 3 H, CH_2CH$_3$, NCHCH_2), 4.95 (q, J = 7.5 Hz, 1H, NCH), 5.91 (s, 1H, 4-H), 7.0 (br d, J = 7.5 Hz, 1H, NH), 7.21 (d, J = 9 Hz, 2H, 2,6-ArH), 7.35 (m, 5H, C$_6$H$_5$), 7.98 (d, J = 9 Hz, 2H, 3,5-ArH). Anal. (C$_{23}$H$_{26}$N$_2$O$_5$) C, H, N

(3*R*,4*S*)-4-[(4-Carboxyphenyl)oxy]-3-ethyl-3-propyl-1-[[[(*R*)-1-(1-phenylpropyl)]amino]carbonyl]azetidin-2-one (44a): derived from **38a** (R_β = *n*-Pr) and (*R*)-1-phenylpropyl isocyanate; NMR ($CDCl_3$–DMSO-d_6) δ 0.90 and 0.94 (2 t, J = 7.5 Hz, 6H, 3-CH$_2$CH$_2$CH_3, NCHCH$_2$CH_3), 1.06 (t, J = 7.5 Hz, 3H, 3-CH$_2$CH_3), 1.1–2.0 (2 m, 8H, 3-CH_2CH$_2$CH$_3$, NCHCH_2CH$_3$, 3-CH_2CH$_3$), 4.78 (q, J = 7.5 Hz, 1H, NCH), 5.71 (s, 1H, 4-H), 6.96 (br d, J = 7.5 Hz, 1H, NH), 7.1–7.4 (m, 7H, C$_6$H$_5$, 2,6-ArH), 8.06 (br s, 2 H, 3,5-ArH). Anal. (C$_{25}$H$_{30}$N$_2$O$_5$) C, H; N: calcd, 6.39; found, 6.81.

(3*R*,4*S*)-4-[(4-Carboxyphenyl)oxy]-3-ethyl-3-methyl-1-[[[(*R*)-1-(1-phenylbutyl)]amino]carbonyl]azetidin-2-one (45a): derived from **10a** and (*R*)-1-phenylbutyl isocyanate; NMR ($CDCl_3$) δ 0.91 (t, J = 7.5 Hz, 3H, CH$_2$CH$_2$CH_3), 1.06 (t, J = 7.5 Hz, 3H, 3-CH$_2$CH_3), 1.1–1.5 (m, 2H, NCHCH$_2$CH_2-CH$_3$), 1.5–2.1 (m, 4H, 3-CH_2CH$_3$, CH_2CH$_2$CH$_3$), 4.89 (q, J = 7.5 Hz, 1H, NCH), 5.78 (s, 1H, 4-H), 6.96 (br d, J = 7.5 Hz, 1H, NH), 7.14 (d, 2H, 2,6-ArH), 7.2–7.4 (m, 5H, C$_6$H$_5$), 8.01 (d, J = 9 Hz, 2H, 3,5-ArH). Anal. (C$_{24}$H$_{28}$N$_2$O$_5$) C, H, N.

(3*S*,4*S*)-4-[(4-Carboxyphenyl)oxy]-3-ethyl-3-propyl-1-[[[(*R*)-1-(1-phenylbutyl)]amino]carbonyl]azetidin-2-one (46a): derived from **38a** (R_β = *n*-Pr) and (*R*)-1-phenylbutyl isocyanate; NMR ($CDCl_3$) δ 0.92 and 0.94 (2 t, J = 7.5 Hz, 3H, 3-CH$_2$CH$_2$CH_3, NCHCH$_2$CH$_2$CH_3), 1.08 (t, J = 7.5 Hz, 3H, 3-CH$_2$CH_3), 1.1–1.9 (2 m, 9H, 3-CH_2CH_2CH$_3$, NCHCH_2CH_2-CH$_3$, 3-CH_2CH$_3$), 1.65 (m, J = 7.5 Hz, 1H, CH_2CH$_3$), 4.88 (q, J = 7.5 Hz, 1H, NCH), 5.74 (s, 1H, 4-H), 6.98 (br d, J = 7.5 Hz, 1H, NH), 7.26 (d, J = 9 Hz, 2H, 2,6-ArH), 7.2–7.4 (m, 5H, C$_6$H$_5$), 8.06 (d, J = 9 Hz, 2H, 3,5-ArH). Anal. (C$_{26}$H$_{32}$N$_2$O$_5$) C, H, N.

Hydrolysis Studies in pH 7.5 MOPS Buffer. Samples of the test compound (3–5 mg) were dissolved at 1 mg/mL in MOPS buffer (containing 0.25 M *N*-acetyl-L-cysteine and adjusted to pH 7.5 with 2 N sodium hydroxide) and incubated in a constant temperature water bath at 37 °C in a capped vial. Periodically, depending on the half-life, 50 μL aliquots were removed and quenched into 50 mL of 2% aqueous TFA. The amount of compound left was determined by HPLC analysis using a Zorbax ODS column (4.6 mm × 15 cm) eluted with 1% TFA/10% MeOH in acetonitrile/water. The integrated areas and time were fit to the first-order decay curve $F(t) = A/2 \times (t/t_{1/2})$, where $F(t)$ is the peak area at time t, A is the calculated initial area, and $t_{1/2}$ is the calculated half-life. The reported errors are the standard deviation of the experimental points.

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Supplementary Material Available: Listing of the HLE inhibition values (k_{obs}/[I]) for selected *tert*-butyl esters of the reported compounds, additional C-4 (*R*) inactive diastereomers, and other 3,3-dialkyl and 3-alkyl-3-alkoxyalkyl compounds which were not reported in Table 1 or 2 (1 page). Ordering information is given on any current masthead page.

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