Orally Active β-Lactam Inhibitors of Human Leukocyte Elastase. 2.[1] Effect of C-4 Substitution

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The effect of changing the C-4 substituent of 3,3-diethyl-1-[(benzylamino)carbonyl]-2-azetidinone on inhibition of HLE and in a model of HLE-induced lung damage in hamsters was explored. Substituents at this position do not appear to interact strongly with HLE with the most potent compounds having $k_{obs}/[I] = 6900\ M^{-1}\ s^{-1}$. However, substituents at this position had a marked effect on in vivo activity. The greatest oral activity in the lung hemorrhage assay was achieved with C-4 aryl carboxylic acid ethers (60–85% inhibition at 30 mg/kg po). Based upon the established mechanism of inhibition by these compounds, the C-4 substituent would be released, and therefore, the pharmacological potential of these C-4 substituents was of considerable concern. Fortunately, compounds containing 4-hydroxybenzoic acid and 4-hydroxyphenylacetic acid ethers at C-4 were among the most active analogs. These phenolic acids are also found as urinary metabolites in healthy humans. Other heteroaryls at C-4 were also orally active in this model despite relatively modest enzyme activity.

The quest for effective low molecular weight synthetic inhibitors of human leukocyte elastase (HLE, EC 3.4.21.37) has been actively pursued in many laboratories[1] (and references cited therein). These efforts have resulted in a wide variety of structure types, but most include reversible or irreversible interactions of the active site serine-195 and/or histidine-57. Many of these compounds have excellent potencies and selectivity, and one is well into clinical evaluation.[2] However, it has also been observed that a peptidyl boronic acid reversible inhibitor of HLE actually exacerbated HLE-induced lung damage in hamsters.[3] In addition, a role for HLE in facilitating neutrophil extravasation has been proposed, and inhibition may prevent leukocytes from reaching sites of injury or inflammation.[4] On the other hand, both small molecular weight and proteinaceous inhibitors of HLE were found to have no effect on neutrophil extravasation in hamsters.[5] Thus, the real utility of the synthetic HLE inhibitors in the safe and efficacious treatment of disease remains unproven.

For our part, we have focused on the development of β-lactam-containing compounds which were originally developed by chemical modification of the cephalosporin nucleus.[6,7] Subsequent work established substituted 2-azetidinone rings as minimal structures necessary for effective HLE inhibition.[8] Further modification of these compounds afforded inhibitors that were efficacious in preventing HLE-induced lung damage in hamsters, albeit only by intratracheal administration.[9] Our ultimate objective was a systemically active agent with high oral bioavailability. By improving the hydrolytic stability and the inhibitory potency of these compounds, the first hints of oral bioavailability were realized.[10] However, it was necessary to further stabilize the 2-azetidinone ring in order to obtain oral activity.[11] In the first paper in this series, the effect of changing substitution on the nitrogen of the 1-aminocarbonyl group was described.[1] The results from that study indicated that the [(4-methylbenzyl)amino]-carbonyl group was among the most potent substitution for in vivo efficacy. Herein, we explore the effect of changing the C-4 substituent of 3,3-diethyl-1-[(benzylamino)carbonyl]-2-azetidinone on enzyme inhibition and on HLE-induced lung damage in hamsters.

Chemistry

Details of the synthesis of 1-[(benzylamino)carbonyl]-3,3-diethyl-4-phenoxy-2-azetidinones have been reported.[1] Ethyl butyraldehyde was converted to its enol acetate in the presence of acetic anhydride and sodium acetate. Cycloaddition with chlorosulfonic isocyanate gave 4-acetoxy-3,3-diethylazetidinone (1). The appropriate phenol was reacted with 1 in the presence of sodium hydroxide to give the C-4 phenolic ethers 2. Acylation of 2 with benzyl isocyanate in the presence of base gave the 1-[(benzylamino)carbonyl]-3,3-diethyl-4-phenoxy-2-azetidinones **3a-ak** (Table I).

Functional groups were modified by straightforward methodologies. Carboxylate esters were hydrolyzed with trifluoroacetic acid in anisole (*tert*-butyl esters) or hydrogenolyzed under hydrogen atmosphere in ethyl acetate in the presence of 10% palladium on carbon (benzyl esters). Nitro groups (in **3k-m**) were reduced by catalytic hydrogenation and the amines subsequently acylated with acetic anhydride or succinic anhydride in the presence of pyridine. The sulfide **3t** was oxidized with 1 or 2 equiv of *m*-chloroperbenzoic acid to yield the sulfoxide **3u** and the sulfone **3v**.

The benzylic, glycolic, and glycerolic ethers **5a–c** were prepared by reaction of 1 with the appropriate alcohol in the presence of magnesium (Scheme I) by the method of Clauss.[12] Acylation with isocyanate followed as above.

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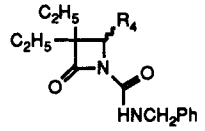
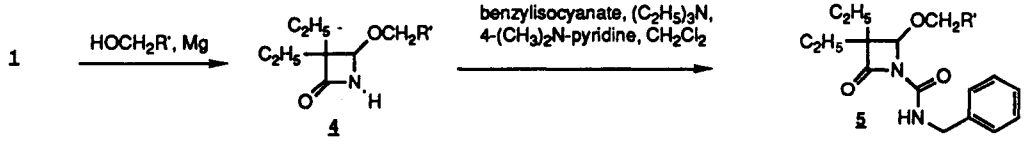
Table I. Effect of C-4 Substitution of 3,3-Diethyl-1-[(benzylamino)carbonyl]-2-azetidinones on Inhibition of Human Leukocyte Elastase (HLE) and HLE-Induced Lung Hemorrhage in Hamsters



compd no.	R_4	method of prepn	elemental analysis	$k_{obs}/[I]$ [$M^{-1}s^{-1}$ (±SE)]	lung hemorrhage[b] [% inh (±SD)]
3a	O-Ph-4-CO_2H	A	C, H, N	1500 (200)	68 (13)
3b	O-Ph-3-CO_2H	A	C, H, N	1800 (100)	33 (17)
3c	O-Ph-3,4-$(CO_2H)_2$	A	C, H, N	570 (30)	−55 (10)
3d	O-Ph-3,5-$(CH_3)_2$-4-CO_2H	A	C, H, N	24 (2)	−55 (54)[c]
3e	O-Ph-2,6-$(CH_3)_2$-4-CO_2H	A	C, H, N	750 (2)	ND
3f	O-Ph-4-CH_2CO_2H	A	C, H, N	3200 (300)	71 (13)[c]
3g	O-Ph-3-CH_2CO_2H	A	C, H, N	1200 (100)	67 (23)
3h	O-Ph-2-CH_2CO_2H	A	C, H, N	44 (1)	45 (34)[c]
3i	O-Ph-4-$CH(OH)CO_2H$	A	C, H, N	2100 (200)	36 (13)
3j	O-Ph-4-$CH_2CH_2CO_2H$	A	C, H, N	2440 (120)	60 (19)[c]
3k	O-Ph-4-NO_2	A	C, H, N	6800 (700)	ND[d]
3l	O-Ph-3-NO_2	A	C, H, N	4800 (600)	ND
3m	O-Ph-2-NO_2	A	C, H, N	890 (80)	ND
3n	O-Ph-4-$NHCOCH_3$	A	C, H, N	3500 (450)	ND
3o	O-Ph-3-$NHCOCH_3$	A	C, H, N	1700 (100)	−17 (−30)
3p	O-Ph-2-$NHCOCH_3$	A	C, H, N	270 (10)	24 (21)
3q	O-Ph-4-$NHCOCH_2CH_2CO_2H$	A	C, H, N	2330 (70)	−3 (23)
3r	O-Ph-3-$NHCOCH_2CH_2CO_2H$	A	C, H, N	2700 (50)	−12 (33)
3s	O-Ph-2-$NHCOCH_2CH_2CO_2H$	A	C, H, N	70 (4)	ND
3t	O-Ph-4-SCH_3	A	C, H, N, S	3500 (300)	2 (27)
3u	O-Ph-4-$S(O)CH_3$	A	C, H, N, S	4200 (100)	−11 (23)
3v	O-Ph-4-$S(O)_2CH_3$	A	C, H, N, S	4500 (400)	16 (20)
3w	O-Ph-4-CH_2-(*S*)-$CH(NH_2)CO_2H$	A	C, H, N	2540 (20)	−21 (36)
3x	O-Ph-4-CH_2-(*S*)-$CH(NHCOPh)CO_2H$	A	C, H, N	5110 (40)	−56 (9)
3y	O-Ph-4-CH_2-(*S*)-$CH[NHCO(CH_2)_2CO_2H]CO_2H$	A	C, H, N	900 (100)	7 (67)
3z	O-Ph	A	C, H, N	1900 (300)	ND
3aa	O-Ph-4-CO-L-proline	A	C, H, N	2900 (40)	−13 (42)
3ab	O-Ph-4-$CONHSO_2Ph$-4-Cl	A	C, H, N	6900 (40)	11 (9)
3ac	O-Ph-4-$CO(CH_2)_2CO_2H$	A	C, H, N	5000 (400)	85 (10)
3ad	O-Ph-4-t-$CH{=}CHCO_2H$	A	C, H, N	1600 (100)	61 (12)[c]
3ae	O-Ph-4-$CH_2N(CH_3)_2$	A	C, H, N	1600 (400)	0 (26)
3af	O-Ph-4-$CH_2N^+(CH_3)_3I^-$	A	C, H, N, I	2430 (10)	4 (21)
3ag	O-1-naphthyl-4-CO_2H	A	C, H, N	2000 (100)	15 (16)
3ah	O-2-naphthyl-6-CO_2H	A	C, H, N	5600 (800)	28 (21)[c]
3ai	O-(3-pyridinyl)	A	C, H, N	1620 (50)	46 (17)
3aj	S-(3-pyridinyl)	A	C, H, N	250 (30)	−5 (21)
3ak	S-(1-methyl-5-tetrazolyl)	A	C, H, N	3760 (20)	26 (26)
5a	OCH_2Ph-4-CO_2H	B	C, H, N	54 (25)[a]	ND
5b	OCH_2CO_2H	B	C, H, N	160 (30)	6 (22)
5c	$OCH_2CH(OH)CH_2OH$	B	C, H, N	800 (200)	46 (9)
7a	1-imidazolyl	A	C, H, N	200 (10)	55 (12)
7b	2-(1,2,4-triazinyl)	A	C, H, N	246 (1)	72 (13)
7c	1-benzo(1,2,3)triazinyl	A	C, H, N	650 (60)	ND
7d	1-(2-oxo-2*H*-pyridinyl)	A	C, H, N	360 (30)	29 (9)
10	COPh	C	C, H, N	22 (4)	ND

[a] K_i = 64 (8) μM. [b] Tested orally at 30 mpk at −30 min predose prior to installation of HLE except as noted. Results are reported as the mean of four animals (± standard deviation). [c] Tested orally at 50 mpk at −30 min predose prior to installation of HLE. [d] ND = not determined.

Scheme I

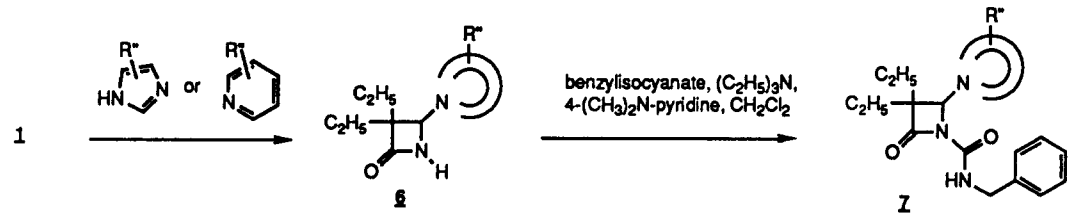


The nitrogen-containing heteroaryls at C-4 (**7a–d**) were also prepared by reaction of the heterocycle with **1** in the presence of sodium hydroxide (Scheme II). The C-4 phenyl ketone **10** was prepared by classical β-lactam methodology of cycloaddition of an imine with an acid chloride in the presence of base (Scheme III). Removal of the *p*-methoxyphenyl group with ceric ammonium nitrate (CAN) followed by acylation with benzyl isocyanate gave **10**.

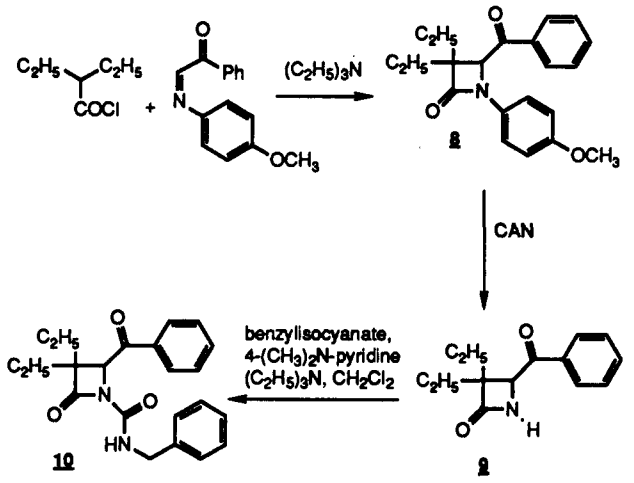
Inhibition of HLE. Inhibition of HLE was assayed spectrophotometrically as described at 25 °C by continuous monitoring of the release of *p*-nitroaniline at 410 nm from the substrate succinyl-Ala-Ala-Pro-Ala-*p*-nitroanilide.[13] Results are listed in Table I and are expressed in terms of the bimolecular rate constant $k_{obs}/[I]$ in $M^{-1}s^{-1}$. Under the conditions of the assay, $k_{obs}/[I]$ is approximately equal to k_{inact}/K_i.[14]

Prevention of HLE-Mediated Damage in the Hamster Lung. The assay to evaluate the inhibition of HLE-mediated lung damage in hamsters has been published in detail.[15] In summary, HLE (50 units) in saline (200 μL) was instilled into the large airways via the trachea of anesthetized hamsters, causing hemorrhage into the air

Scheme II



Scheme III



spaces of the lung. Inhibitors were initially screened at 30 or 50 mg/kg and were administered orally 30 min prior to instillation of enzyme. Hemorrhage was determined 3 h after instillation with HLE by spectrophotometric evaluation of hemoglobin content in lung lavage fluid. Results are listed in Table I and expressed as percent inhibition at 30 or 50 mg/kg po.

Results and Discussion

The results of changing the C-4 substituent on inhibition of HLE and in the HLE-induced lung hemorrhage in hamsters are reported in Table I. With respect to enzyme inhibition in the phenolic series (**3a–ai**), ortho substitution (e.g., **3e**, **3h**, **3m**, **3p**, **3s**) is not well tolerated by HLE. Generally speaking with a given substituent, there does not appear to be a real preference by HLE for meta or para substitution. These results are consistent with a molecular modeling study of a Michaelis complex of one of these types of inhibitors within the active site of HLE.[1] This model suggests that the C-4 phenolic group is oriented toward the P_2 subsite of HLE with the meta and para positions pointing toward solvent. The ortho positions would then be oriented toward the enzyme surface.

Nearly all β-lactam inhibitors of HLE exhibit time-dependent inhibition including the compounds reported herein. A simple mechanism for the inhibition of HLE by these compounds invokes the acylation of Ser-195 in the active site with concerted or subsequent elimination of the C-4 substituent; that is, if it can leave. The acylated enzyme can undergo rapid hydrolysis to re-form active enzyme or nucleophilic addition, possibly of water or His-57, to the acyl imine can occur to form a species that undergoes a slower hydrolysis to active enzyme. Alkylation of His-57 was evident in the cephalosporin series to form a "double hit" enzyme[16] and has been proposed in a related monocyclic β-lactam study.[17] Active-site acylation/alkylation has been proposed as the mechanism of inhibition in series of 1-aryl-2-azetidinones.[18] The details of the mechanism of inhibition are the subject of continued studies.[19]

Within the present discussion, the nature of the leaving group might be thought to influence the initial rate of acylation: the better the leaving group, the better the acylating agent. However, close examination of the enzyme inhibition data for the para-substituted phenols is only suggestive of a weak correlation with leaving group ability as estimated by pK_a of the phenol. The corresponding phenols of the 4-nitro (**3k**), 4-sulfone (**3v**), and keto acid (**3ac**) derivatives would be expected to have the lowest pK_a's and are among the more potent inhibitors. The differences in the inhibition data for many of the remaining compounds is probably not significant. Of course, this correlation ignores specific interactions of the substituents with HLE in and around the active site which might effect initial binding as well as the subsequent chemistry of inactivation.

A number of nonphenolic C-4 substituents were also prepared. The alkyl ethers **5a–c** were significantly less potent than the aryl ethers. The heteroaryl compounds **7a–d** were also less active as enzyme inhibitors. The molecular model of the Michaelis complex seems to suggest that an additional atom is needed between the C-4 carbon and the aryl ring for steric reasons. The phenyl ketone **10** which might be thought of as an "electronic sink"[8] for acylation of Ser-195 was also poorly active, but still displayed some degree of time-dependent inhibition.

While the enzyme inhibition data for the more potent compounds is relatively similar, it is only in the in vivo evaluation that a few of the inhibitors distinguish themselves. The carboxylic acids **3a**, **3f**, **3g**, **3j**, **3ac**, and **3ad** and the heteroaryls **7a** and **7b** were the only compounds to have significant oral activity in the HLE-induced lung damage assay in hamsters as measured by inhibition of hemorrhage caused by intratracheal instillation of HLE. Without detailed pharmacokinetic data, it is impossible to assess why these compounds had oral in vivo activity and others did not. Also, there is little correlation with in vitro potency (e.g., **3a** vs **7a**).

The identification of orally active compounds with 4-hydroxybenzoic acid and 4-hydroxyphenyl acetic acid as leaving groups in **3a** and **3f** was fortuitous. As suggested by the mechanism of inhibition wherein the C-4 substituent is a leaving group, this substituent is going to be released whenever HLE is inhibited or if nonspecific hydrolysis occurs. Therefore, the pharmacological potential of the C-4 leaving group was considered important as it should not have biological effects of its own. While the L-tyrosine analogs **3w–y** were attractive from a safety aspect, they were inactive in the lung hemorrhage assay. Glycerol and glycolic acid derivatives **5b** and **5c** were poor as inhibitors of both the enzyme and the HLE-induced lung hemorrhage. The acetamide **3n** would release acetaminophen which has its own pharmacology.

4-Hydroxybenzoic acid and 4-hydroxyphenylacetic acid are found in the urine of healthy adults.[20] The latter is a product of *p*-tyrosine metabolism.[21] 3-Hydroxyphenylacetic acid such as would be formed from **3g** was also found in human urine. The *p*-hydroxycinnamic acid that would be formed from **3ad** has been found to cause reversible testicular atrophy in mice.[22] The hydroxyphenyl acids from the other in vivo active compounds **3j** and **3ac** have unknown pharmacology. Fortunately, the HLE inhibitors containing 4-hydroxybenzoic acid (**3a**) and 4-hydroxyphenylacetic acid (**3f**) as C-4 leaving groups were also among the most orally active inhibitors in the lung hemorrhage assay. Thus, the formation of these phenolic acids as potential metabolites of HLE inhibition would not be expected to cause adverse side effects.

In summary, the effect of changing the C-4 substituents of 3,3-diethyl-1-[(benzylamino)carbonyl]-2-azetidinone on inhibition of HLE and in a model of HLE-induced lung damage has been explored. Consistent with results of molecular modeling studies, substituents at this position do not appear to interact strongly with HLE. However, the C-4 substituents are very important for achieving oral activity. Based upon the established mechanism of inhibition by these compounds, the C-4 substituent would be released. Therefore, the pharmacological potential of these C-4 substituents was of considerable concern. Fortunately, compounds containing 4-hydroxybenzoic acid and 4-hydroxyphenylacetic acid ethers at C-4 were among the most active analogs. These phenolic acids are also found as urinary metabolites in healthy humans. Other heteroaryls at C-4 were also orally active in this model despite relatively modest enzyme activity. Further development of these compounds to improve both in vitro and in vivo potencies is continuing and will be reported shortly.

Experimental Section

Chemistry. General Procedures. Proton NMR spectra were recorded on a Varian XL-200 NMR spectrometer. Chemical shifts are given on the δ scale. Spectra were measured at ambient temperature for solutions in chloroform-*d* with tetramethylsilane ($\delta = 0.00$) as the internal standard. Infrared spectra were obtained as thin films on sodium plates on Perkin-Elmer 295 or 1310 spectrophotometers. Mass spectra were determined on a LKB 9000 mass spectrometer. Analytical results for compounds followed by elemental symbols were ±0.4% of calculated values unless otherwise indicated and were determined by the Micro-Analytical Laboratory of Merck & Co., Inc., or Robertson-Microlit Laboratories, Inc., Madison, NJ. Thin-Layer chromatography was performed on precoated silica gel-GHLF$_{254}$ plates (Analtech), and visualization was effected with UV light, iodine, or ceric sulfate (1%)–sulfuric acid (10%) spray. Preparative flash column chromatography was performed on silica gel 60 (E. Merck, 40–63 μm).

General Procedure for the Preparation of 4-(Aryloxy)-1-[(benzylamino)carbonyl]-3,3-diethyl-2-azetidinones (3a–ak) (Method A). The procedures for the preparation of 4-(aryloxy)-1-(*N*'-benzylcarbamoyl)-3,3-diethyl-2-azetidinones from 4-acetoxy-3,3-diethyl-2-azetidinone (1) have been reported in detail.[1] Procedures for compounds reported herein were analogous and their respective spectral data comparable. The preparation of **3ac** from 1 as described below is typical.

4-[(4-Carboxyphenyl)oxy]-1-[(benzylamino)carbonyl]-3,3-diethyl-2-azetidinone, L-Proline Amide (3aa). Carbonyldiimidazole (225 mg, 1.4 mmol) and 4-(dimethylamino)pyridine (10 mg) were added to a solution of **3a** (500 mg, 1.26 mmol) in methylene chloride (3 mL). After stirring at room temperature for 30 min, L-proline, *tert*-butyl ester (237 mg, 1.39 mmol) was added. The solution was stirred at room temperature for 3 h, and then ethyl acetate (100 mL) was added. The solution was washed successively with 1 N HCl (3 × 20 mL), saturated sodium bicarbonate solution (3 × 20 mL), water (2 × 20 mL), and saturated salt solution (20 mL) and dried over anhydrous sodium sulfate powder. The solvent was removed by rotoevaporation and the residue purified by flash column chromatography on silica gel eluted with 30–40% ethyl acetate in hexanes. The *tert*-butyl ester was isolated as a clear, colorless foam (411 mg, 57% yield): ^{1}H NMR ($CDCl_3$) 0.97 (t, J = 7 Hz, 3 H), 1.04 (t, J = 7 Hz, 3 H), 1.48 (s, 9 H), 1.68–2.55 (m, 8 H), 3.62 (m, 2 H), 4.46 (d, J = 6 Hz, 2 H), 4.70 (m, 1 H), 5.72 (s, 1 H), 6.89 (br d, 2 H), 7.23–7.75 (m, 5 H), 7.61 (d, J = 8 Hz, 2 H); IR 1780, 1720, 1635 cm^{-1}.

Cold trifluoroacetic acid (1 mL) was added to an ice-cooled solution of the *tert*-butyl ester (411 mg, 0.72 mmol) and anisole (0.3 mL). After the solution was stirred for 3 h at room temperature, the solvent was removed by rotoevaporation and the product purified by preparative thin-layer chromatography on silica gel eluted with 1% acetic acid in 50% ethyl acetate/hexanes. The free acid **3aa** was isolated as a clear foam (280 mg, 79% yield): ^{1}H NMR ($CDCl_3$) 1.00 (t, J = 7 Hz, 3 H), 1.06 (t, J = 7 Hz, 3 H), 1.72–2.60 (m, 8 H), 3.62 (m, 2 H), 4.52 (d, J = 6 Hz, 2 H), 4.78 (m, 1 H), 5.74 (s, 1 H), 6.92 (br d, 2 H), 7.26–7.36 (m, 5 H), 7.58 (d, J = 8 Hz, 2 H); IR 1775, 1715, 1610 cm^{-1}.

4-[(4-Carboxyphenyl)oxy]-1-[(benzylamino)carbonyl]-3,3-diethyl-2-azetidinone, 4-Chlorobenzenesulfonamide (3ab). Dicyclohexylcarbodiimide (470 mg, 2.27 mmol) was added to a solution of **3a** (900 mg, 2.27 mmol) and 4-(dimethylamino)pyridine (277 mg, 2.27 mmol) in methylene chloride (3 mL). After stirring for 20 min at room temperature, *p*-chlorobenzenesulfonamide (440 mg, 2.27 mmol) was added and the solution stirred overnight. Ethyl acetate (100 mL) was added and the solution washed with water (20 mL) and dried over anhydrous sodium sulfate. The solvent was removed by rotoevaporation and the product purified by flash column chromatography on silica gel eluted with 0.5% acetic acid in 20–25% ethyl acetate/hexanes and isolated as a clear foam (846 mg, 65% yield): ^{1}H NMR ($CDCl_3$) 1.00 (t, J = 7 Hz, 3 H), 1.02 (t, J = 7 Hz, 3 H), 1.50–2.00 (m, 4 H), 4.48 (d, J = 6 Hz, 2 H), 5.80 (s, 1 H), 6.97 (t, J = 6 Hz, 1 H), 7.15 (d, J = 8 Hz, 2 H), 7.31 (br s, 5 H), 7.49 (d, J = 8 Hz, 2 H), 7.68 (d, J = 9 Hz, 2 H), 8.03 (d, J = 8 Hz, 2 H); IR 1780, 1720, 1695, 1608 cm^{-1}.

4-[[4-(3-Carboxypropanoyl)phenyl]oxy]-1-[(benzylamino)carbonyl]-3,3-diethyl-2-azetidinone (3ac). Boron tribromide (2.7 mL) was slowly added to a solution of 3-(*p*-methoxybenzoyl)propanoic acid (3.00 g, 14.4 mmol) in methylene chloride (14 mL) at −78 °C. The solution turned deep red and slowly precipitated an orange solid as the temperature was warmed to room temperature. After stirring for 20 **h**, ethyl acetate (100 mL) and 1 N HCl (25 mL) were added. The solution was successively washed with 1 N HCl (2 × 20 mL) and water (2 × 20 mL). The product was extracted into 1 N NaOH (4 × 20 mL) which was subsequently washed with ethyl acetate (20 mL). The solution was acidified with 6 N HCl (20 mL) and extracted with ethyl acetate (3 × 50 mL). The solution was successively washed with water (2 × 20 mL) and saturated salt solution (20 mL) and dried over anhydrous sodium sulfate. The solvent was removed by rotoevaporation and the red solid purified by flash column chromatography on silica gel eluted with 1% acetic acid in 25% ethyl acetate/hexanes. The 3-(*p*-hydroxybenzoyl)propanoic acid was recrystallized from ethyl acetate/hexanes as an off-white solid and used in the subsequent reaction (740 mg, 26% yield): ^{1}H NMR ($CDCl_3$ + DMSO-d_6) 2.43 (t, J = 7 Hz, 2 H), 2.97 (t, J = 7 Hz, 2 H), 6.61 (d, J = 9 Hz, 2 H), 7.60 (d, J = 9 Hz, 2 H).

A solution of *N*,*N*'-diisopropyl-*O*-*tert*-butylisourea (5.2 gm, 26 mmol) in *tert*-butyl alcohol (5 mL) was added to a solution of 3-(*p*-hydroxybenzoyl)propanoic acid (5.1 g, 26 mmol) in *tert*-butyl alcohol (20 mL). After the mixture was stirred overnight at room temperature, ethyl acetate (100 mL) was added and the solution dried over anhydrous sodium sulfate. The solvent was removed by rotoevaporation and the resultant brown gum purified by flash column chromatography on silica gel eluted with 20–30% ethyl acetate/hexanes. *tert*-Butyl 3-(*p*-hydroxybenzoyl)propanoate was isolated as a white solid (1.4 g, 22% yield): ^{1}H NMR ($CDCl_3$) 1.48 (s, 9 H), 2.71 (t, J = 7 Hz, 2 H), 3.22 (t, J = 7 Hz, 2 H), 6.86 (d, J = 9 Hz, 2 H), 7.83 (d, J = 9 Hz, 2 H).

A solution of 2.5 N NaOH (2.3 mL) was added to an ice-cooled solution of *tert*-butyl 3-(*p*-hydroxybenzoyl)propanoate (1.42 g, 5.7 mmol) in acetone (5 mL). After the mixture was stirred for 20 min at 0 °C, 1 (1.05 gm, 5.7 mmol) was added and the solution stirred for 20 h at room temperature. Diethyl ether (100 mL) was added and the solution successively washed with 1 N NaOH (3 × 20 mL), water (3 × 20 mL), and saturated salt solution (20 mL). The solvent was removed by rotoevaporation and the 4-[[4-[3-(*tert*-butyloxycarbonyl)propanoyl]phenyl]oxy]-3,3-diethyl-2-azetidinone isolated as a yellow oil (2.1 g, ~100% yield): ^{1}H NMR ($CDCl_3$) 0.97 (t, J = 7 Hz, 3 H), 1.00 (t, J = 7 Hz, 3 H), 1.39 (s, 9 H), 1.57–1.96 (m, 4 H), 2.60 (t, J = 7 Hz, 2 H), 3.15 (t, J = 7 Hz, 2 H), 5.37 (s, 1 H), 6.88 (d, J = 9 Hz, 2 H), 7.91 (d, J = 7 Hz, 2 H).

Benzyl isocyanate (0.36 mL, 2.9 mmol) was added to a solution of 4-[[4-[3-(*tert*-butyloxycarbonyl)propanoyl]phenyl]oxy]-3,3-diethyl-2-azetidinone (549 mg, 1.5 mmol), triethylamine (0.41 mL, 2.9 mmol), and 4-(dimethylamino)pyridine (10 mg) in methylene chloride (2 mL). After the reaction mixture was stirred for 2 h at room temperature, ethyl acetate (100 mL) was added and the solution successively washed with 1 N HCl (3 × 20 mL), saturated sodium bicarbonate solution (20 mL), water (20 mL), and saturated salt solution (20 mL). The solution was dried over anhydrous sodium sulfate and the solvent removed by rotoevaporation. 4-[[4-[3-(*tert*-Butyloxycarbonyl)propanoyl]phenyl]-oxy]-1-[(benzylamino)carbonyl]-3,3-diethyl-2-azetidinone was purified by flash column chromatography on silica gel eluted with 20% ethyl acetate/hexanes and isolated as a yellow oil (474 mg, 57% yield): ^{1}H NMR ($CDCl_3$) 1.02 (t, J = 7 Hz, 3 H), 1.06 (t, J = 7 Hz, 3 H), 1.46 (s, 9 H), 1.72–2.04 (m, 4 H), 2.88 (t, J = 7 Hz, 2 H), 3.20 (t, J = 7 Hz, 2 H), 4.50 (d, J = 6 Hz, 2 H), 5.80 (s, 1 H), 6.92 (t, J = 6 Hz, 1 H), 7.28 (d, J = 8 Hz, 2 H), 7.32 (s, 5 H), 7.98 (d, J = 8 Hz, 2 H).

The *tert*-butyl ester from above was dissolved in methylene chloride (2 mL) and cooled to 0 °C, and trifluoroacetic acid (0.5 mL) was added. After stirring at 0 °C for 4 h, the solvent was removed by rotoevaporation and the product purified by flash column chromatography on silica gel eluted with 1% acetic acid in 40% ethyl acetate/hexanes. 4-[[4-(3-Carboxypropanoyl)-phenyl]oxy]-1-[(benzylamino)carbonyl]-3,3-diethyl-2-azetidinone (**3ac**) was isolated as white needles from ethyl acetate/hexanes (400 mg, 94% yield): ^{1}H NMR ($CDCl_3$) 1.00 (t, J = 7 Hz, 3 H), 1.03 (t, J = 7 Hz, 3 H), 1.68–2.04 (m, 4 H), 2.77 (t, J = 7 Hz, 2 H), 3.25 (t, J = 7 Hz, 2 H), 4.46 (d, J = 6 Hz, 2 H), 5.77 (s, 1 H), 6.90 (t, J = 6 Hz, 1 H), 7.26 (d, J = 9 Hz, 2 H), 7.30 (s, 5 H), 7.97 (d, J = 9 Hz, 2 H); IR 1780, 1718, 1690, 1608 cm^{-1}.

4-[[4-[(Dimethylamino)methyl]phenyl]oxy]-1-[(benzylamino)carbonyl]-3,3-diethyl-2-azetidinone (3ae). To a solution of 4-[(4-carbonylphenyl)oxy]-1-[(benzylamino)carbonyl]-3,3-diethyl-2-azetidinone (prepared from 1, 4-hydroxybenzaldehyde, and benzyl isocyanate as for **3ac** above; 1.00 g, 2.63 mmol) in methanol (6 mL) and tetrahydrofuran (4 mL) were added dimethylamine hydrochloride (1.29 g, 15.8 mmol), solid sodium bicarbonate (0.88 g, 10.5 mmol), and sodium cyanoborohydride (116 mg, 1.84 mmol). After the mixture was stirred for 2 h at room temperature, ethyl acetate (100 mL) was added and the solution successively washed with saturated sodium bicarbonate solution (3 × 20 mL), water (2 × 20 mL), and saturated salt solution (20 mL). The solution was dried over anhydrous sodium sulfate and the solvent removed rotoevaporation. The product was purified by flash column chromatography on silica gel, eluted with 30–100% ethyl acetate, and isolated as a clear oil that crystallized upon standing (250 mg, 23% yield): ^{1}H NMR ($CDCl_3$) 1.00 (t, J = 7 Hz, 3 H), 1.08 (t, J = 7 Hz, 3 H), 1.74–2.04 (m, 4 H), 2.22 (s, 6 H), 3.38 (s, 2 H), 4.50 (d, J = 6 Hz, 2 H), 5.68 (s, 1 H), 6.94 (br t, J = 6 Hz, 1 H), 7.18 (d, J = 8 Hz, 2 H), 7.28 (d, J = Hz, 2 H), 7.32 (s, 5 H); IR 1775, 1715, 1610 cm^{-1}.

4-[[4-[(Trimethylammonio)methyl]phenyl]oxy]-1-[(benzylamino)carbonyl]-3,3-diethyl-2-azetidinone Iodide (3af). Methyl iodide (32 μL, 0.51 mmol) was added to a solution of **3ae** (194 mg, 0.47 mmol) in diethyl ether (1 mL). After being stirred for 15 min at room temperature, the cloudy solution was cooled for 2 h in an ice bath. The solids were filtered and recrystallized from hot ethyl acetate as a white powder (70 mg, 27% yield): ^{1}H NMR (acetone-d_6) 1.03 (t, J = 7 Hz, 3 H), 1.06 (t, J = 7 Hz, 3 H), 1.73–2.07 (m, 4 H), 3.39 (s, 9 H), 4.52 (d, J = 6 Hz, 2 H), 4.99 (s, 2 H), 5.98 (s, 1 H), 7.29 (br t, J = 6 Hz, 1 H), 7.37 (br s, 5 H), 7.41 (d, J = 9 Hz, 2 H), 7.76 (d, J = 9 Hz, 2 H).

4-[(4-Carboxyphenyl)methoxy]-1-[(benzylamino)carbonyl]-3,3-diethyl-2-azetidinone (5a) (Method B, Scheme I). Sodium borohydride (0.80 g, 21 mmol) was added to a solution of 4-(benzyloxycarbonyl)benzaldehyde (5.50 g, 23 mmol) in ethanol (23 mL) at 0 °C. After the mixture was stirred for 3 h at room temperature, acetic acid was added (2 mL) and the solvent removed by rotoevaporation. Ethyl acetate (100 mL) was added and the solution successively washed with 1 N HCl (3 × 20 mL), saturated sodium bicarbonate solution (3 × 20 mL), water (2 × 20 mL), and saturated salt solution (20 mL). The solution was dried over anhydrous sodium sulfate and the solvent removed by rotoevaporation. The product, benzyl 4-(hydroxymethyl)benzoate, was purified by flash column chromatography on silica gel eluted with 25–30% ethyl acetate in hexanes and isolated as a cakey white solid (1.80 gm, 33% yield): ^{1}H NMR ($CDCl_3$) 1.88 (br s, 1 H), 4.78 (s, 2 H), 5.36 (s, 2 H), 7.40 (d, J = 8 Hz, 2 H), 7.46 (s, 5 H), 8.08 (d, J = 8 Hz, 2 H).

A solution of *tert*-butylmagnesium chloride (1.7 mL of a 2.0 M solution in hexanes, 3.4 mmol) was added to an ice-cooled solution of benzyl 4-(hydroxymethyl)benzoate (0.83 g, 3.4 mmol) in dry tetrahydrofuran (3 mL). After stirring at 0 °C for 15 min, a solution of 1 (630 mg, 3.4 mmol) in tetrahydrofuran (1 mL) was added and the solution stirred for 3 h at room temperature. Ethyl acetate (100 mL) was added and the solution successively washed with 1 N HCl (3 × 20 mL), saturated sodium bicarbonate solution (3 × 20 mL), water (2 × 20 mL), and saturated salt solution (20 mL). The solution was dried over anhydrous sodium sulfate and the solvent removed by rotoevaporation. The product was purified by flash column chromatography on silica gel eluted with 30% ethyl acetate in hexanes and 4-[[4-(benzyloxycarbonyl)-phenyl]methoxy]-3,3-diethyl-2-azetidinone was isolated as a clear oil (400 mg, 32% yield): ^{1}H NMR ($CDCl_3$) 0.88 (t, J = 7 Hz, 6 H), 1.38–2.06 (m, 4 H), 4.70 and 4.86 (AB q, J = 13 Hz, 2 H), 4.76 (s, 1 H), 5.36 (s, 2 H), 7.40 (m, 7 H), 8.06 (d, J = 8 Hz, 2 H).

Benzyl isocyanate (0.27 mL, 2.2 mmol) was added to a solution of 4-[[4-(benzyloxycarbonyl)phenyl]methoxy]-3,3-diethyl-2-azetidinone (400 mg, 1.1 mmol), triethylamine (0.30 mL, 2.2 mmol), and 4-(dimethylamino)pyridine (10 mg) in methylene chloride (2 mL). After the mixture was stirred for 6 h at reflux, ethyl acetate (100 mL) was added and the solution was successively washed with 1 N HCl (3 × 20 mL), saturated sodium bicarbonate solution (20 mL), water (20 mL), and saturated salt solution (20 mL). The solution was dried over anhydrous sodium sulfate and the solvent removed by rotoevaporation. 4-[[4-(Benzyloxycarbonyl)phenyl]methoxy]-1-[(benzylamino)carbonyl]-3,3-diethyl-2-azetidinone was purified by flash column chromatography on silica gel, eluted with 20% ethyl acetate in hexanes, and isolated as a clear oil (220 mg, 40% yield): ^{1}H NMR ($CDCl_3$) 0.85 (t, J = 7 Hz, 6 H), 1.68–1.81 (m, 4 H), 4.32 (d, J = 6 Hz, 2 H), 4.67 and 4.82 (AB q, J = 12 Hz, 2 H), 4.73 (s, 1 H), 5.35 (s, 2 H), 7.25 (s, 5 H), 7.40 (m, 5 H), 7.44 (d, J = 8 Hz, 2 H), 8.05 (d, J = 8 Hz, 2 H).

A mixture of 4-[[4-(benzyloxycarbonyl)phenyl]methoxy]-1-[(benzylamino)carbonyl]-3,3-diethyl-2-azetidinone (220 mg, 0.44 mmol) in ethyl acetate (8 mL) and acetic acid (2 mL) containing 10% palladium on carbon (40 mg) was hydrogenolyzed on a Paar shaker at 40 psi of hydrogen pressure for 3 h. The mixture was filtered through Solka-Floc filter aid and the pad washed with ethyl acetate (20 mL). The combined filtrates were rotoevaporated, and 4-[(4-carboxyphenyl)methoxy]-1-[(benzylamino)-carbonyl]-3,3-diethyl-2-azetidinone (**5a**) was purified by flash column chromatography on silica gel eluted with 0.5% acetic acid in 25% ethyl acetate/hexanes and recrystallized from ethyl acetate/hexanes as a white powder (150 mg, 83% yield): ^{1}H NMR ($CDCl_3$) 0.89 (t, J = 7 Hz, 6 H), 1.72–1.04 (m, 4 H), 4.33 (d, J = 6 Hz, 2 H), 4.65 and 4.93 (AB q, J = 12 Hz, 2 H), 4.77 (s, 1 H), 7.40 (m, 5 H), 7.51 (d, J = 8 Hz, 2 H), 8.03 (d, J = 8 Hz, 2 H).

4-(Carboxymethoxy)-1-[(benzylamino)carbonyl]-3,3-diethyl-2-azetidinone (5b). A solution of 1 (672 mg, 3.6 mmol) and magnesium metal (45 mg, 1.85 mmol) in allyl alcohol was heated to 70 °C for 24 h. Ethyl acetate (50 mL) was added and the solution successively washed with 1 N HCl (3 × 10 mL), saturated sodium bicarbonate solution (10 mL), water (10 mL), and saturated salt solution (10 mL). The solution was dried over

anhydrous sodium sulfate, and the solvent was removed by rotoevaporation to give 246 mg of a product containing ~80% 4-(allyloxy)-3,3-diethyl-2-azetidinone [^{1}H NMR ($CDCl_3$) 0.95 (t, J = 7 Hz, 3 H), 1.01 (t, J = 7 Hz, 3 H), 1.56–1.94 (m, 4 H), 4.06 (d, J = 5 Hz, 2 H), 4.13 (s, 1 H), 5.22 (dd, J = 10, 2 Hz, 1 H), 5.32 (dd, J = 16, 2 Hz, 1 H), 5.92 (m, 1 H)] and ~20% unreacted starting material 1.

Benzyl isocyanate (0.33 mL, 2.7 mmol) was added to a solution containing 4-(allyloxy)-3,3-diethyl-2-azetidinone (~1.0 mmol), triethylamine (0.37 mL, 2.7 mmol), and 4-(dimethylamino)-pyridine (10 mg) in methylene chloride (2 mL). After the mixture was stirred for 24 h at room temperature, ethyl acetate (50 mL) was added and the solution successively washed with 1 N HCl (3 × 10 mL), saturated sodium bicarbonate solution (10 mL), water (10 mL), and saturated salt solution (20 mL). The solution was dried over anhydrous sodium sulfate and the solvent removed by rotoevaporation. 4-(Allyloxy)-1-[(benzylamino)carbonyl]-3,3-diethyl-2-azetidinone was purified by flash column chromatography on silica gel eluted with 10% ethyl acetate in hexanes and isolated as a clear oil (242 mg, 77% yield): ^{1}H NMR ($CDCl_3$) 0.94 (t, J = 7 Hz, 3 H), 1.01 (t, J = 7 Hz, 3 H), 1.64–1.96 (m, 4 H), 4.36 and 4.58 (m, 2 H), 4.50 (d, J = 6 Hz, 2 H), 5.09 (s, 1 H), 5.19 (dd, J = 11, 2 Hz, 1 H), 5.32 (dd, J = 17, 2 Hz, 1 H), 5.94 (m, 1 H), 7.00 (br t, J = 6 Hz, 1 H), 7.31 (s, 5 H).

To an ice-cooled solution of 4-(allyloxy)-1-[(benzylamino)-carbonyl]-3,3-diethyl-2-azetidinone (240 mg, 0.76 mmol) and periodic acid (710 mmol, 3.1 mmol) in carbon tetrachloride (1.5 mL), acetonitrile (1.5 mL), and water (2.3 mL) was added ruthenium trichloride trihydrate (4 mg). [**Caution**: exothermic reaction.] After the mixture was stirred for 3 h at room temperature, methylene chloride (20 mL) was added and the aqueous layer extracted with fresh methylene chloride (3 × 20 mL). The combined organic extracts were dried over anhydrous sodium sulfate. The solvent was removed by rotoevaporation and the residue redissolved in diethyl ether (50 mL). The solution was filtered through Celite filter aid and the solvent removed by rotoevaporation. The product was purified by flash column chromatography on silica gel eluted with 1% acetic acid in 35% ethyl acetate/hexanes. 4-(Carboxymethyl)-1-[(benzylamino)-carbonyl]-3,3-diethyl-2-azetidinone (**5b**) was recrystallized from methylene chloride/hexanes and isolated as a white solid (165 mg, 65% yield): ^{1}H NMR ($CDCl_3$) 0.98 (t, J = 7 Hz, 3 H), 1.01 (t, J = 7 Hz, 3 H), 1.68–2.00 (m, 4 H), 4.38 and 4.64 (AB q, J = 17 Hz, 2 H), 4.47 (d, J = 6 Hz, 2 H), 5.11 (s, 1 H), 6.96 (br t, J = 6 Hz, 1 H), 7.30 br s, 5 H); IR 1775, 1720, 1705 cm^{-1}.

4-[(2(*R*,*S*),3-Dihydroxypropyl)oxy]-1-[(benzylamino)carbonyl]-3,3-diethyl-2-azetidinone (5c). A solution of *m*-chloroperbenzoic acid (0.55 gm, 3.2 mmol) in methylene chloride (8 mL) was added to an ice-cooled solution of 4-(allyloxy)-1-[(benzylamino)carbonyl]-3,3-diethyl-2-azetidinone (870 mg, 2.9 mmol) in methylene chloride (5 mL). After the mixture was stirred for 3 h at room temperature, ethyl acetate (30 mL) was added and the solution successively washed with saturated sodium bicarbonate solution (3 × 10 mL), water (2 × 10 mL), and saturated salt solution (10 mL). The solution was dried over anhydrous sodium sulfate and the solvent removed rotoevaporation. The epoxide was purified by flash column chromatography on silica gel eluted with 20% ethyl acetate in hexanes and used in the subsequent step. The ^{1}H NMR was very complex.

To a solution of the epoxide (0.20 gm, 0.6 mmol) in 10% aqueous acetone (5 mL) was added 50W Dowex ion-exchange resin (H^+ form, 50 mg). After being stirred overnight at room temperature, the mixture was filtered and the solution dissolved in ethyl acetate (250 mL). The solution was washed with water (2 × 30 mL) and saturated salt solution (50 mL) and dried over anhydrous sodium sulfate. The product was purified by flash column chromatography on silica gel eluted with 2:1 ethyl acetate/hexanes and isolated as a clear oil (97 mg, 46% yield): ^{1}H NMR ($CDCl_3$) 0.96 (t, J = 7 Hz, 3 H), 1.00 (t, J = 7 Hz, 3 H), 1.54–1.98 (m, 4 H), 3.25–4.00 (br m, 5 H), 4.46 (d, J = 6 Hz, 2 H), 5.10 and 5.14 (2 s, 1 H), 7.04 (br t, J = 6 Hz, 1 H), 7.32 (s, 5 H); IR 3400, 1770, 1710 cm^{-1}.

4-(1-Imidazolyl)-1-[(benzylamino)carbonyl]-3,3-diethyl-2-azetidinone (7a). Imidazole (1.0 g, 14.7 mmol) and 1 N NaOH (2.9 mL) was added to a solution of 1 (0.54 g, 2.9 mmol) in acetone (7 mL) and stirred for 2 h at room temperature. Ethyl acetate (100 mL) was added and the solution washed with water (4 × 20 mL) and saturated salt solution (20 mL). After the mixture was dried over anhydrous sodium sulfate, the solvent was removed by rotoevaporation to yield 4-(1-imidazolyl)-3,3-diethyl-2-azetidinone as a clear oil (300 mg, 54% yield). This material was dissolved in methylene chloride (3 mL), and triethylamine (0.42 mL, 3 mmol), 4-(dimethylamino)pyridine (10 mg), and benzyl isocyanate (0.37 mL, 3 mmol) were added. After stirring overnight, ethyl acetate was added and the solution washed with water (3 × 20 mL). After drying over anhydrous sodium sulfate, the solvent was rotoevaporated and the product purified by flash column chromatography on silica gel eluted with 0–4% methanol in chloroform. 4-(1-Imidazolyl)-1-[(benzylamino)carbonyl]-3,3-diethyl-2-azetidinone (**7a**) was isolated as a slightly yellow oil (211 mg, 22% yield from 1): ^{1}H NMR ($CDCl_3$) 0.78 (t, J = 7 Hz, 3 H), 1.06 (t, J = 7 Hz, 3 H), 1.37 (hex, J = 7 Hz, 2 H), 1.89 (m, 2 H), 4.48 (m, 2 H), 5.79 (s, 1 H), 6.87 (br t, J = 6 Hz, 1 H), 7.00 (s, 1 H), 7.13 (s, 1 H), 7.35 (m, 5 H), 7.61 (s, 1 H); IR 1780, 1716 cm^{-1}.

4-Benzoyl-1-[(benzylamino)carbonyl]-3,3-diethyl-2-azetidinone (10) (Method C, Scheme III). *p*-Anisidine (6.15 g, 50 mmol) was added to a solution of phenylglyoxal hydrate (7.6 g, 50 mmol) in methylene chloride (125 mL) at room temperature. Molecular sieves (4 Å, ~50 mL) was added and the mixture stirred for 1.5 h. The mixture was filtered through a pad of Celite filter aid and anhydrous sodium sulfate and the filtrate heated to 70 °C. Triethylamine (6.0 g, 59 mmol) was added followed by a solution of 2-ethyl-*n*-butyryl chloride (6.8 g, 50 mmol) in 1,2-dichloroethane (10 mL). After the mixture was heated for 1 h, more triethylamine (2 mL) and acid chloride (1 gm) were added, and the solution was heated at 85 °C for 4 h, and cooled to room temperature, and 2 N HCl (100 mL) was added. The layers were separated, and the organic layer was stirred over saturated sodium bicarbonate solution (100 mL). The organic layer was dried by filtering through a pad of anhydrous sodium sulfate and the solvent removed by rotoevaporation. The product was purified by column chromatography on silica gel eluted with 10–25% ethyl acetate in hexanes. 4-Benzoyl-3,3-diethyl-1-(*p*-methoxyphenyl)-2-azetidinone was recrystallized from ether/hexanes as a white solid (9.23 g, 55% yield): ^{1}H NMR ($CDCl_3$) 0.86 (t, J = 7 Hz, 3 H), 1.14 (t, J = 7 Hz, 3 H), 1.30–2.20 (m, 4 H), 3.76 (s, 3 H), 5.30 (s, 1 H), 6.84 (d, J = 9 Hz, 2 H), 7.24 (d, J = 9 Hz, 2 H), 7.40–7.74 (m, 3 H), 7.96 (d, J = 9 Hz, 2 H). Anal. Calcd for $C_{21}H_{23}NO_3 + 0.14H_2O$: C, 74.20; H, 6.90; N, 4.12. Found: C, 74.16; H, 6.99; N, 4.13.

To a solution of 4-benzoyl-3,3-diethyl-1-(*p*-methoxyphenyl)-2-azetidinone (8.96 g, 26.5 mmol) in acetonitrile (75 mL) and water (25 mL) at −5 to 0 °C was added in portions over 5 min solid ceric ammonium nitrate (45 g, 82 mmol). Water (100 mL) was added and the solution extracted with methylene chloride (3 × 50 mL). The organic solution was dried through a pad of anhydrous sodium sulfate and the solvent removed by rotoevaporation. The product, 4-benzoyl-3,3-diethyl-1-(*p*-methoxyphenyl)-2-azetidinone, was purified by column chromatography on silica gel eluted with 10% ethyl acetate in hexanes (1.2 g, 20% yield): ^{1}H NMR ($CDCl_3$) 0.82 (t, J = 7 Hz, 3 H), 1.18 (t, J = 7 Hz, 3 H), 1.26–2.20 (m, 4 H), 4.92 (s, 1 H), 6.12 (br s, 1 H), 7.48–7.66 (m, 3 H), 7.88 (dd, J = 9, 2 Hz, 2 H). Anal. Calcd $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.55; H, 7.41; N, 6.04.

Benzyl isocyanate (0.2 mL, 1.6 mmol) was added to a solution of 4-benzoyl-3,3-diethyl-1-(*p*-methoxyphenyl)-2-azetidinone (100 mg, 0.43 mmol), triethylamine (0.3 mL, 2.2 mmol), and 4-(dimethylamino)pyridine (10 mg) in methylene chloride (3 mL). After being stirred for 24 h at room temperature, the solution was transferred to a centrifuge tube and 2 N HCl (5 mL) was added. The tube was vortexed and then centrifuged. The organic layer was dried through a pad of anhydrous sodium sulfate and the solvent removed by rotoevaporation. The product was purified by column chromatography on silica gel eluted with 28% ethyl acetate in hexanes to give 4-benzoyl-1-[(benzylamino)carbonyl]-carbonyl]-3,3-diethyl-2-azetidinone (**10**) as white crystals (155 mg, ~100% yield): ^{1}H NMR ($CDCl_3$) 0.82 (t, J = 7 Hz, 3 H), 1.14 (t, J = 7 Hz, 3 H), 1.26–2.16 (m, 4 H), 4.54 (d, J = 6 Hz, 2 H), 5.32 (s, 1 H), 6.86 (br t, J = 6 Hz, 1 H), 7.22–7.70 (m, 8 H), 7.94 (dd, J = 9, 2 Hz, 2 H).

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