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Preparation of β-Lactams from Azetidine-2-carboxylic Acids and Esters

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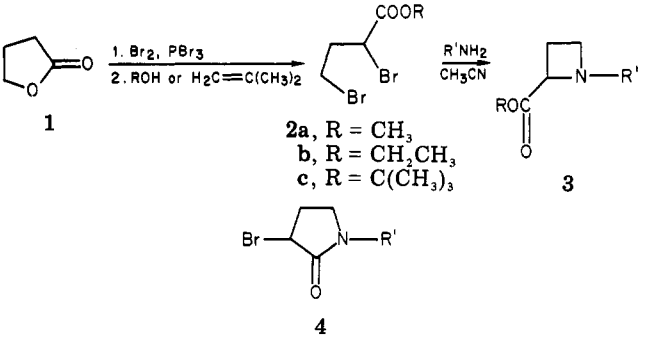
Azetidine carboxylic acids or esters have been converted to β-lactams by three types of oxidative decarboxylation. The procedures involve (a) dianion oxygenation followed by decomposition of the α-hydroperoxy carboxylic acid, (b) addition of a peracid to the iminium salt formed from the acid chloride, followed by pyridine-promoted β elimination, and (c) cleavage by singlet oxygen of the enamino ketene acetal formed by enol silylation.

In recent years there has been renewed interest in the development of efficient methods[1-10] for the production of β-lactams because of the importance of these systems in the penicillins,[11] in cephalosporins,[12] and in related antibiotics such as thienamycin.[13] The discovery of antibiotic activity among monocyclic β-lactams including the nocardicins[14] and wildfire toxin,[15] along with the isolation of the β-lactamase inhibitor clavulanic acid,[16] incorporating a 2-azetidinone unit, has intensified research directed toward the synthesis of this system.

Among the procedures which have been developed for β-lactam synthesis as recently reviewed[17,18] are the addition of ketenes to Schiff bases,[1] ring closure of amino acids, ring-contraction procedures, as in the photo-Wolff rearrangement of 4-oxo-2-pyrrolidones[5] or the periodate-induced contraction of 3-oxo-2-pyrrolidones,[6] ring expansion of cyclopropanones,[7,8] the cyclization of β-halopropionamides and the [3 + 1] cyclization of α-phenylthioacetamide derivatives.[19] In all of the above methods, the β-lactam ring is formed by the cyclization of a suitable open-chain precursor or derived from a three- or five-membered-ring species. We now describe the details of a novel route to 2-azetidinones utilizing readily available azetidine-2-carboxylic acid or ester precursors.[2-4] Introduction of the amide carbonyl takes place via oxidative cleavage of the carboxylate substituent at the 2-position.

In the following discussion we report several methods for accomplishing the azetidinecarboxylate–azetidinone transformation. All of these procedures (A–C) involve the initial preparation of an azetidine carboxylic acid ester (3) which is easily derived from γ-butyrolactone by slight

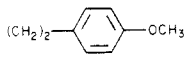
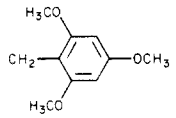
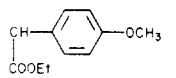
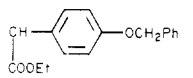
Scheme I



(1) Bose, A. K.; Dayal, B.; Chawla, H. P. S.; Manhas, M. S. *Tetrahedron Lett.* **1972** 2823. Bose, A. K.; Kapur, J. C.; Sharma, S. D.; Manhas, M. S. *Ibid.* **1973**, 2319. Bose, A. K.; Chawla, H. P. S.; Dayal, B.; Manhas, M. S. *Ibid.* **1973**, 2503.
(2) Wasserman, H. H.; Lipshutz, B. H. *Tetrahedron Lett.* **1976**, 4613.
(3) Wasserman, H. H.; Tremper, A. W. *Tetrahedron Lett.* **1977**, 1449.
(4) Wasserman, H. H.; Lipshutz, B. H.; Wu, J. S. *Heterocycles* **1977**, 7, 321.
(5) Lowe, G.; Ridley, D. D. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2024. Stork, G.; Szajewski, R. *J. Am. Chem. Soc.* **1974**, *96*, 5787.
(6) Bender, D. R.; Bjeldanes, L. F.; Knapp, D. R.; McKean, D. R.; Rapoport, H. *J. Org. Chem.* **1973**, *38*, 3439. Bender, D.; Rapoport, H.; Bordner, J. *Ibid.* **1975**, *40*, 3208.
(7) Wasserman, H. H.; Glazer, E. *J. Org. Chem.* **1975**, *40*, 1505.
(8) Wasserman, H. H.; Adickes, H. W.; de Ochoa, O. E. *J. Am. Chem. Soc.* **1971**, *93*, 5586.
(9) Nakatsuka, S.; Tanino, H.; Kishi, Y. *J. Am. Chem. Soc.* **1975**, *97*, 5008, 5010.
(10) Scott, A. I.; Yoo, S. E.; Chung, S. K.; Lacadie, J. A. *Tetrahedron Lett.* **1976**, 1137.
(11) Clarke, H. T.; Johnson, J. R.; Robinson, R. "Chemistry of Penicillin"; Princeton University Press: Princeton, NJ, 1949.
(12) Flynn, E. H., Ed. "Cephalosporins and Penicillins"; Academic Press: New York, 1972.
(13) For leading references, See: Johnston, D. B. R.; Schmitt, S. M.; Bouffard, F. A.; Christensen, B. G. *J. Am. Chem. Soc.* **1978**, *100*, 313.
(14) Hashimoto, M.; Komori, T.; Kamiya, T. *J. Am. Chem. Soc.* **1976**, *98*, 3023.
(15) Stewart, W. W. *Nature (London)* **1971**, *229*, 174.
(16) Howarth, T. J.; Brown, A. G.; King, T. J. *J. Chem. Soc., Chem. Commun.* **1976**, 266.
(17) Mukerjee, A. K.; Srivastava, R. C. *Synthesis* **1973**, 327.
(18) Isaacs, N. S. *Chem. Rev.* **1976**, *76*, 181.
(19) Hirai, K.; Iwano, Y. *Tetrahedron Lett.* **1979**, 2031.

0022-3263/81/1946-2991$01.25/0

Table I. Azetidine Carboxylic Esters from the Condensation of Primary Amines with 1,3-Dibromobutyrates

azetidine	R'	R	yield, %
3a	$C(CH_3)_3$	CH_3	70[21]
b	$C(CH_3)_3$	$C(CH_3)_3$	70
c	c-C_6H_{11}	CH_3	61[21]
d	c-C_6H_{11}	$C(CH_3)_3$	59
e	$CH_2CH(OCH_3)_3$	CH_3	60
f	$CH_2CH(OCH_3)_3$	CH_2CH_3	66
g	$CH_2CH{=}CH_2$	$C(CH_3)_3$	41
h	n-C_5H_{11}	CH_3	50
i	c-C_8H_{15}	CH_3	56
j	$(CH_2)_3N(CH_3)_2$	CH_2CH_3	28
k	$CH(Ph)_2$	CH_2CH_3	73
l		CH_2CH_3	50
m	$(CH_2)_2Ph$	CH_3	59
n		$C(CH_3)_3$	44
o	$CH_2C_6H_5$	CH_3	79[21]
p	$CH_2C_6H_5$	$C(CH_3)_3$	52
q	$CH_2CH_2C_6H_5$	$C(CH_3)_3$	65
r	$CH_2C_6H_4$-p-OMe	$C(CH_3)_3$	55
s	$C(CH_3)_2COOEt$	$C(CH_3)_3$	83
t	$CH(COOEt)CH(CH_3)_2$	$C(CH_3)_3$	87
u		$C(CH_3)_3$	82
v		$C(CH_2)_3$	63

modifications of existing procedures.[20,21] The azetidine esters obtained in this way may be directly converted to β-lactams by procedure C (vide infra) or may be hydrolyzed to the corresponding β-amino acids and then oxidatively transformed to 2-azetidinones by either procedure A or B.

Preparation of Azetidine Precursors. The preparation of 2,4-dibromobutyrates (2) was accomplished by the reaction of γ-butyrolactone (1) with bromine and phosphorus tribromide according to Wladislaw's procedures.[20] Treatment of the crude reaction mixture with isobutylene, methanol, or ethanol in the presence of an acid catalyst gave the 2,4-dibromobutyrates in good yield. Formation of azetidine-2-carboxylic esters generally took place as shown in Scheme I. Reaction of the dibromides with 3 equiv of a primary amine in acetonitrile according to the method of Rodebaugh and Cromwell[21] gave the azetidines in satisfactory yield. Alternatively, 1 equiv of amine could be used if 2 equiv of another base was added to consume the acid generated during the reaction. Triethylamine was well suited for this purpose. However, it was found that the reaction of α-amino esters with dibromides 2 (entries t–v in Table I) gave little of the corresponding azetidines under the conditions cited above, possibly due to the formation of lactam 4. In the latter case, the use of sodium or potassium carbonate in either acetonitrile or alcoholic solvents gave good results. The azetidine esters 3 prepared by these methods are listed in Table I. Hydrolysis of the azetidinecarboxylic esters (3) to the corresponding acids was accomplished as reported

Scheme II

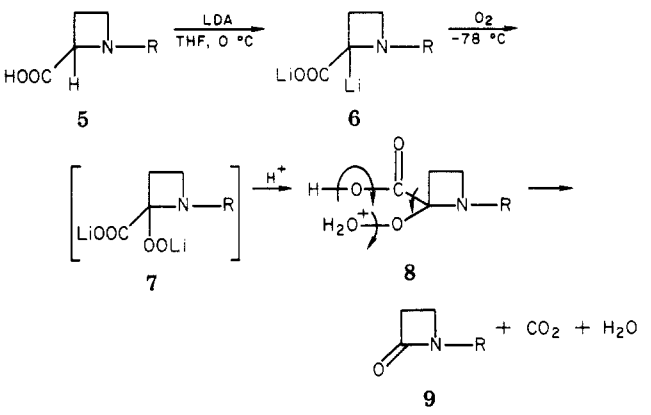


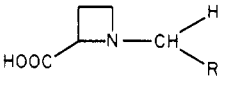
Table II. Preparation of β-Lactams 9 by Hydrolysis and Oxidative Decarboxylation of Azetidine Esters 3 (Dianion Oxygenation)

R	yield, % acid 5	yield, % β-lactam 9
t-Bu	100 (5a)[21]	60 (9a)
c-C_6H_{11}	77 (5b)[21]	47 (9b)
$CH_2CH(OCH_3)_2$	93 (5c)	50 (9c)
$(CH_2)_4CH_3$	88 (5d)	61 (9d)
c-C_8H_{15}	100 (5e)	52 (9e)
$(CH_2)_3N(CH_3)_2$	40 (5f)	45 (9f)
$CH_2CH_2C_6H_4$-p-OCH_3	93 (5g)	47 (9g)
$CH_2CH_2C_6H_5$	94 (5h)	55 (9h)

earlier[21] by heating with barium hydroxide in water to reflux for 1 h followed by cooling to 0 °C and treatment with a stream of CO_2. Filtration of the barium carbonate and concentration of the solution yielded the amino acid as a hygroscopic white paste, usually in excellent yields.

Oxidative Decarboxylation via Oxygenation of Dianions. (Procedure A). Oxidative decarboxylation[2] takes place on oxygenation of the dianions 6 of amino acids 5 formed at low temperature by the reaction of 5 with 2 equiv of lithium diisopropylamide (LDA) in tetrahydrofuran (THF). The solutions of these dianions react rapidly with oxygen in ether at −78 °C, forming peroxidic products assigned structures 7. Neutralization of the dilithium salts 7 with 2 equiv of p-toluenesulfonic acid (TsOH) leads directly to the corresponding β-lactams (9) most probably through intermediates 8 (Scheme II). Compounds prepared by the above route are listed in Table II.

In investigating the scope of oxidation, it was found that when the amine component contains activated protons (benzylic, allylic) as in 10, proton abstraction from the



10a, R = Ph
b, R = CH=CH$_2$

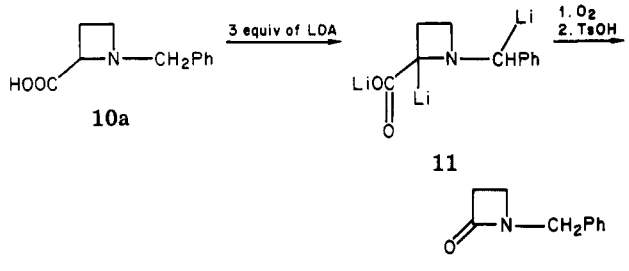
benzylic or allylic position[22,23] competes favorably with the desired dianion formation in the conversion of 5 to 6, and in these cases, the lactam could not be obtained. Use of the more sterically hindered (and potentially more selective) amide bases such as lithium hexamethyldisilazide[24] gave similar negative results. Addition of 3 equiv of LDA

(20) Wladislaw, B. *J. Org. Chem.* **1961**, *26*, 711.
(21) Rodebaugh, R. M.; Cromwell, N. H. *J. Heterocycl. Chem.* **1968**, *5*, 309; **1969**, *6*, 435.
(22) Durst, T.; Van Den Elzen, R.; LeBelle, M. J. *J. Am. Chem. Soc.* **1972**, *94*, 9261.
(23) Fraser, R. R.; Boussard, G.; Postescu, I. D.; Whiting, J. J.; Wigfield, Y. Y. *Can. J. Chem.* **1973**, *51*, 1109.
(24) Rathke, M. W. *J. Am. Chem. Soc.* **1970**, *92*, 3222.

Table III. Conversion of Azetidine-2-carboxylic Acids to β-Lactams via Iminium Salts

R for 5	yield, % iminium salt 12	yield, % β-lactam 9
$C(CH_3)_3$	97 (12a)	77 (9a)
c-C_6H_{11}	98 (12b)	80 (9b)
CH_2Ph[21]	100 (12c)	80 (9i)
CH_2CH_2Ph	96 (12d)	71 (9h)
$CH_2CH_2C_6H_4$-p-OCH_3		77 (9g)

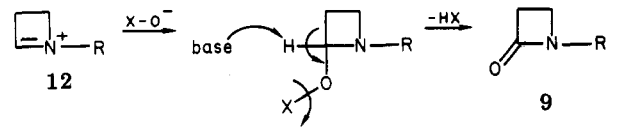
to **10** in order to form the trianion **11**, followed by oxygenation with 1 equiv of oxygen and then decarboxylation, did afford the desired β-lactam **9**, but in low yield.



10a 11 9i (1)

Formation and Oxidation of Iminium Salts (Procedure B). The recently reported decarbonylation of α-tertiary amino acids to iminium salts by phosphorus oxychloride or oxalyl chloride[25,26] appeared to represent a convenient way of forming azetidinium salts which might undergo addition of a nucleophilic oxidizing agent and lead to azetidinone formation. In exploring this idea, we found that the use of oxalyl chloride, followed by perchloric acid, is effective in converting azetidine-2-carboxylic acids to the corresponding iminium salts nearly quantitatively. Thionyl chloride and phosphorus oxychloride also bring about the same conversion, but in poorer yields.

It was anticipated that the addition of a peroxidic nucleophile to the highly electrophilic iminium salt could lead to 2-azetidinone formation by the addition–elimination sequence shown in eq 2.

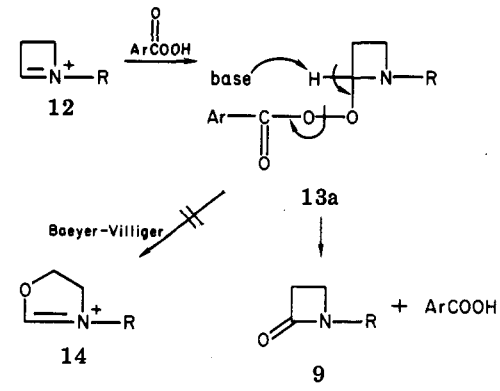


12 13 9 (2)

In studying reagents of this type, including sodium hydroperoxide, alkyl peroxide anions, and percarboxylic acid conjugate bases, we found that the combination of *m*-chloroperbenzoic acid in methylene chloride with 2 equiv of pyridine was most effective in the formation of β-lactams **9** (see Table III).

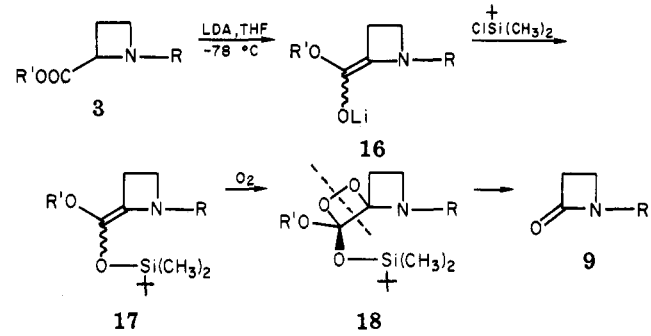
The mechanism of this oxidation has not been studied in detail, but it may be pictured in terms of an initial addition of the percarboxylate anion to the iminium salts, producing the intermediate **13a**. This transient species can then undergo loss of *m*-chlorobenzoic acid by a β-elimination to give the lactam **9**. This reaction course is particularly interesting in view of the possibility of a competing Baeyer–Villiger type of reaction[27,28] which could

Scheme III



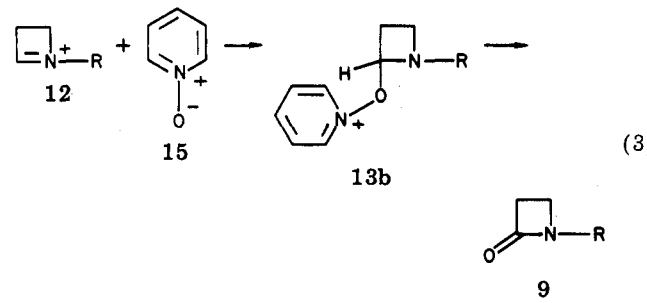
12 13a 14 9

Scheme IV



3 16 17 18 9

result in ring enlargement (i.e., **13a** → **14**, Scheme III). The possibility was considered that in this reaction, *m*-chloroperbenzoic acid may be oxidizing pyridine to pyridine *N*-oxide (**15**)[29] which could then add to the azetidinium salt **12**, giving an intermediate (**13b**, eq 3). Loss of



12 15 13b 9 (3)

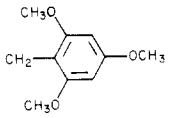
pyridine would then result in the observed product as shown. This pathway is considered unlikely, however, since we have found that no reaction takes place on addition of pyridine *N*-oxide to a methylene chloride solution containing an iminium salt and 1 equiv of pyridine.

Oxidative Cleavage of Enamino *O*-Silylketene Acetals (Procedure C). The possibility that azetidinecarboxylic acid *esters* might be converted directly to β-lactams by oxidation of silyl enolates at the 2-position was next investigated. Such a direct oxidation would eliminate the hydrolysis step common to both procedures A and B.

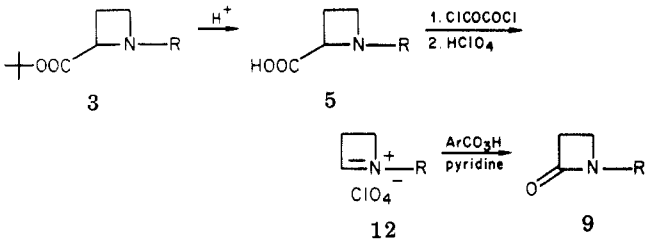
Formation of the monoanion **16** by reaction of an azetidinecarboxylate (**3**) with LDA in THF at −78 °C yielded the enolate **16** which reacted readily[30] with *tert*-butyldimethylchlorosilane[31] to form the enamino *O*-silylketene

(25) Dean, R. T.; Padgett, H. C.; Rapoport, H. *J. Am. Chem. Soc.* **1976**, *98*, 7448.
(26) Weinstein, B.; Craig, A. R. *J. Org. Chem.* **1976**, *41*, 875.
(27) Hassall, C. H. *Org. React.* **1957**, *9*, 73.
(28) Criegee, R. *Justus Liebigs Ann. Chem.* **1948**, *560*, 127.
(29) Craig, J. C.; Purushothaman, K. H. *J. Org. Chem.* **1970**, *35*, 1721.
(30) Rathke, M. W.; Sullivan, D. F. *Synth. Commun.* **1973**, *3*, 67. Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868. Rasmussen, J. K. *Synthesis* **1977**, 91.
(31) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

Table IV. β-Lactams 9 by Singlet Oxygen Oxygenation of Enamino Ketene Acetals 17

compd 17 R′	compd 17 R	yield of 9, %
CH_3	c-C_6H_{11}	46 (9b)
CH_3CH_2	$CH_2CH(OCH_3)_2$	56 (9c)
$C(CH_3)_3$	$CH_2CH_2C_6H_4$-p-OCH_3	66 (9g)
$C(CH_3)_3$		56 (9j)
$C(CH_3)_3$	$CH_2CH{=}CH_2$	48 (9k)
CH_3CH_2	$CH(C_6H_5)_2$	55 (9l)

Scheme V



acetal 17. These enamino ketene acetals, containing a highly electron-rich double bond system, were not isolated but were allowed to react in situ with singlet oxygen. The β-lactams 9 were formed as the only isolable products, presumably via cleavage of the dioxetanes 18[32] as shown in Scheme IV.

Table IV lists β-lactams prepared by this method. Several of the examples are noteworthy in that they represent cases which were not amenable to the dianion approach (procedure A) discussed earlier where benzylic or allylic protons interfered. It is significant that although esters **3g,k–m** each contain labile protons of this type on the α-carbon of the residue attached to nitrogen, reaction with *1 equiv* of LDA at −78 °C permits the selective abstraction of the proton α to the carboxylate group. When ozone was used instead of singlet oxygen in attempts to cleave the enamine double bond in 17, very little (<10%) of the desired lactam was obtained.

Formation and Oxidation of Iminium Salts from *tert*-Butylazetidine Esters (Modified Procedure B). The limitations of the dianion oxygenation and silylation–oxidation procedures A and C stemming from the use of strongly basic conditions prompted an investigation of other methods for the oxidative conversion of azetidine-2-carboxylic esters to β-lactams. We found that azetidine *tert*-butyl esters can be deprotected with acid and then converted to the corresponding β-lactams by the decarbonylation–peracid oxidation method as indicated in Scheme V.

The method differs from procedure B in that the generation of azetidine-2-carboxylic acids is accomplished without basic hydrolysis. It will be shown in an accompanying paper on 3-ANA synthesis that this modification is particularly useful for the synthesis of azetidine monoesters 19 by selective deprotection of the ring-substituted carboxyl group. Subsequent decarbonylation–oxidation of these intermediates via iminium salts 20 gives β-lactam esters (21, Scheme VI) which are not available by any of the previous azetidine procedures.

Scheme VI

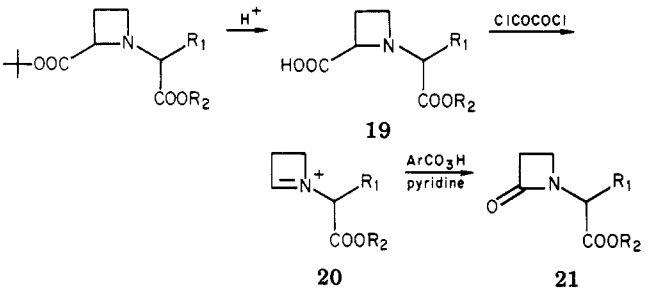
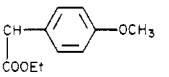
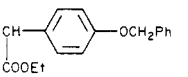


Table V

(A) (*tert*-Butylcarboxyl)azetidine-β-Lactam Conversions via Iminium Salts[a]

azetidine	R	yield of β-lactam, %
3b	$C(CH_3)_3$	77 (9a)
3d	c-C_6H_{11}	80 (9b)
3p	CH_2Ph	80 (9i)
3q	CH_2CH_2Ph	71 (9h)
3r	$CH_2C_6H_4$-p-OCH_3	70 (9m)

(B) Azetidine Diester–β-Lactam Conversions via Iminium Salts

azetidine diester	R′	yield of β-lactam, %
3s	$C(COOEt)(CH_3)_2$	71 (21a)
3t	$C(COOEt)HCH(CH_3)_2$	61 (21b)
3u		61 (21c)
3v		53 (21d)

[a] The yield of iminium salts 12a-d for 3b,d,p,q, respectively, was 99%.

The use of azetidine *tert*-butyl esters as precursors of β-lactams was studied with a variety of systems as summarized in Table V. In each case, formation of the intermediate iminium salt took place nearly quantitatively by first adding trifluoroacetic acid to a methylene chloride solution of the ester at 0 °C, followed by treatment with oxalyl chloride. Addition of perchloric acid then generated the desired perchlorate salt in nearly quantitative yield. In the next step these salts were converted to β-lactams according to procedure B.

β-Lactam Esters from Azetidine Diester. As shown by the preparation of β-lactams **3s–v** the selective hydrolysis of the *tert*-butyl esters permits the use of azetidine diesters as precursors of β-lactams where ester functionality is desired in the final product. This modification of route B has been employed in the synthesis of 3-ANA as will be described in the accompanying paper.[33]

Experimental Section

Melting points were obtained in a Melt-Temp apparatus and are uncorrected. Infrared spectra were recorded in chloroform or neat by using a Perkin-Elmer 700A spectrometer. NMR spectra were obtained with either a Perkin-Elmer R-32 90-MHz or a Bruker 270-MHz instrument using tetramethylsilane as an internal standard. Mass spectra were recorded on a Hitachi RMU-6

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spectrometer operated at 70 eV. Elemental analyses were performed by Dr. Robert Rittner, Olin Laboratories. Thin-layer chromatography (TLC) was performed by using precoated silica gel 60 F-254 plates (0.25-mm layer, E. Merck). Temperatures for Kugelrohr distillations refer to the heating oven.

Ethyl 2,4-Dibromobutyrate (2b). The procedure of Wladislaw[20] was followed for this preparation. γ-Butyrolactone (50 g, 0.58 mol), freshly distilled from barium oxide, was placed in a 250-mL 3-necked flask along with 1 mL of phosphorus tribromide. The solution was heated to 100 °C with stirring, and 30 mL (0.58 mol) of bromine was added dropwise beneath the surface of the liquid by means of a long-stemmed addition funnel. The pot temperature was maintained at 110–115 °C by the rate of bromine addition. When the rate of bromine uptake decreased, as evidenced by the color and decrease in reaction temperature, 0.25 mL of phosphorus tribromide was added, and heating was resumed to maintain the reaction temperature. Bromine addition was continued until the evolution of hydrogen bromide gas was evident. The mixture was then cooled slowly to room temperature and chilled with an ice bath. Absolute ethanol (100 mL) was added, and dry hydrogen chloride gas was bubbled through the solution for 5 min. The resulting solution was then stirred for 48 h with gentle heating (50 °C). The product was isolated by concentration of the reaction mixture in vacuo followed by extraction of the residue with ether. The combined extracts were washed with a 3% sodium bicarbonate solution and a saturated sodium chloride solution and dried over anhydrous sodium sulfate. Removal of solvent by rotary evaporation followed by distillation at 65 °C (0.04 mm) afforded 116.9 g (74%) of a colorless liquid: IR (liquid film) 1738 cm^{-1}; NMR ($CDCl_3$) δ 4.49 (1 H, m), 4.24 (2 H, q, J = 7 Hz), 3.54 (2 H, t, J = 6 Hz), 2.44 (2 H, m), 1.29 (3 H, t, J = 7 Hz).

Anal. Calcd for $C_6H_{10}O_2Br_2$: C, 26.28; H, 3.65. Found: C, 26.61; H, 3.85.

***tert*-Butyl 2,4-Dibromobutyrate (2c).** To a solution of 0.5 mL of phosphorus tribromide in 14.0 g of γ-butyrolactone (1) at 115 °C was added 7.9 mL of bromine over 0.5 h. After this time the reaction mixture was allowed to cool to room temperature, and the excess bromine was removed in a stream of nitrogen. The resulting yellow liquid was poured into a pressure bottle to which was added 75 mL of isobutylene and 1 mL of concentrated sulfuric acid. Following an initial exothermic reaction the bottle was sealed, and the reaction mixture was allowed to stir for 15 h at room temperature. After this time the nearly colorless solution was poured into cold sodium bicarbonate solution. Extraction of the bicarbonate solution twice with ether followed by washing the ethereal layer five times with saturated sodium bicarbonate, two times with saturated salt solution, drying over anhydrous magnesium sulfate, and removal of the solvent under reduced pressure gave a yellow liquid. Chromatography on neutral alumina eluted with 5% ethyl acetate–hexane gave 39.0 g (80%) of a colorless oil. The boiling point of this material was 85–98 °C (6 mmHg), but distillation resulted in a significant amount of decomposition. The structure was assigned as *tert*-butyl 2,4-dibromobutyrate (2) on the basis of the following data: IR (neat) 1725 cm^{-1}; NMR ($CDCl_3$, 60 MHz) δ 1.50 (9 H, s), 2.47 (2 H, q, J = 7.0 Hz), 3.35 (2 H, t, J = 7.0 Hz), 4.40 (1 H, t, J = 7.0 Hz).

Anal. Calcd for $C_8H_{14}Br_2O_2$: C, 31.82; H, 4.67. Found: C, 32.12; H, 4.85.

Preparation of Azetidine-2-carboxylic Acid Esters. Method A (Use of 3 Equiv of Amine). *N*-Cyclohexyl-2-(carbo-*tert*-butoxy)azetidine (3d). To a solution of 3.0 g (9.9 mmol) of *tert*-butyl 2,4-dibromobutyrate (2c) in 10 mL of acetonitrile was added 3.0 g (30.0 mmol) of cyclohexylamine. The mixture was stirred at 25 °C for 1 h and then heated at 55 °C for 24 h. Removal of the solvent under reduced pressure gave a semisolid residue which was dissolved in 50 mL of 5% sodium bicarbonate solution and extracted with ether (3 × 100 mL). The combined ethereal extracts were dried over anhydrous magnesium sulfate and concentrated in vacuo. Gradient column chromatography over silica gel with petroleum ether–ethyl acetate gave 2.9 g of a yellow oil. Final purification by bulb-to-bulb distillation provided 1.4 g (59%) of pure azetidine (**3d**): colorless oil; bp 78 °C (0.1 mmHg); IR (neat) 1730 cm^{-1} (split); NMR (CCl_4) δ 3.40 (1 H, t, J = 7.1 Hz), 3.28 (1 H, m), 2.76 (2 H, m), 2.19–0.63 (12 H, m), 1.18 (9 H, s).

Anal. Calcd for $C_{14}H_{25}NO_2$: C, 70.25; H, 10.53; N, 5.85. Found: C, 70.55; H, 10.32; N, 5.80.

Method B (Use of Triethylamine). *N*-(2-*p*-Methoxyphenethyl)-2-carbethoxyazetidine (3l). To a 200-mL round-bottomed flask were added sequentially 5.48 g (20 mmol) of ethyl 2,4-dibromobutyrate, 50 mL of acetonitrile, 3.02 g (20 mmol) of *p*-methoxyphenethylamine, and 30 mL of triethylamine. The colorless solution was heated to 55 °C for 6 h, and the yellow mixture worked up in the usual fashion to give a yellow oil. Application of the oil obtained to a 15 × 2 cm neutral alumina column packed and eluted with 10% ethyl acetate–hexane afforded 2.60 g (50%) of essentially colorless to very pale yellow product: IR (liquid film) 1730 cm^{-1}; NMR ($CDCl_3$) δ 7.11 (4 H, dd, J = 8, 24 Hz), 4.30 (2 H, q, J = 7 Hz), 3.84 (3 H, s), 3.71 (1 H, t, J = 9 Hz), 3.48 (1 H, m), 3.16–2.16 (7 H, m), 1.31 (3 H, t, J = 7 Hz). This product was characterized as its picrate, mp 113–114 °C.

Anal. Calcd for $C_{15}H_{21}NO_3$: C, 51.22; H, 4.91; N, 11.38. Found: C, 51.11; H, 4.92; N, 11.53.

Method C (Use of Sodium Carbonate). *N*-(Dimethylcarbethoxymethyl)-2-(carbo-*tert*-butoxy)azetidine (3s). To a solution of 4.7 g (15.6 mmol) of *tert*-butyl 2,4-dibromobutyrate (2c) in 25 mL of absolute ethanol were added 2.6 g (15.6 mmol) of 1,1-dimethylglycine ethyl ester[33] JO7B1 S*tert* 3.3 g (31.1 mmol) of anhydrous sodium carbonate. The mixture was heated to 55 °C for 4 days. Removal of the solvent under reduced pressure gave a semisolid residue which was dissolved in 50 mL of 5% sodium carbonate solution and extracted with ether (3 × 100 mL). The combined ethereal extracts were dried over magnesium sulfate and concentrated in vacuo to give 4.3 g of yellow oil. Column chromatography over alumina with ether elution provided 3.5 g (83%) of pure azetidine **3s**: IR (neat) 1730 cm^{-1} (split); NMR (CCl_4) δ 4.14 (3 H, m), 3.26 (2 H, m), 2.09 (2 H, m), 1.43 (9 H, s), 1.30 (3 H, t, J = 6.6 Hz), 1.14 (3 H, s), 1.12 (3 H, s).

The analytical samples was prepared by molecular distillation [40 °C (0.3 mmHg), 12 h].

Anal. Calcd for $C_{14}H_{25}NO_4$: C, 61.97; H, 9.29; N, 5.16. Found: C, 61.88; H, 9.27; N, 5.49.

Properties of Additional Azetidine-2-carboxylic Acid Esters. *N*-*tert*-Butyl-2-(carbobutoxy)azetidine (3b) by method B: yield 70%; bp 60 °C (0.5 mmHg); IR (neat) 1730 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 3.31 (1 H, t, J = 9.0 Hz), 3.05–3.25 (2 H, m), 1.95–2.30 (9 H, m), 1.44 (9 H, s), 0.90 (9 H, s).

Anal. Calcd for $C_{12}H_{23}NO_2$: C, 67.59; H, 10.87; N, 6.75. Found: C, 67.55; H, 10.90; N, 6.52.

***N*-(2,2-Dimethoxyethyl)-2-(carbomethoxy)azetidine (3e) by method A:** yield 60%; bp 95 °C (0.21 mmHg); IR (liquid film) 1745 cm^{-1}; NMR ($CDCl_3$) δ 4.72 (1 H, t, J = 6 Hz), 4.04 (3 H, s) 3.62 (3 H, s), 3.60 (1 H, t), 3.57 (3 H, s), 3.20 (2 H, m), 2.86 (2 H, d, J = 6Hz), 2.28 (2 H, m).

Anal. Calcd for $C_{10}H_{19}NO_4$: C, 53.19; H, 8.43; N, 6.89. Found: C, 53.46; H, 8.58; N, 6.81.

***N*-(2,2-Dimethoxyethyl)-2-carbethoxyazetidine (3f) by method B:** yield 66%; bp 125 °C (0.19 mmHg); IR (neat) 1930 and 1370 cm^{-1}; NMR ($CDCl_3$) δ 4.42 (1 H, t, J = 5.0 Hz), 4.19 (2 H, q, J = 7.0 Hz), 3.72 (1 H, t, J = 8.0 Hz), 3.60–3.25 (7 H, m), 3.34 (3 H, s), 3.29 (3 H, s), 3.15–2.85 (1 H, m), 2.68 (2 H, d, J = 5.0 Hz), 2.48–2.12 (2 H, m), 1.28 (3 H, t, J = 7.0 Hz).

Anal. Calcd for $C_{10}H_{19}NO_4$: C, 55.28; H, 8.81; N, 6.45. Found: C, 55.04; H, 9.01; N, 6.45.

***N*-(2-Propenyl)-2-(carbo-*tert*-butyoxy)azetidine (3g) by method B:** yield 41%, decomposes on distillation; IR (neat) 1730, 1640 cm^{-1}; NMR ($CDCl_3$) δ 5.92 (1 H, m), 5.26 (2 H, m), 3.58 (1 H, t, J = 8.0 Hz), 3.48–2.64 (4 H, m), 2.24 (2 H, m), 1.49 (9 H, s).

***N*-*n*-Pentyl-2-(carbomethoxy)azetidine (3h) by method B:** yield 50%; bp 80 °C (0.14 mmHg); IR (neat) 1740 cm^{-1}; NMR ($CDCl_3$) δ 3.72 (3 H, s), 3.59 (1 H, t, J = 8.0 Hz), 3.40 (1 H, m), 2.80 (1 H, m), 2.31 (4 H, m), 1.10 (6 H, m), 0.88 (3 H, m).

***N*-Cyclooctyl-2-(carbomethoxy)azetidine (3i) by method A:** yield 56%; bp 105–110 °C (0.1 mmHg); IR (neat) 1750, 1725 cm^{-1}; NMR ($CDCl_3$) δ 3.75 (3 H, s), 3.64 (1 H, t, J = 8.0 Hz), 3.45 (1 H, m), 2.85 (1 H, m), 2.25 (3 H, m), 1.53 (14 H, m).

Anal. Calcd for $C_{13}H_{23}NO_2$: C, 69.29; H, 10.29; N, 6.22. Found: C, 69.38; H, 10.16; N, 6.09.

***N*-[3-(Dimethylamino)-*n*-propyl]-2-carbethoxyazetidine (3j)**: yield 28%; bp 90 °C (0.2 mmHg); IR (neat) 1740 cm^{-1}; NMR ($CDCl_3$) δ 4.14 (2 H, q, J = 7 Hz), 3.53 (1 H, t, J = 8 Hz), 3.33 (1 H, m), 2.96–2.11 (13 H, m) containing 2.17 (6 H, s), 1.60 (2 H, m), 1.26 (3 H, t, J = 7 Hz).

***N*-Benzhydryl-2-carbethoxyazetidine (3k) by method A**: yield 73%; mp 73–75 °C; IR (melt) 1735 cm^{-1}; NMR ($CDCl_3$) δ 7.54–7.05 (10 H, m), 4.45 (1 H, s), 3.92–3.58 (3 H, m), 3.38 (1 H, dt, J = 4 Hz), 2.85 (1 H, d, J = 8 Hz), 2.53–1.88 (2 H, m), 0.95 (3 H, t, J = 6 Hz).

Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.58; H, 7.29; N, 4.85.

***N*-(2-Phenethyl)-2-(carbomethoxy)azetidine (3m) by method A**: yield 59%; bp 110 °C (0.02 mmHg); IR (neat) 1738 cm^{-1}; NMR ($CDCl_3$) δ 7.74 (5 H, s), 3.92 (3 H, s), 3.60 (1 H, t, J = 8 Hz), 2.96 (6 H, m), 2.40 (2 H, m).

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.49; H, 7.94; N, 6.29.

***N*-(2,4,6-Trimethoxybenzyl)-2-(carbo-*tert*-butoxy)azetidine (3n) by method B**: yield 44%; IR (neat) 1738 cm^{-1}; NMR ($CDCl_3$) δ 6.06 (2 H, s), 3.74 (11 H, m), 3.61 (1 H, t, J = 9 Hz), 3.02 (2 H, m), 2.13 (2 H, m), 1.38 (9 H, s); mass spectrum, m/e 337 (M^+).

***N*-Benzyl-2-(carbo-*tert*-butoxy)azetidine (3p) by method A**: yield 52%; IR (neat) 1740 cm^{-1}; NMR (CCl_4, 270 MHz) δ 7.21 (5 H, m), 3.85 (1 H, d, J = 12.5 Hz), 3.49 (1 H, t, J = 8.1 Hz), 3.34 (1 H, d, J = 12.5 Hz), 3.19 (1 H, m), 2.76 (1 H, m), 2.27 (1 H, m), 2.06 (1 H, m), 1.40 (9 H, s).

The analytical sample was prepared by molecular distillation [35 °C (0.1 mmHg), 12 h].

Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.89; H, 8.62; N, 5.86.

***N*-(2-Phenylethyl)-2-(carbo-*tert*-butoxy)azetidine (3q) by method A**: yield 65%; IR (neat) 1740 cm^{-1}; NMR (CCl_4) δ 7.14 (5 H, m), 3.40 (1 H, t, J = 7.1 Hz), 3.28 (1 H, m), 2.87 (1 H, m), 2.73 (1 H, m), 2.58 (2 H, m), 2.26 (1 H, m), 2.04 (1 H, m), 1.44 (9 H, s).

The analytical sample was prepared by molecular distillation [40 °C 0.3 mmHg), 12 h].

Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.72; H, 8.70; N, 5.21.

***N*-(*p*-Methoxybenzyl)-2-(carbo-*tert*-butoxy)azetidine (3r) by method A**: yield 55%; IR (neat) 1725 cm^{-1}; NMR (CCl_4) δ 7.11 (2 H, d, J = 8.9 Hz), 6.80 (2 H, d, J = 8.9 Hz), 3.77 (1 H, d, J = 13.3 Hz), 3.45 (1 H, t, J = 7.5 Hz), 3.33 (1 H, d, J = 13.3 Hz), 3.12 (1 H, m), 2.72 (1 H, m), 2.24 (1 H, m), 2.03 (1 H, m), 1.41 (9 H, s).

The analytical sample was prepared by molecular distillation [40 °C (0.2 mmHg), 12 h].

Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.21; H, 8.28; N, 4.98.

***N*-(2,2-Dimethyl-1-carbethoxyethyl)-2-(carbo-*tert*-butoxy)azetidine (3t) by method C**: yield 87%; 2:1 mixture of diastereomers (R_f 0.66 and 0.66 and 0.61, hexane–ethyl acetate, 1:1); IR (neat) 1730 cm^{-1}; NMR (CCl_4) δ 4.15 (2 H, q, J = 7.5 Hz), 3.68 (1 H, t, J = 8.1 Hz), 3.48 (1 H, m), 3.14 (1 H, m), 1.44 (9 H, s), 1.30 (3 H, t, J = 7.5 Hz), 0.97 (3 H, d, J = 6.7 Hz), 0.86 (3 H, d, J = 6.7 Hz), and δ 4.14 (2 H, q, J = 7.5 Hz), 3.68 (1 H, t, J = 8.1 Hz), 3.33 (1 H, m), 3.04 (1 H, m), 2.70 (1 H, d, J = 8.8 Hz), 2.21 (1 H, m), 2.09 (1 H, m), 1.74 (1 H, m), 1.44 (9 H, s), 1.30 (3 H, t, J = 7.5 Hz), 0.99 (3 H, d, J = 7.2 Hz), 0.83 (3 H, d, J = 7.2 Hz).

The analytical sample was prepared by molecular distillation [40 °C (0.1 mmHg), 12 h].

Anal. Calcd for $C_{15}H_{27}NO_4$: C, 63.13; H, 9.54; N, 4.91. Found: C, 62.94; H, 9.35; N, 4.88.

***N*-(α-Carbethoxy-*p*-methoxybenzyl)-2-(carbo-*tert*-butoxyazetidine (3u) by method C**: yield 82%; 1:1 mixture of diastereomers (R_f 0.59 and 0.51; hexane–ethyl acetate, 1:1); IR (neat) 1730 cm^{-1}; NMR (CCl_4) δ 7.22 (2 H, d, J = 9 Hz), 6.74 (2 H, d, J = 9 Hz), 4.19 (1 H, s), 4.05 (2 H, q, J = 7 Hz), 3.76 (3 H, s), 3.63 (1 H, t, J = 8 Hz), 3.22 (1 H, m), 2.98 (1 H, m), 2.17 (2 H, m), 1.41 (9 H, s), 1.20 (3 H, t, J = 7 Hz), and δ 7.22 (2 H, d, J = 9 Hz), 6.77 (2 H, d, J = 9 Hz), 4.19 (1 H, s), 4.03 (2 H, q, J = 7 Hz), 3.75 (3 H, s), 3.63 (1 H, t, J = 8 Hz), 3.22 (1 H, m), 2.98 (1 H, m), 2.17 (2 H, m), 1.33 (9 H, s), 1.19 (3 H, t, J = 7 Hz).

The analytical sample was prepared by molecular distillation [50 °C (0.1 mmHg), 3 days].

Anal. Calcd for $C_{19}H_{27}NO_5$: C, 65.31; H, 7.79; N, 4.01. Found: C, 65.02; H, 7.71; N, 4.17.

***N*-[α-Carbethoxy-*p*-(benzyloxy)benzyl]-2-(carbo-*tert*-butoxy)azetidine (3v) by method C**: yield 63%; 1:1 mixture of diastereomers (R_f 0.76 and 0.65; hexane–ethyl acetate, 1:1); IR ($CHCl_3$) 1735, 1610, 1510 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 7.30 (7 H, m), 6.90 (2 H, d, J = 9 Hz), 5.01 (2 H, s), 4.21 (1 H, s), 4.12 (2 H, q, J = 7 Hz), 3.79 (1 H, t, J = 8 Hz), 3.56–2.90 (2 H, m), 2.34–2.05 (2 H, m), 1.28 (9 H, s), 1.17 (3 H, t, J = 7 Hz), and δ 7.30 (7 H, m), 6.88 (2 H, d, J = 9 Hz), 5.01 (2 H, s), 4.32 (1 H, s), 4.10 (2 H, q, J = 7 Hz), 3.79 (1 H, t, J = 8 Hz), 3.56–2.90 (2 H, m), 2.34–2.05 (2 H, m), 1.40 (9 H, s), 1.17 (3 H, t, J = 7 Hz).

When allowed to stand for a prolonged time in dry heptane, one of the diastereomers (R_f 0.76) crystallized as a white solid. An analytical sample was prepared from this material following three recrystallizations from ether–methyl acetate–heptane; mp 108–109 °C.

Anal. Calcd for $C_{25}H_{31}NO_5$: C, 70.57; H, 7.34; N, 3.29. Found: C, 70.44; H, 7.21; N, 3.24.

Hydrolysis of Azetidine-2-carboxylic Acid Esters to the Corresponding Acids. The following general procedure was used in the hydrolysis of the azetidine esters to the carboxylic acids.[21] These amino acids were exceedingly hygroscopic, and satisfactory elemental analyses could therefore not be obtained at this stage.

***N*-(2,2-Dimethoxyethyl)azetidine-2-carboxylic Acid (5c).** In a 100-mL round-bottomed flask was placed 1.2 g (6.8 mmol) of ester **3e**, together with 1.4 g (4.4 mmol) of barium hydroxide octahydrate in 50 mL of water. The mixture was heated to reflux for 1 h, cooled to 0 °C, and then treated with a stream of carbon dioxide for 15 min. The resulting milky suspension was filtered through Celite, and the filtrate was concentrated to give a white paste. This solid residue was dissolved in hot chloroform, and the extract was dried over anhydrous magnesium sulfate. Removal of the solvent afforded 1.0 g (93%) of the amino acid **5c** as a white solid: mp 141–143 °C; IR ($CHCl_3$) 3320, 1630 cm^{-1}; NMR ($CDCl_3$) δ 9.52 (1 H, s), 4.78 (1 H, t, J = 5 Hz), 4.08 (1 H, m), 3.84 (1 H, m), 3.60 (6 H, s), 3.30 (1 H, m), 3.04 (2 H, d, J = 5 Hz), 2.44 (2 H, m).

***N*-*n*-Pentylazetidine-2-carboxylic acid (5d)**: yield 88%; mp 148–149 °C; IR ($CHCl_3$) 3320, 1630 cm^{-1}; NMR ($CDCl_3$) δ 11.00 (1 H, s), 4.72 (1 H, t, J = 9 Hz), 4.42 (1 H, m), 3.82 (1 H, dd, J = 9, 12 Hz), 3.28 (2 H, m), 2.79 (2 H, m), 1.80 (2 H, m), 1.40 (4 H, m), 0.95 (3 H, distorted t).

***N*-Cyclooctylazetidine-2-carboxylic acid (5e)**: yield 100%; mp 140–141 °C; IR ($CHCl_3$) 3300, 1635 cm^{-1}; NMR ($CDCl_3$) δ 9.13 (1 H, s), 4.43 (1 H, t, J = 9 Hz), 4.30 (1 H, m), 3.58 (1 H, q, J = 9 Hz), 3.10 (1 H, m), 2.57 (2 H, m), 1.95 (14 H, m).

***N*-[3-(Dimethylamino)-*n*-propyl]azetidine-2-carboxylic acid (5f)**: yield 40%; mp 127–128 °C; IR ($CHCl_3$) 3300, 1610 cm^{-1}; NMR ($CDCl_3$) δ 12.57 (1 H, s), 3.80 (1 H, t, J = 9 Hz), 3.63 (1 H, m), 3.17–2.17 (8 H, m), 2.50 (6 H, s), 1.79 (2 H, dd, J = 5, 7 Hz).

***N*-[2-*p*-Methoxyphenylethyl]azetidine-2-carboxylic acid (5g)**: yield 93%; mp 133–136 °C; IR ($CHCl_3$) 3300, 1625 cm^{-1}; NMR ($CDCl_3$) δ 10.06 (1 H, br), 7.22 (4 H, dd, J = 9, 24 Hz), 4.37 (1 H, t, J = 9 Hz), 4.10 (1 H, m), 3.69 (3 H, m), 3.50–2.35 (7 H, m).

***N*-Phenethylazetidine-2-carboxylic acid (5h)**: yield 94%; mp 139–141 °C; IR ($CHCl_3$) 3300, 1635 cm^{-1}; NMR ($CDCl_3$) δ 10.05 (1 H, s), 7.10 (5 H, s), 4.34 (1 H, t, J = 9 Hz), 4.04 (1 H, m), 3.44–2.10 (7 H, m).

General Procedure for the Oxygenation of Azetidine-2-carboxylic Acid Dianions. *N*-*tert*-Butyl-2-azetidinone (9a). To a solution containing 7 mmol of lithium diisopropylamide in tetrahydrofuran at 0 °C was added 0.47 g (3 mmol) of azetidinecarboxylic acid **5a** in one portion. The resulting solution was stirred at 0 °C for 1 h, cooled to −78 °C, and then transferred by syringe to a photooxygenation apparatus containing 50 mL of anhydrous ether.[33] Following the uptake of approximately 67 mL of oxygen, a solution of *p*-toluenesulfonic acid (1.33 g, 7.0 mmol) in 10 mL of dry tetrahydrofuran was added dropwise at −78 °C. Upon completion of the addition, the mixture was warmed to 25 °C and filtered through Celite. The filtrate was dried over anhydrous magnesium sulfate and concentrated under reduced

pressure. The resulting liquid was then chromatographed over neutral alumina (3:1 chloroform–ether) to give 0.23 g (60%) of *N*-*tert*-butyl-2-azetidinone (**9a**), bp 75 °C (3.6 mm). The identity of this compound was confirmed by comparison of its IR and NMR spectra with those of an authentic sample.[8]

***N*-Cyclohexyl-2-azetidinone (9b).** From 0.55 g (3 mmol) of amino acid **5b** there was obtained by the above procedure 0.22 g (47%) of *N*-cyclohexyl-2-azetidinone (**9b**): IR (neat) 1740 cm^{-1}; NMR ($CDCl_3$) δ 3.43 (1 H, br s), 3.21 (2 H, t, J = 4 Hz), 2.83 (2 H, t, J = 4 Hz), 1.50 (10 H, m). The product spectra were identical with those recorded for an authentic sample.[8]

***N*-(2,2-Dimethoxyethyl)-2-azetidinone (9c).** From 0.92 g (5 mmol) of amino acid **5c** there was obtained by the above procedure 0.40 g (50%) of a pale yellow liquid, *N*-(2,2-dimethoxyethyl)-2-azetidinone (**9c**). Kugelrohr distillation at 75 °C (0.23 mm) gave analytically pure material: IR (neat) 1742 cm^{-1}; NMR ($CDCl_3$) δ 4.47 (1 H, t, J = 5 Hz), 3.38 (6 H, s), 3.36 (2 H, t, J = 4 Hz), 3.33 (2 H, m), 2.95 (2 H, t, J = 4 Hz); mass spectrum, m/e 159 (M^+).

Anal. Calcd for $C_7H_{13}NO_3$: C, 52.82; H, 8.23; N, 8.80. Found: C, 52.92; H, 8.15; N, 8.87.

***N*-*n*-Pentyl-2-azetidinone (9d).** From 0.51 g (3 mmol) of amino acid **5d** there was obtained by the above procedure 0.26 g (61%) of a pale yellow liquid, *N*-*n*-pentyl-2-azetidinone (**9d**). Kugelrohr distillation at 90 °C (0.20 mm) gave the analytical sample: IR (neat) 1745 cm^{-1}; NMR ($CDCl_3$) δ 3.13 (4 H, m), 2.84 (2 H, t, J = 4 Hz), 1.32 (6 H, m), 0.88 (3 H, t, J = 6 Hz); mass spectrum, m/e 141 (M^+).

Anal. Calcd for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 67.87; H, 10.68; N, 9.87.

***N*-Cyclooctyl-2-azetidinone (9e).** From 0.63 g (3 mmol) of amino acid (**5e**) there was obtained by the above procedure 0.28 g (52%) of a pale yellow liquid, *N*-cyclooctyl-2-azetidinone (**9e**). Kugelrohr distillation at 105 °C (0.15 mm) gave analytically pure material: IR (neat) 1740 cm^{-1}; NMR ($CDCl_3$) δ 3.75 (H, br s), 3.19 (2 H, t, J = 4 Hz), 2.80 (2 H, t, J = 4 Hz), 1.65 (14 H, m); mass spectrum, m/e 181 (M^+).

Anal. Calcd for $C_{11}H_{19}NO$: C, 72.88; H, 10.56; N, 7.73. Found: C, 73.08; H, 10.49; N, 7.60.

***N*-[3-(Dimethylamino)-*n*-propyl]-2-azetidine (9f).** From 0.37 g (2 mmol) of amino acid **5f** there was obtained by the above procedure 0.14 g (45%) of *N*-[3-(dimethylamino)-*n*-propyl]-2-azetidine (**9f**). The analytical sample was prepared by Kugelrohr distillation at 110 °C (0.04 mmHg): IR (neat) 1745 cm^{-1}; NMR ($CDCl_3$) δ 3.23 (4 H, m), 2.89 (2 H, t, J = 4 Hz), 2.25 (2 H, m), 2.21 (6 H, s), 1.77 (2 H, m); mass spectrum, m/e 156 (M^+).

Anal. Calcd for $C_8H_{16}N_2O$: C, 61.51; H, 10.32; N, 17.93. Found: C, 61.32; H, 10.15; N, 17.68.

***N*-[2-(*p*-Methoxyphenyl)ethyl]-2-azetidinone (9g).** From 0.47 g (2 mmol) of amino acid **5g** there was obtained by the above procedure 0.16 g (47%) of *N*-[2-(*p*-methoxyphenylethyl)]-2-azetidinone. An analytical sample was obtained by Kugelrohr distillation at 120 °C (0.07 mmHg): IR (neat 1740 cm^{-1}; NMR ($CDCl_3$) δ 7.08 (4 H, dd, J = 10, 20 Hz), 3.79 (3 H, s), 3.45 (2 H, t, J = 7 Hz), 3.10 (2 H, t, J = 4 Hz), 2.83 (4 H, m); mass spectrum, m/e 205 (M^+).

Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 69.95; H, 7.48; N, 6.73.

***N*-(2-Phenethyl)-2-azetidinone (9h).** From 0.62 g (3 mmol) of amino acid **5h** there was obtained by the above procedure 0.29 g (55%) of pale yellow *N*-phenethylazetidinone (**9h**). An analytically pure sample was prepared by Kugelrohr distillation at 120 °C (0.17 mm): IR (neat) 1745 cm^{-1}; NMR (CCl_4) δ 7.20 (5 H, s), 3.42 (2 H, t, J = 7 Hz), 3.10 (2 H, t, J = 4 Hz), 2.85 (2 H, t, J = 7 Hz), 2.77 (2 H, t, J = 4 Hz); mass spectrum, m/e 175 (M^+).

Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.44; H, 7.63; N, 8.17.

General Procedure for the Formation of 2-Azetidinium Perchlorates from Azetidine-2-carboxylic Acids. The perchlorates are thermally and hydrolytically unstable and were characterized as outlined below by IR and NMR.

***N*-Benzyl-Δ¹-azetinium Perchlorate (12c).** To 6 mL of oxalyl chloride at 0 °C was added 0.58 g of *N*-benzyl-2-azetidinecarboxylic acid.[21] The resulting yellow solution was warmed to 45 °C and maintained at this temperature for 10 min. After this time, the reaction mixture was poured into 25 mL of ether, and 1.5 mL of 70% perchloric acid was added. The resulting slurry was stirred at 0 °C for 10 min, the ether was decanted, and the resulting oily solid was suspended in fresh ether. Filtration gave 0.81 g (100%) of a white solid (mp 129–130 °C) which was assigned the structure *N*-benzyl-Δ¹-azetinium perchlorate (**12c**) on the basis of the following data: IR (KBr) 1730, 1080 cm^{-1}; NMR (acetone-d_6, 90 MHz) δ 7.70–7.40 (5 H, m), 5.52 (1 H, t, J = 9.0 Hz), 4.75 (2 H, s), 4.65–4.25 (2 H, m), 3.20–2.68 (2 H, m).

***N*-Cyclohexyl-Δ¹-azetinium Perchlorate (12b).** In a similar fashion, 183 mg of *N*-cyclohexyl-2-azetidinecarboxylic acid (**5b**) was treated with 2 mL of oxalyl chloride and 0.5 mL of 70% perchloric acid to give 230 mg (98%) of *N*-cyclohexyl-Δ¹-azetinium perchlorate: mp 125–127 °C; IR (KBr) 1715, 1095 cm^{-1}; NMR (acetone-d_6, 90 MHz) δ 5.93 (1 H, t, J = 9.0 Hz), 4.42–4.15 (2 H, m), 3.65–3.27 (1 H, m), 2.95 (2 H, dd, J = 9.0, 10.0 Hz), 2.20–1.05 (10 H, m).

***N*-*tert*-Butyl-Δ¹-azetinium Perchlorate (12a).** In a similar fashion, 0.25 g of *N*-*tert*-butylazetidinecarboxylic acid (**5a**) was treated with 2.5 mL of oxalyl chloride and 0.5 mL of 70% perchloric acid to give 0.52 g (97%) of N-*tert*-butyl-Δ¹-azetinium perchlorate (**12a**): mp 134–138 °C; IR (KBr) 1800, 1060 cm^{-1}; NMR (acetone-d_6, 90 MHz) δ 6.17–5.80 (1 H, t, J = 11 Hz), 4.60–4.20 (2 H, t, J = 9.0 Hz), 3.40–2.82 (2 H, m), 1.49 (9 H, s).

***N*-(2-Phenylethyl)-Δ¹-azetinium Perchlorate (12d).** In a similar fashion, 0.14 g of *N*-(2-phenylethyl)-2-azetidinecarboxylic acid (**5h**) was treated with 1.4 mL of oxalyl chloride and 0.2 mL of 70% perchloric acid to give 0.17 g (96%) of *N*-(2-phenylethyl)-Δ¹-azetinium perchlorate (**12d**): mp 134–138 °C; IR (KBr) 1780, 1090 cm^{-1}; NMR (acetone-d_6, 90 MHz) δ 7.30 (5 H, s), 6.05 (1 H, t, J = 10 Hz), 4.45 (2 H, t, J = 8.0 Hz), 3.70–4.00 (2 H, m), 3.45–2.90 (4 H, m).

Decarbonylation and Oxidation of *N*-[(*p*-Methoxyphenyl)ethyl]azetidine-2-carboxylic Acid (5g). In a similar fashion, 0.22 g of *N*-[(*p*-methoxyphenyl)ethyl]-2-azetidine carboxylic acid (**5g**) was treated with 2 mL of oxalyl chloride and 0.5 mL of 70% perchloric acid. The usual workup afforded an oil (0.30 g, 100%) which could not be crystallized. To a suspension of 0.3 g of this oil in 5 mL of methylene chloride at 0 °C were added 0.18 g of *m*-chloroperbenzoic acid and 0.17 mL of pyridine. The reaction was stirred 40 min at 0 °C and poured into water, and the organic layer was separated. The resulting methylene chloride solution was washed with 5% hydrochloric acid, 5% sodium bicarbonate solution, and saturated salt solution and dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure gave 0.15 g (77%) of *N*-[(*p*-methoxyphenylethyl)]-2-azetidinone (**9g**), identical in alll respects with an authentic sample described earlier.

General Procedure for the Oxidation of 2-Azetinium Perchlorate with *m*-Chloroperbenzoic Acid. To a suspension of 0.01 mol of the perchlorate salt in 150 mL of methylene chloride at 0 °C were added 1.79 g of 100% *m*-chloroperbenzoic acid and 1.7 mL of pyridine. The reaction mixture was allowed to stir for 40 min at 0 °C and then poured into water. The resulting organic layer was separated, washed with cold 5% hydrochloric acid, cold 5% sodium bicarbonate solution, and cold saturated salt solution, and then dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure gave the crude 2-azetidinone which could be purified by column chromatography or vacuum distillation.

2-Azetidinones Prepared by the Above Method. *N*-*tert*-Butyl-2-azetidinone (9a). A solution of 0.5 g of *N*-*tert*-butyl-2-azetinium perchlorate (**12a**) in methylene chloride was oxidized by using the above procedure to give 200 mg (77%) of *N*-*tert*-butyl-2-azetidinone (**9a**) identical with an authentic sample.

***N*-Cyclohexyl-2-azetidinone (9b).** A solution of 0.25 g of *N*-cyclohexyl-2-azetinium perchlorate (**12b**) in methylene chloride was oxidized by using the above procedure to give 0.14 g (80%) of *N*-cyclohexyl-2-azetidinone (**9b**) identical with an authentic sample described earlier.

***N*-Benzyl-2-azetidinone (9i).** A solution of 0.23 g of *N*-benzyl-2-azetinium perchlorate (**12c**) in methylene chloride was oxidized according to the above procedure to give 0.14 g (80%) of *N*-benzyl-2-azetidinone (**9i**): bp 110 °C (0.01 mm); IR (neat) 1735 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 2.91 (2 H, t, J = 4.0 Hz), 3.09 (2 H, t, J = 4.0 Hz), 4.33 (2 H, s), 7.22–7.23 (5 H, m).

Anal. Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.55; H, 6.82; N, 8.97.

N-Phenethyl-2-azetidinone (9h). A solution of 0.24 g of N-phenethyl-2-azetinium perchlorate (**12d**) in methylene chloride was oxidized according to the above procedure to give 125 mg (71%) of N-phenethyl-2-azetidinone (**9h**) identical with an authentic sample described earlier.

General Procedure for the Silylation–Photooxidation of Azetidinecarboxylic Acid Esters. N-Benzhydryl-2-azetidinone (9l). To a solution of lithium diisopropylamide (2.2 mmol) in 15 mL of tetrahydrofuran cooled to −78 °C was added, dropwise with stirring, 0.54 g (2 mmol) of ester **3k** dissolved in 4 mL of tetrahydrofuran. After the mixture was stirred for 20 min at this temperature, 0.40 g (2.7 mmol) of *tert*-butyldimethylchlorosilane in 2 mL tetrahydrofuran was added dropwise to the orange solution over a 2-min period. Stirring was continued at −78 °C for 5 min, and the cooling bath was then removed. The solution was warmed slowly to 0 °C, where it was maintained for 30 min, and then warmed to room temperature for 30 min of additional stirring. Photooxygenation included transferring the resulting solution to an oxygenation well[34] containing Rose Bengal (10 mg) dissolved in 50 mL of tetrahydrofuran. The solution was diluted with an equal volume of pentane, cooled to 0 °C, and photooxygenated internally. Uptake of 1 equiv (45 mL) of oxygen occurred over a 5-min period. The solution was poured into 50 mL of an aqueous ammonium chloride solution and extracted several times with ether. The combined extracts were washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. Removal of solvents by rotary evaporation gave an orange oil which was applied to a 10 × 2 cm neutral alumina column packed as a slurry in hexanes. Elution with 2:1 hexane–ethyl acetate gave 0.23 g of pale yellow oil (55%). Crystalline product was obtained by dissolving the oil in 0.5 mL of tetrahydrofuran and adding the solution dropwise to 100 mL of pentane cooled to −78 °C: mp 63–65 °C; IR (neat) 1740 cm^{-1}; NMR ($CDCl_3$) δ 7.25 (10 H, m), 6.15 (1 H, s), 3.17 (2 H, t, J = 4 Hz), 2.90 (2 H, t, J = 4 Hz); mass spectrum, calcd for $C_{16}H_{15}NO$ m/e 237.1153, found m/e 237.1162.

N-Cyclohexyl-2-azetidinone (9b). From 0.40 g of N-cyclohexyl-2-(carbomethoxy)azetidine (**3c**) was obtained by the above procedure 0.14 g (46%) of N-cyclohexyl-2-azetidinone (**9b**). The spectral properties (IR, NMR) of this compound were identical with those described earlier.

N-(2,2-dimethoxyethyl)-2-azetidinone (9c). From 0.43 g of N-(2,2-dimethoxyethyl)-2-carbethoxyazetidine (**3f**) was obtained by the above procedure 0.18 g (56%) of N-(2,2-dimethoxyethyl)-2-azetidinone (**9c**). The spectral properties of this compound were identical with those reported earlier.

N-[2-(p-Methoxyphenyl)ethyl]-2-azetidinone (9g). From 0.58 g of N-[2-(p-methoxyphenyl)ethyl]-2-(carbo-*tert*-butoxy)-azetidine (**3r**) was obtained by the above procedure 0.27 g (66%) of N-[2-(p-methoxyphenyl)ethyl]-2-azetidinone (**9g**).

N-(2-Propenyl)-2-azetidinone (9k). From 0.34 g of N-(2-propenyl)-2-(carbo-*tert*-butoxy)azetidine (**3g**) was obtained by the above procedure 0.10 g (48%) of N-(2-propenyl)-2-azetidinone (**9k**): bp 90 °C (0.5 mm); IR (neat) 1740 cm^{-1}; NMR ($CDCl_3$) δ 5.80 (1 H, m), 5.23 (1 H, H), 5.13 (1 H, m), 3.82 (2 H, d, J = 7 Hz), 3.22 (2 H, t, J = 4 Hz), 2.93 (2 H, t, J = 4 Hz); mass spectrum, calcd for C_6H_9NO m/e 111.0684, found m/e 111.0675.

N-(2,4,6-Trimethoxybenzyl)-2-azetidinone (9j). From 0.34 g of N-(2,4,6-trimethoxybenzyl)-2-(carbo-*tert*-butoxy)azetidine (**3n**) was obtained by the above procedure 0.14 g (56%) of N-(2,4,6-trimethoxybenzyl)-2-azetidinone (**9j**): IR (neat) 1745 cm^{-1}; NMR ($CDCl_3$) δ 6.09 (2 H, s), 4.36 (2 H, s), 3.79 (6 H, s), 3.75 (3 H, s), 2.98 (2 H, t, J = 4 Hz), 2.74 (2 H, t, J = 4 Hz); mass spectrum, calcd for $C_{13}H_{17}NO_4$ m/e 251.1156, found m/e 251.1176.

Preparation of the Hydroperchlorate Salt of N-tert-Butylazetidine-2-carboxylic Acid (5a) from N-tert-Butyl-2-(carbo-tert-butoxy)azetidine (3b). Method A. To a stirred solution of 0.5 g (2.3 mmol) of N-*tert*-butyl-2-(carbo-*tert*-butoxy)azetidine (**3b**) in 2 mL of dry methylene chloride at 0 °C was added dropwise 0.5 mL of anhydrous trifluoroacetic acid. After being stirred at 25 °C for 1 h, the mixture was poured onto 50 mL of ice-cold ether and treated with 2 drops of 70% perchloric acid to give a crystalline precipitate. The solid was collected by filtration, washed with ether, and dried under vacuum to provide 0.59 g (100%) of amino acid hydroperchlorate salt **5a**: mp 164–166 °C IR (KBr) 3400, 2800–2200 (scalloped), 1735 cm^{-1}; NMR (D_2O, 90 MHz) δ 5.03 (1 H, t, J = 10 Hz), 4.10 (2 H, m), 2.15 (2 H, m), 1.30 (9 H, s).

Method B. To a suspension of 0.5 g (3.2 mmol) of N-*tert*-butylazetidine-2-carboxylic acid (**5a**) in 5 mL of dry ice-cold methylene chloride was added 3 drops of 70% perchloric acid. After being stirred for 1 h, the mixture was poured onto 50 mL of ice-cold ether to give a crystalline precipitate. The solid was collected by filtration, washed with ether, and dried under vacuum to give 0.81 g (98%) of amino acid hydroperchlorate salt **5a**. The IR, NMR, and melting point of this material were identical with those described above.

General Procedure for the Conversion of tert-Butyl Azetidine-2-carboxylates to 2-Azetinium Perchlorates. N-tert-Butyl-Δ¹-azetinium Perchlorate (12a). To a stirred solution of 214 mg (1.0 mmol) of N-*tert*-butyl-2-(carbo-*tert*-butoxy)azetidine (**3b**) in 1 mL of dry methylene chloride at 0 °C was added dropwise 0.5 mL of anhydrous trifluoroacetic acid. After completion of the addition, the reaction was allowed to warm to room temperature for 1 h and then recooled to 0 °C. Oxalyl chloride (1 mL) was then added dropwise, resulting in vigorous gas evolution. After 1 h, the mixture was poured onto 78 mL of cold anhydrous ether, acidified with 10 drops of 70% perchloric acid, and filtered to give 210 mg (99%) of N-*tert*-butyl-Δ¹-azetinium perchlorate (**12a**).

N-Cyclohexyl-Δ¹-acetinium Perchlorate (12b). By the above procedure, 100 mg of N-cyclohexyl-2-(carbo-*tert*-butoxy)azetidine (**3d**) was converted to 96 mg (99%) of N-cyclohexyl-Δ¹-azetinium perchlorate (**12b**) identical with an authentic sample.

N-Benzyl-Δ¹-azetinium Perchlorate (12c). By the above procedure, 100 mg of N-benzyl-2-(carbo-*tert*-butoxy)azetidine (**3p**) was converted to 97 mg (99%) of N-benzyl-Δ¹-azetinium perchlorate (**12c**) identical with an authentic sample.

N-(2-Phenethyl)-Δ¹-azetinium Perchlorate (12d). By the above procedure, 100 mg of N-(2-phenethyl)-2-(carbo-*tert*-butoxy)azetidine (**3g**) was converted to 98 mg (99%) of N-(2-phenethyl)-Δ¹-azetinium perchlorate (**12d**) identical with an authentic sample.

General Procedure for the Deprotection–Oxidative Decarbonylation of tert-Butyl Azetidine-2-carboxylates. N-(p-Methoxybenzyl)azetidin-2-one (9m). To a stirred solution of 277 mg (1.0 mmol) of N-(p-methoxybenzyl)-2-(carbo-*tert*-butoxy)azetidine (**3r**) in 1 mL of dry methylene chloride at 0 °C was added dropwise 1 mL of cold anhydrous trifluoroacetic acid. The reaction was stirred at room temperature for 2 h, cooled to 0 °C, and treated dropwise with 1 mL of cold oxalyl chloride. After gas evolution ceased (2.5 h), the mixture was poured onto 100 mL of cold anhydrous ether, acidified with 10 drops of 70% perchloric acid, and refrigerated for 2 h. The solvent was removed by decantation to give an oily residue which was dissolved in 15 mL of dry methylene chloride, cooled to 0 °C, and treated with 192 mg (1.1 mmol) of 100% *m*-chloroperbenzoic acid followed by 174 mg (2.2 mmol) of dry pyridine. After 40 min, the reaction was diluted with methylene chloride–ether (15 mL) and washed successively with water (10 mL), cold 1 N hydrochloric acid (10 mL), and 5% sodium bicarbonate (10 mL). The extract was dried over anhydrous magnesium sulfate and then concentrated to give 162 mg of a yellow oil. Preparative layer chromatography on silica gel (ether elution) followed by bulb-to-bulb distillation gave 134 mg (70%) of β-lactam **9m** as a colorless oil: bp 70 °C (0.1 mmHg); IR (neat) 1730, 1610 cm^{-1}; NMR ($CDCl_3$, 270 MHz) δ 7.09 (2 H, d, J = 8.4 Hz), 6.77 (2 H, d, J = 8.4 Hz), 4.23 (2 H, s), 3.75 (3 H, s), 3.05 (2 H, t, J = 4.1 Hz), 2.86 (2 H, t, J = 4.1 Hz).

The analytical sample was prepared by molecular distillation [30 °C (0.01 mmHg), 12 h].

Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 68.91; H, 6.82; N, 7.48.

Ethyl (α,α-Dimethyl)-2-oxo-1-azetidineacetate (21a). By the above procedure, 271 mg of N-(1,1-dimethyl-1-carbethoxymethyl)-2-(carbo-*tert*-butoxy)azetidine (**3s**) was converted to 132 mg (71%) of ethyl (α,α-dimethyl)-2-oxo-1-azetidineacetate (**21a**): bp 100 °C (0.1 mmHg); IR (neat) 1735 cm^{-1}; NMR (CCl_4, 270

(34) Foote, C. S.; Vickers, R. S. *Boll. Chim. Farm.* **1970**, *109*, 599.

MHz) δ 4.18 (2 H, q, J = 7.0 Hz), 3.28 (2 H, t, J = 4.4 Hz), 2.85 (2 H, t, J = 4.4 Hz), 1.55 (6 H, s), 1.26 (3 H, t, J = 7.0 Hz); high-resolution mass spectrum, calcd for $C_9H_{15}NO_3$ m/e 185.1047, found m/e 185.1049.

Ethyl α-Isopropyl-2-oxo-1-azetidineacetate (21b). By the above procedure, 285 mg of *N*-(2,2-dimethyl-1-carbethoxyethyl)-2-(carbo-*tert*-butoxy)azetidine (**3t**) was converted to 121 mg (61%) of ethyl α-isopropyl-2-oxo-1-azetidineacetate (**21b**) identical with an authentic sample.[35]

Ethyl α-(*p*-Methoxyphenyl)-2-oxo-1-azetidineacetate (21c). By the above procedure, 700 mg of *N*-(α-carbethoxy-*p*-methoxybenzyl)-2-(carbo-*tert*-butoxy)azetidine (**3u**) was converted to 320 mg (61%) of ethyl α-(*p*-methoxyphenyl)-2-oxo-1-azetidineacetate (**21c**): IR (neat) 1740 (split) cm^{-1}; NMR (CCl_4) δ 7.15 (2 H, d, J = 8.1 Hz), 6.82 (2 H, d, J = 8.1 Hz), 5.38 (1 H, s), 4.16 (2 H, s), 3.78 (3 H, s), 3.56 (1 H, m), 2.98 (1 H, m), 2.90 (1 H, m), 2.73 (1 H, m), 1.25 (3 H, t, J = 7.3 Hz).

Molecular distillation [80 °C (0.1 mmHg), 7 days] gave the analytical sample as a colorless oil.

Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.66; H, 6.39; N, 5.29.

Ethyl α-[*p*-(Benzyloxy)phenyl]-2-oxo-1-azetidineacetate (21d). By the above procedure 425 mg of *N*-[*p*-(benzyloxy)-α-carbethoxyphenyl]-2-(carbo-*tert*-butoxy)azetidine (**3y**) was converted to 180 mg (53%) of ethyl α-[(*p*-benzyloxy)phenyl]-2-oxo-1-azetidineacetate (**21d**): mp 57-59 °C; IR ($CHCl_3$) 1740 (split) cm^{-1}; NMR ($CDCl_3$, 270 MHz) δ 7.33 (5 H, m), 7.14 (2 H, d, J = 8.8 Hz), 6.91 (2 H, d, J = 8.8 Hz), 5.46 (1 H, s), 4.99 (2 H, s), 4.14 (2 H, q (split), J = 6.6 Hz), 3.54 (1 H, m), 2.99 (1 H, m), 2.92 (1 H, m), 2.76 (1 H, m), 1.18 (3 H, t, J = 6.6 Hz).

The analytical sample was prepared by two recrystallizations from ether-heptane, mp 61-62 °C.

(35) Wasserman, H. H.; Glazer, E. *J. Org. Chem.* **1975**, *40*, 1505.

Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.50; H, 6.14; N, 4.02.

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Registry No. 1, 96-48-0; **2a**, 29547-04-4; **2b**, 36847-51-5; **2c**, 71725-02-5; **3a**, 18085-35-3; **3b**, 77647-92-2; **3c**, 18085-36-4; **3d**, 72089-77-1; **3e**, 62664-93-1; **3f**, 71556-69-9; **3g**, 72089-76-0; **3h**, 62664-90-8; **3i**, 62664-92-0; **3j**, 77647-97-3; **3k**, 71556-64-4; **3l**, 72081-67-5; **3m**, 62664-91-9; **3n**, 65219-09-2; **3o**, 18085-37-5; **3p**, 77647-98-4; **3q**, 77647-99-5; **3r**, 77648-00-1; **3s**, 77648-01-2; **3t** (isomer 1), 77648-02-3; **3t** (isomer 2), 77648-03-4; **3u** (isomer 1), 77648-04-5; **3u** (isomer 2), 77648-05-6; **3v** (isomer 1), 77648-06-7; **3v** (isomer 2), 77648-07-8; **5a**, 18085-38-6; **5a**·$HClO_4$, 77648-08-9; **5b**, 18085-39-7; **5c**, 62664-97-5; **5d**, 62664-94-2; **5e**, 62664-96-4; **5f**, 77648-09-0; **5g**, 64264-57-9; **5h**, 62664-95-3; **9a**, 34094-42-3; **9b**, 34094-39-8; **9c**, 62665-01-4; **9d**, 62664-98-6; **9e**, 62665-00-3; **9f**, 77648-10-3; **9g**, 64218-77-5; **9h**, 62664-99-7; **9i**, 4458-64-4; **9j**, 65219-06-9; **9k**, 65219-07-0; **9l**, 65219-08-1; **9m**, 70875-47-7; **10a**, 18085-40-0; **12a**, 77648-11-4; **12b**, 77648-12-5; **12c**, 70339-93-4; **12d**, 77648-13-6; **17** (R = *c*-C_6H_{11}; R′ = CH_3), 77648-15-8; **17** (R = $CH_2CH_2C_6H_4$-*p*-OCH_3; R′ = $C(CH_3)_3$), 77648-16-9; **17** (R = CH_2-2,4,-trimethoxyphenyl; R′ = $C(CH_3)_3$), 65219-12-7; **17** (R = CH_2CH = CH_2; R′ = $C(CH_3)_3$), 77648-17-0; **17** (R = $CH(C_6H_5)_2$; R′ = CH_2CH_3), 77648-18-1; **21a**, 70875-38-6; **21b**, 54643-15-1; **21c**, 77648-19-2; **21d**, 70875-48-8; cyclohexylamine, 108-91-8; *p*-methoxyphenethylamine, 55-81-2; 1,1-dimethylglycine ethyl ester, 1113-49-1; *tert*-butylamine, 75-64-9; 2,2-dimethoxyethylamine, 22483-09-6; allylamine, 107-11-9; *n*-pentylamine, 110-58-7; cyclooctylamine, 5452-37-9; *N,N*-dimethyl-1,3-propanediamine, 109-55-7; 1,1-diphenylmethylamine, 91-00-9; phenethylamine, 64-04-0; 2,4,6-trimethoxybenzylamine, 77648-20-5; benzylamine, 100-46-9; *p*-methoxybenzylamine, 2393-23-9; ethyl 2-amino-3-methylbutyrate, 13893-45-3; ethyl α-amino-*p*-methoxyphenylacetate, 77648-21-6; ethyl α-amino-*p*-(benzyloxy)phenylacetate, 70875-50-2.

Application of New β-Lactam Syntheses to the Preparation of (±)-3-Aminonocardicinic Acid[1,2]

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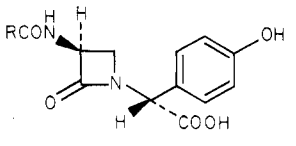
Three novel β-lactam-forming reactions have been applied to the synthesis of (±)-3-aminonocardicinic acid (3-ANA). These procedures include (a) ring expansion of a cyclopropanolamine, (b) azetidine carboxylate oxidative decarbonylation, and (c) β-halopropionamide ring closure.

The nocardicins (1), isolated from a strain of *Nocardia*,[3,4] are the first monocyclic β-lactams to exhibit high antibacterial activity.[5] One of the major constituents of these cultures, nocardicin A (2), shows relatively high activity against gram-negative bacteria. Other less abundant



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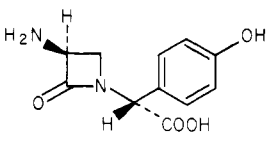

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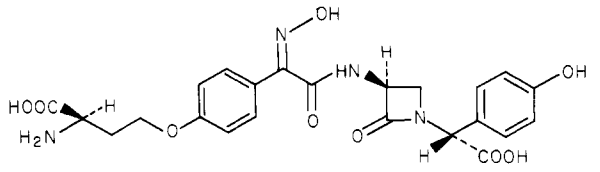

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members of this group consist of varied acyl derivatives of 3-aminonocardicinic acid (3, 3-ANA), the nucleus of this family of antibiotics.

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