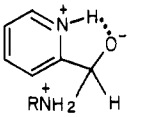
II. The catalytic rate constants yield satisfactory Brønsted plots from which values of 0.82 and 0.65 were obtained for the 4- and 3-aldehydes, respectively. These values are similar to those previously determined for general-acid catalysis of the same reaction of 4- and 3-formyl-1-methylpyridinium ions.[2]

General-acid catalysis for 2-pyridinecarboxaldehyde phenylhydrazone formation could not be detected in cyanoacetate, chloroacetate, formate, β-bromopropionate, and acetate buffers (pH range 1.9–4.7) up to a concentration of the acidic form of the buffer of 0.1 M. This means that neither amine addition or carbinolamine dehydration is subject to detectable general-acid catalysis. In this respect also, phenylhydrazone formation from 2-pyridinecarboxaldehyde is distinct from that with 2-formyl-1-methylpyridinium ion, for which general-acid catalysis of carbinolamine dehydration ($\alpha = 0.7$) is observed.[2] The general-acid catalysis of most addition reactions of nitrogen nucleophiles to the carbonyl group involves trapping of the zwitterionic intermediate, $T^{\pm}$, by diffusion-controlled proton transfer.[10,11,13] For the intermediate $T^{\pm}$ from this aldehyde, the necessary proton transfer could probably occur intramolecularly, as shown below, or through a water molecule, with a rate that is even



faster than diffusion together of $T^{\pm}$ and an external catalyst, thus avoiding the need for general-acid catalysis, as observed.

Registry No. CNAcOH, 372-09-8; ClAcOH, 79-11-8; HCOOH, 64-18-6; $BrCH_2AcOH$, 590-92-1; AcOH, 64-19-7; 4-pyridinecarboxaldehyde, 872-85-5; 3-pyridinecarboxaldehyde, 500-22-1; 2-pyridinecarboxaldehyde, 1121-60-4; phenylhydrazine, 100-63-0; 4-pyridinecarboxaldehyde phenylhydrazone, 7757-39-3; 3-pyridinecarboxaldehyde phenylhydrazone, 57023-37-7; 2-pyridinecarboxaldehyde phenylhydrazone, 7727-07-3.

(13) Sayer, J. M.; Peskin, M.; Jencks, W. P. *J. Am. Chem. Soc.* **1973**, *95*, 4277.

Monobactams. Preparation of (*S*)-3-Amino-2-oxoazetidine-1-sulfonic Acids from L-α-Amino-β-hydroxy Acids via Their Hydroxamic Esters

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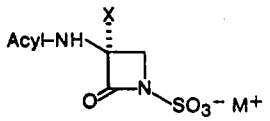
The cyclization of the *O*-methylhydroxamates **13–15** afforded excellent yields of the 1-methoxyazetidinones **16–18**. Reductive cleavage of the methoxy group gave N-1-unsubstituted azetidinones **9**, **19**, and **20** which were sulfonated and deprotected, yielding zwitterions **29–31**. These materials serve as general intermediates for the preparation of a large variety of monobactam antimicrobial agents.

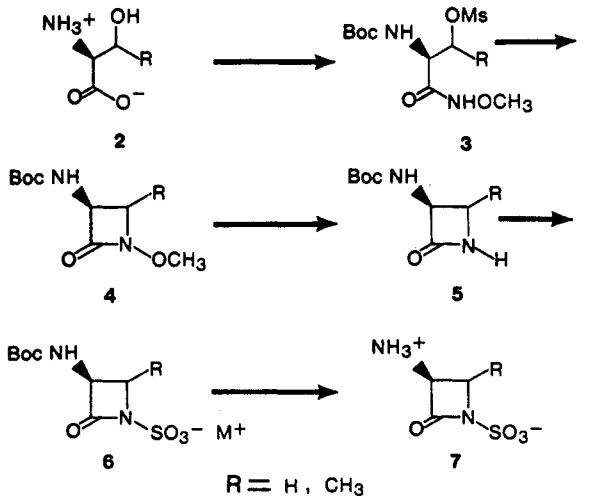
In previous papers we have described the isolation and structure determination of several members of a new class of β-lactam antibiotics, the monobactams **1**.[2] We have also



1 X = H, OCH_3

communicated synthetic routes to these N-1-sulfonated monocyclic azetidinone antimicrobials employing as the starting materials either 6-aminopenicillanic acid (6-APA)[3] or L-α-amino-β-hydroxy acids.[4] In this paper we describe an additional route to these systems from L-α-amino-β-hydroxy acids which proceeds through an N-1-unsubstituted azetidinone. Since our interest in monobactam analogues containing alkyl substituents at C-4 precluded the use of 6-APA degradation,[3] we have concentrated on totally synthetic routes from α-amino acids. On the basis of our initial 6-APA derived route,[3] the problem reduced

Scheme I



(1) Current address: Agricultural Chemical Group, FMC Corp., P.O. Box 8, Princeton, NJ 08540.

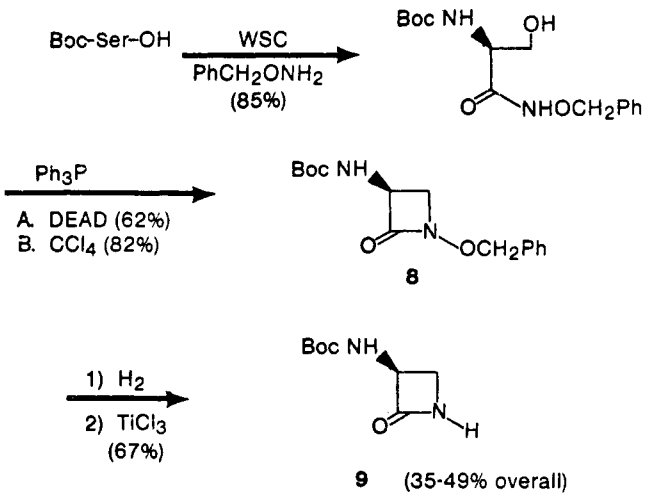
(2) Sykes, R. B.; Cimarusti, C. M.; Bonner, D. P.; Bush, K.; Floyd, D. M.; Georgopapadakou, N. H.; Koster, W. H.; Liu, W. C.; Parker, W. L.; Principe, P. A.; Rathnum, M. L.; Slusarchyk, W. A., Trejo, W. H.; Wells, J. S. *Nature (London)* **1981**, *291*, 489. Parker, W. L.; Koster, W. H.; Cimarusti, C. M.; Floyd, D. M.; Liu, W. C.; Rathnum, M. L. *J. Antibiot.* 1982.

(3) Cimarusti, C. M.; Applegate, H. E.; Chang, H. W.; Floyd, D. M.; Koster, W. H.; Slusarchyk, W. A.; Young, M. G. *J. Org. Chem.* **1982**, *47*, 179.

(4) Floyd, D. M.; Fritz, A. W.; Cimarusti, C. M. *J. Org. Chem.* **1982**, *47*, 176.

0022-3263/82/1947-5160$01.25/0

Scheme II



to the stereospecific synthesis of 4-alkylated azetidinones such as **5** (Scheme I) and their subsequent sulfonation (**5** → **6**). To this end we have modified the work of Miller[5] and developed an efficient procedure for preparing large quantities of the desired azetidinones involving the cyclization of β-mesyloxy hydroxamates (**3** → **4**) derived from α-amino-β-hydroxy acids **2**. Subsequent reductive removal of the N-1 methoxy function affords **5** in excellent yields. Sulfonation of **5** under a variety of conditions, followed by deprotection, provided zwitterions **7** which are key intermediates for the preparation of monobactam analogues.

Prior to the onset of this work, Miller communicated an extremely efficient method of preparing 3-[carbobenzoxy-(Z) or *tert*-butoxycarbonyl- (Boc)-amino]-1-(benzyloxy)-2-azetidinones employing, as the key step, the cyclization of a β-substituted hydroxamic acid derivative derived from an α-amino acid.[5] This work significantly expanded the utility of Testa's observation that β-bromo hydroxamates cyclize under mildly basic conditions.[6] The use of an *O*-alkyl or *O*-acyl hydroxamate in place of a primary amide results in significant lowering of the amide pK_a, allowing for selective deprotonation and inhibiting proton-transfer processes. Without this selectivity, direct methods of preparing 3-(acylamino)-2-azetidinones from the corresponding acyclic primary amides fail.[7] Although Miller's elegant application of the Mitsunobu reaction[8] for the closure of hydroxamates derived from Boc- or Z-substituted serine was extremely efficient, the process requires chromatographic separation of the product from the reaction byproducts. In a later publication, which appeared after much of this work had been completed, Miller described a two-step procedure for the removal of the benzyloxy group (Scheme II, **8** → **9**).[9] This completed the preparation of **9** from serine by a very direct route. The results of Miller's work, based on his published data, are summarized in Scheme II. Subsequent to the completion of our studies, a third paper appeared dealing with an alternative to the diethyl azodicarboxylate mediated closure employing carbon tetrachloride and triphenylphosphine.[10] Although the yield of **8** was improved (Scheme II), column chromatography was still necessary for the removal of triphenylphosphine oxide. This paper also described the use of threonine and *allo*-threonine as starting materials.

Results and Discussion

In our work we employed the desired L amino acid[11] as the starting point and, in a single reaction vessel, protected the amino function as the Boc derivative, adjusted to the appropriate pH, and performed the aqueous coupling reaction using 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide (WSC) as the coupling agent. The use of methoxyamine rather than the previously employed (benzyloxy)amine in the coupling reaction was expected, after the cyclization, to eliminate competitive C–O cleavage during our attempts to effect reductive N–O bond cleavage.[12] Unlike the coupling reaction using (benzyloxy)amine with Boc-substituted serine, we found that the reaction of Boc-Ser with methoxyamine did not result in the precipitation of the product **10**. It was necessary to thoroughly saturate the reaction mixture with sodium chloride and perform several extractions to obtain good yields of the desired, highly water soluble products. Thus, in a single operation, serine was converted to the *O*-methyl hydroxamate **10** by reaction with di-*tert*-butyl pyrocarbonate (Boc_2O) under basic conditions in a mixture of water and *tert*-butyl alcohol followed by the addition of 1.5 equiv of methoxyamine hydrochloride, adjustment to pH 4.2, and addition of WSC either as a solid or as a concentrated aqueous solution. The coupling reaction was found to be complete in less than 0.5 h and, after an extractive workup, gave **10** in 89–95% yields. Under these conditions, hydroxamates **11** and **12** were obtained in good yields from threonine and *allo*-threonine, respectively. Although hydroxamates **10** and **12** could be recrystallized, the crude products were very clean by TLC and spectral analysis and were used without purification.

The cyclization of **10** to azetidinone **16** by using Miller's procedures was an extremely facile and clean reaction. However, the attendant yields of pure **16** were only 65–70% due to the necessity for chromatographic separation of the undesired adducts. We then examined the conversion of the β-hydroxy function into a leaving group and subsequent cyclization under basic conditions. The byproducts from this approach were expected to be water soluble and easily separable from desired product.

The reaction of the serine-derived hydroxamate **10** with methanesulfonyl chloride (MsCl) and triethylamine in methylene chloride at −10 °C[13] gave a rather complex mixture of products which, interestingly, contained some of the desired azetidinone **16** by TLC analysis. If, however, the reaction was conducted in cold pyridine, the pure mesylate **13** could be isolated in better than 90% yields. The mesylation of threonine-derived hydroxamate **11** was investigated in some detail, owing to our interest in 4α-methylmonobactams.[3,4] In general, the yield of **11** was not determined since it was obtained as a hygroscopic gum. Treatment of crude **11** under the above conditions gave the mesylate **14** in 65–78% overall yields of analytically

(5) Mattingly, P. G.; Kerwin, J. F., Jr.; Miller, M. J. *J. Am. Chem. Soc.* **1979**, *101*, 3983.
(6) Nicolaus, B. J. R.; Bellosio, E.; Pogani, G.; Testa, E. *Gazz Chim. Ital.* **1963**, *93*, 618.
(7) For a discussion and references see: Bose, A. K.; Sahu, D. P.; Manhas, M. S. *J. Org. Chem.* **1981**, *46*, 1229.
(8) Mitsunobu, O.; Wada, M.; Sano, T. *J. Am. Chem. Soc.* **1972**, *94*, 679. Wada, M.; Mitsunobu, O. *Tetrahedron Lett.* **1972**, 1279.
(9) Mattingly, P. G.; Miller, M. J. *J. Org. Chem.* **1980**, *45*, 410.
(10) Miller, M. J.; Mattingly, P. G.; Morrison, M. A.; Kerwin, J. F. *J. Am. Chem. Soc.* **1980**, *102*, 7026.
(11) The serine, threonine, and synthetic *allo*-threonine described in this paper were always L amino acids; i.e., they have the *S* configuration at C-2 of the amino acid.
(12) Miller demonstrated that the methoxy group of azetidinone **16** was partially hydrogenolyzed over W-6 Raney Ni after an extended reaction period. No details concerning the preparation or characterization of **16** were presented, however.[9]
(13) Crossland, R. K.; Servis, K. L. *J. Org. Chem.* **1970**, *35*, 3195.

pure material from threonine. Although differing somewhat in solubility characteristics, mesylate **15** was obtained in 80% yield from **12**.

The critical cyclization step turned out to be incredibly simple. We first examined the reaction of mesylate **13** at a 5×10^{-2} M concentration in refluxing acetone containing 3 equiv of potassium carbonate. Under these conditions we observed smooth cyclization to azetidinone **16** with essentially no other products formed by TLC analysis. In general, the reactions were conducted by bringing the acetone–carbonate slurry to reflux and then adding a concentrated acetone solution of the mesylate. After 1 h of reflux, mesylate **13** and **14** were converted to azetidinones **16** and **17** in 94–98% and 85–90% yields, respectively, *without* the need for chromatographic purification. It was possible to lower the amount of solvent used in the cyclization by adding the mesylate in several portions over a 1-h period (see Acknowledgment). However, the real limiting factor to the amount of solvent turned out to be the viscosity of the slurry formed from the precipitation of the potassium mesylate. This material, for all practical purposes, is completely insoluble in hot acetone. Thus, much below 10^{-1} M the slurry becomes so thick that efficient stirring cannot be effected. The product azetidinones were, however, stable for extended periods under the reaction conditions.

The cyclization of mesylate **15** under these conditions was slower and required reaction times of 3–4 h. This observation is completely consistent with the increased steric interactions between the α-amino and β-methyl groups in the transition states leading to **18** compared to **17**. Nevertheless, the desired azetidinone **18** was obtained in greater than 90% yield. An alternate method of cyclization was examined in this case. It was found that **15** could be smoothly transformed to **18** in under 20 min by employing phase-transfer conditions in refluxing aqueous 1,2-dichloroethane. In a single experiment, **18** was isolated in 83% yield.

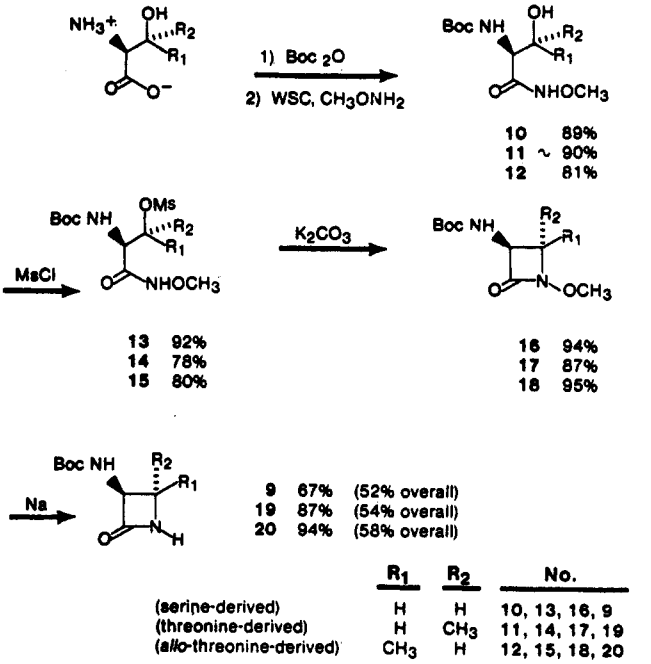
It is therefore possible to prepare and cyclize the mesylates derived from these α-amino hydroxamates under a variety of conditions. In no case was rigorous purification of intermediates necessary, and clean products were simply isolated without employing chromatographic techniques.

Having reached our first goal, we needed to develop a method of removing the N-1 methoxy group in a single reductive operation. It was quite clear from the literature that N–O bond reductions could be performed under mild conditions as demonstrated by Keck.[14] It was also known that azetidinones could survive strong reducing systems.[15]

Following Keck's lead, we attempted to reduce **16** to the desired **9** employing sodium amalgam in buffered ethanol but obtained only ring-opened products. Use of large excess of aluminum amalgam (Al/Hg; 40 °C, 12–24 h) in aqueous tetrahydrofuran (THF) gave only 15–20% isolated yields of **9**. Milder reducing systems such as $TiCl_3$ or $CrCl_3$ gave no reaction as did attempted hydrogenation over palladium catalysts.[12]

On the other hand, the addition of a THF solution of **16** to a −40 °C solution of sodium in ammonia gave the desired azetidinone **9** in essentially quantitative yield. For most purposes, this crude product could be employed without further purification. Recrystallization afforded analytically pure **9** in 65–70% yields. The reduction of **17** and **18** similarly gave the corresponding products **19** and **20** in excellent yields (Scheme III).

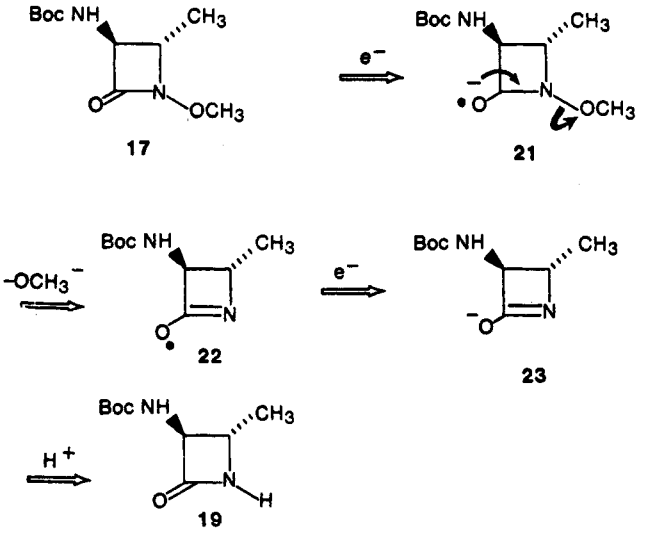
Scheme III



	R_1	R_2	No.
(serine-derived)	H	H	10, 13, 16, 9
(threonine-derived)	H	CH_3	11, 14, 17, 19
(*allo*-threonine-derived)	CH_3	H	12, 15, 18, 20

Although the reductive cleavage of the N-1 methoxy group formally requires 2 molar equiv of sodium, we usually observed that an excess of sodium was needed for complete conversion. Consequently, the reaction was run either by initially employing a 10–15% excess of sodium or by adding an excess after the addition of the substrate was complete. At the extreme, it was possible to initially dissolve the starting material in ammonia and then add sodium to the reaction until a blue solution was maintained. However, unless this latter sequence was performed with some degree of rapidity, significant amounts of aminolysis products were observed (see Acknowledgement). Unlike the N-1-methoxylated azetidinones **16–18**, the azetidinone products **9**, **19**, and **20** appeared very stable to liquid ammonia.

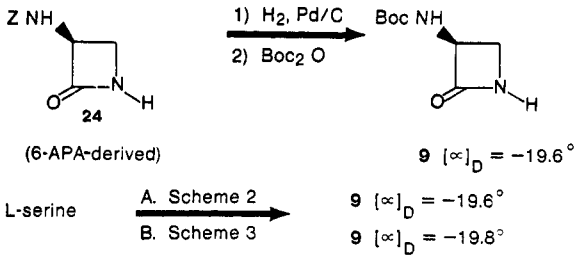
Scheme IV



The reduction is most likely proceeding by an initial electron transfer to the lactam carbonyl, giving radical anion **21** as the first intermediate. Subsequent loss of methoxide would afford the radical **22** which would be quickly reduced to anion **23** (Scheme IV). Under the nonprotic conditions employed for the reaction, **23** is ap-

(14) Keck, G. E.; Webb, R. *Tetrahedron Lett.* **1979**, 1185. Keck, G. E.; Fleming, S.; Nickell, D.; Weider, P. *Synth. Commun.* **1979**, *9*, 281.
(15) Bestian, H.; Jensen, H. German Patent 1 807 498, 1970; *Chem. Abstr.* **1970**, *73*, 45312.

Scheme V[a,b]



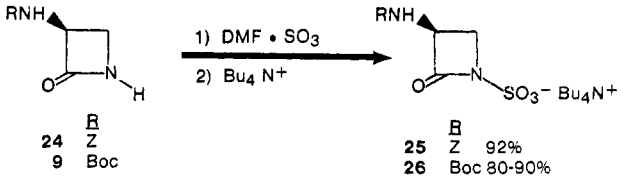
[a] All samples were analytically pure. [b] Rotations in methanol (c 1).

parently protected from further reaction. The overall success of this step is thus due to several factors. First, the reduction is extremely fast relative to aminolysis of the starting material **17**; second, the primary product **23** is protected from further reduction due to its anionic character; third, following protonation, the product **19** is quite stable to liquid ammonia.

Miller has provided proof that the preparation of β-lactams by his procedures is stereospecific.[5] To show that the modifications we employed did not cause substantial racemization, we compared the optical rotations of recrystallized **9** obtained by three different procedures. Azetidinone **24**, derived from 6-APA,[3] was hydrogenated (Pd/C) to remove the Z group and then treated with Boc_2O in basic aqueous *tert*-butyl alcohol to yield **9**. Comparing the rotation of **9** derived from 6-APA to that of **9** prepared by the methods in Scheme III showed the samples to be of identical optical purity. A sample of **9** prepared from serine by Miller's procedures (Scheme II) was also the pure *S* isomer on the basis of optical rotations. In the case of azetidinone **19**, derived from threonine, epimerization at C-3 would produce a mixture of diastereomers, one of which would formally correspond to a product derived from D-*allo*-threonine. Comparison of ^1H and ^{13}C NMR spectra of crude **19** and **20** (derived from L-*allo*-threonine) clearly demonstrated that, within the limits of NMR analysis, no epimerization had occurred in either case (Scheme V).

With a ready supply of monocyclic azetidinones on hand, we began to evaluate methods to perform the sulfonation reaction. Considering that the reaction converts a water-insoluble azetidinone to the corresponding water-soluble sulfonate (**5** → **6**), the mechanics of isolation and purification of the product were potentially complex, especially on a large scale. Thus, the development of proper workup and isolation procedures became one of the most important aspects of the process. An excellent solution to these problems was found by using tetra-*n*-butylammonium hydrogen sulfate (TBAHS) as a phase-transfer agent.[3] In general, sulfonation reaction mixtures were poured into 0.5–1 N aqueous solutions of KH_2PO_4 and extracted with methylene chloride. This initial extraction served to remove any unreacted starting material and other organic byproducts. The aqueous solution (pH 4.5) was then treated with 1 equiv of TBAHS and again extracted with methylene chloride. In the second extraction, the product sulfonate was quantitatively transferred into the organic layer, leaving undesired inorganic salts and very polar organic compounds behind in the aqueous layer. The product could then be isolated by concentration of the organic extracts. In all cases, the products were essentially free from extraneous salts and organic impurities and required no further purification. In some cases, the products crystallized upon simple trituration with diethyl ether or ethyl acetate.

Scheme VI



Much of the initial work in determining sulfonation conditions was conducted on azetidinone **24** due to its availability from 6-APA. One generally applied method for converting **24** to its sulfonate **25** was to use pyridine–sulfur trioxide complex (Pyr·SO_3) in dimethylformamide (DMF) at room temperature.[3] Although these conditions gave good results, the success of the reaction depended upon the use of rigorously anhydrous conditions, with reaction times and the amount of Pyr·SO_3 being variable. One explanation for this observation is that an equilibrium exists between the Pyr·SO_3 and the solvent DMF to generate small amounts of DMF·SO_3.[16] Unlike Pyr·SO_3, which is relatively unreactive toward water, DMF·SO_3 is rapidly decomposed. The net effect being the steady, and presumably competitive, destruction of the sulfonating agent by adventitious water (eq 1).

$$\text{Pyr} \cdot SO_3 \underset{}{\overset{\text{DMF}}{\rightleftharpoons}} \text{Pyr} + \text{DMF} \cdot SO_3 \qquad (1a)$$

$$\text{DMF} \cdot SO_3 \xrightarrow[\text{Pyr}]{H_2O} \text{DMF} + \text{PyrH}^+ HSO_4^- \qquad (1b)$$

The reaction of **24** with DMF·SO_3 in DMF at 0 °C for 20 min gave analytically pure **25** in 92% yield (Scheme VI). The reagent was generated by adapting recently published procedures for the preparation of other SO_3 complexes.[17] Thus, trimethylsilyl chlorosulfonate[18] was added to DMF at 0 °C, and the resulting trimethylsilyl chloride was removed under vacuum. Compared to the variable reaction time for the Pyr·SO_3–DMF system, the use of DMF·SO_3 in DMF gives an extremely fast reaction. Application of this reagent to the Boc-protected azetidinone **9** gave good yields of the sulfonate **26**. However, it was observed that the yield of **26** decreased as the length of reaction increased. This suggested that due to the acidity of the system (the product would be the DMF salt of the azetidinesulfonic acid) the Boc group was being partially lost during the reaction. Another problem, with respect to large-scale work, was that rigorously anhydrous conditions were still necessary. We therefore examined alternative methods to perform the sulfonation reaction.

Returning to a very classical approach,[19] treatment of azetidinone **9** with 3 equiv of Pyr·SO_3 in hot pyridine for 30 min followed by an ion-pair workup gave the sulfonate **26** in 89–91% yields. This procedure was found to be sensitive to the quality of Pyr·SO_3 and to the length of reaction, but no precautions were needed with respect to solvent purity. The presence of the methyl group on azetidinones **19** and **20** slowed the reaction, and a 45-min reaction period was necessary to attain maximum yields of **27** and **28**, respectively.

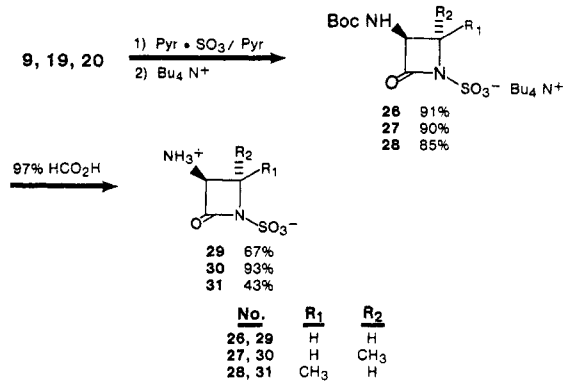
(16) Galpin, I. J.; Kenner, G. W.; Marston, A. *Bioorg. Chem.* **1979**, *8*, 323. This equilibrium was demonstrated for the $Ph_3P \cdot SO_3$ complex in DMF.

(17) Hofmann, K.; Simchen, G. *Synthesis* **1979**, 699.

(18) Duffaut, N.; Calas, R.; Dunogues, J. *Bull. Soc. Chim. Fr.* **1963**, 512.

(19) For a comprehensive survey see: Gilbert, E. E. "Sulfonation and Related Reactions"; Interscience: New York, 1965.

Scheme VII



Although the choice of Boc protection was initially made on the basis of compatibility with the reaction conditions encountered during the preparation of azetidinones **9**, **19**, and **20**, the acid lability of the Boc group proved ideal for the final step of the sequence (Scheme VII). Simply dissolving the sulfonated azetidinone **26** in 97% formic acid at a 0.3 M concentration and stirring for 5 h gave a white precipitate of the desired zwitterion **29** in 61% yield based on the amount of **9** used to prepare **26**. These reaction conditions were maximized for zwitterion **30** which was obtained in 93% yield from the sulfonated azetidinone **27** (84% overall from the starting threonine-derived azetidinone **19**). The results were less satisfactory in the *allo*-threonine series, and zwitterion **31** was obtained in only 43% yield. The differences in yields are mostly due to solubility differences between the three products and exactly parallel the observed solubilities of the zwitterions in water; **31** > **29** > **30**. In all cases, the products were isolated by simple filtration and found to be analytically pure. Thus, the Boc group not only provided suitable protection for all of the steps leading to the sulfonated azetidinones **26–28** but also provided for an extremely efficient method of isolation and purification of the desired zwitterionic products **29–31**.

As noted above, the quality of the Pyr·SO_3 used in the sulfonation reaction was very important. Best results were obtained by using material prepared either by the addition of trimethylsilyl chlorosulfonate to pyridine in methylene chloride[17] or, more simply, by adding chlorosulfonic acid to a cold solution of pyridine in methylene chloride. In the latter case, the isolated complex usually contained small amounts of pyridinium hydrochloride. This did not appear to overtly affect the results of the reaction. It was subsequently observed that Pyr·SO_3 purchased directly from the producer was of sufficient quality to obtain the desired yield of product.[20]

Several attempts were made to generate Pyr·SO_3 in situ from sulfamic acid in pyridine at 100 °C. Addition of the substrate to the mixture afforded a very sluggish reaction even with large excesses of sulfamic acid and resulted in only moderate yields of sulfonated azetidinones. The low yield of product is a function of the extended reaction period since it has been shown that the products are not stable under these reaction conditions. Thus, under the successful reaction conditions with Pyr·SO_3 complex in hot pyridine, we employ an excess of Pyr·SO_3 complex to allow for a reduced reaction time and, consequently, maximal yield of product. In terms of simplicity, reproducibility, and overall yield, the sulfonation of azetidinones with Pyr·SO_3 in hot pyridine is the best method we have encountered for medium- to large-scale work.

(20) Purchased in bulk from Upjohn Fine Chemical Division, North Haven, CT.

Conclusion

Significant modification of published procedures has resulted in a facile, stereospecific preparation of 3-[(*tert*-butoxycarbonyl)amino]-2-azetidinones by starting from readily available α-amino-β-hydroxy acids. Under these conditions, serine was converted to analytically pure azetidinone **9** in 52% overall yield without significant purification of any of the synthetic intermediates. Crude **9** was, however, very pure by TLC and spectral analysis, and the actual conversion is well over 70%. As evidenced by Scheme III, equally good results were obtained with both threonine and *allo*-threonine. Comparison of these results with those reported by Miller[5,9,10] (Scheme II) demonstrates that these modifications give improved yields and eliminate the necessity of chromatographic purifications. Overall, the same number of steps is involved in each scheme.

Sulfonation of azetidinones **9**, **19**, and **20** under a variety of conditions followed by simple deprotection procedures affords good yields of the target zwitterions **29–31**. In the case studied most intensively, azetidinone **19** was sulfonated with Pyr·SO_3 in hot pyridine and deprotected to afford zwitterion **30** in 83% overall yield. This constitutes the synthesis of **30** in 45% overall yield from threonine in six synthetic operations.

The zwitterionic products serve as precursors to a wide variety of synthetic monobactams which are potent antimicrobial agents. The procedures described above have been used to prepare multikilogram batches of zwitterion **30**.

Experimental Section

All reagents and solvents were used directly as purchased unless otherwise noted. With the exception of aqueous reactions, all reactions were conducted under a nitrogen atmosphere. Melting point were obtained on a Thomas-Hoover capillary apparatus and are uncorrected. Optical rotations were determined by using a Perkin-Elmer 141 polarimeter. Proton magnetic resonance (^{1}H NMR) spectra were recorded on either Varian T-60 or XL-100 instruments. Values are reported in δ units relative to Me_4Si. In most cases, signals due to exchangeable protons have been omitted. Carbon magnetic resonance (^{13}C NMR) spectra were recorded on either a JOEL FX-60Q or a Varian XL-100 and are reported in parts per million relative to the solvent except where noted. Infrared (IR) spectra were obtained on a Perkin-Elmer 257 spectrometer except for samples run in KBr where a Perkin-Elmer 621 spectrometer was used. Microanalytical data were obtained in these laboratories. Ethyl[3-(3-dimethylamino)propyl]carbodiimide hydrochloride salt (WSC) was purchased from JBL Chemical Co.

Serinehydroxamate 10. A solution of L-serine (5.25 g, 50 mmol) in 50 mL of 1.8 N aqueous KOH was treated with 12.0 g (55 mmol) of Boc_2O in 25 mL of *tert*-butyl alcohol. The resulting mixture was stirred for 5 h and then judged completed by TLC analysis (EtOAc–acetone–HOAc, 19:2:2; silica gel 60). Subsequently, 6.23 g (75 mmol) of methoxyamine hydrochloride was added slowly followed by the addition of 6 N aqueous HCl to pH 4.2. Solid WSC (9.60 g, 50 mmol) was then added in several portions over a 5-min period. The homogenous solution was stirred for 1 h and saturated with NaCl followed by extraction with ethyl acetate (4 × 100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated to yield 10.37 g (89%) of crude, crystalline product **10**: mp 84–86 °C (EtOAc-Et_2O); $[\alpha]_D$ −21.78° (*c* 10, MeOH); ^{1}H NMR (C_3D_6O) 4.05 (1 H, m), 3.75 and 3.64 (5 H, overlapping d + s), and 1.39 (9 H, s); ^{13}C NMR (C_3D_6O) 168.1, 155.3, 78.9, 63.3, 62.1, 68.6, 27.7; IR ($CHCl_3$) 3420, 3250 (vbr), 3000, 2980, 2940, 1735 (br), 1500, 1395, 1370, 1310, 1250, 1210, 1160, 1050 cm^{-1}. Anal. Calcd for $C_9H_{18}N_2O_5$: C, 46.15; H, 7.69; N, 11.97. Found: C, 45.88; H, 7.78; N, 11.89.

Threoninehydroxamate 11. Treatment of 11.9 g (100 mmol) of L-threonine under the above conditions afforded 21.6 g (87%) of the desired product as a hygroscopic foam: ^{1}H NMR (C_3D_6O) 4.42–3.88 (2 H, m), 3.72 (3 H, s), 1.47 (9 H, s), 1.15 (3 H, d, J = 6 Hz); ^{13}C NMR (C_3D_6O) 168.0, 155.5, 78.8, 66.8, 63.0, 55.9, 27.5, 18.8; IR (film) 3300 (vbr), 2980, 2930, 1690 (vbr), 1510 (br), 1395, 1370, 1255, 1170 cm^{-1}.

L-*allo*-Threonine. The amino acid was prepared from L-threonine by known procedures.[21] We found, however, that it was unnecessary to purify the intermediate obtained from the reaction between *N*-benzoylthreonine methyl ester and thionyl chloride. In general, the crude product was hydrolyzed directly in 6 N HCl to afford the *allo*-threonine: mp 273–274 °C (lit. mp 273–274 °C); $[\alpha]_D$ +35.7° (*c* 8.2, 1 N HCl) (lit.[21] $[\alpha]_D$ +32.5° (1 N HCl).

***allo*-Threoninehydroxamate 12.** The reaction of L-*allo*-threonine (11.9 g, 100 mmol) under the above conditions gave 20.3 g (81%) of crystalline product **12**: mp 142–144 °C (acetone); $[\alpha]_D$ −37.2° (*c* 2.96, MeOH); ^{1}H NMR ($CDCl_3$) 4.15–3.59 (5 H, m with s at 3.80), 1.45 (9 H, s), 1.26 (3 H, d, J = 6 Hz); ^{13}C NMR (CD_3OD) 169.9, 157.3, 80.8, 68.4, 64.4, 59.4, 28.7, 20.1; IR (KBr) 3320, 3240, 2980, 1670, 1530, 1370, 1305, 1245, 1175, 1045, 995, 880 cm^{-1}. Anal. Calcd for $C_{10}H_{20}N_2O_5$: C, 48.38; H, 8.12; N, 11.28. Found: C, 48.10; H, 8.18; N, 11.20.

Mesylate 13. A 7.04-g (30 mmol) batch of crude hydroxamate **10** was dissolved in 30 mL of anhydrous pyridine and cooled to 0 °C. After the slow addition of 2.78 mL (36 mmol) of methanesulfonyl chloride, the mixture was stirred for 1 h and poured into 150 mL of cold 1 N aqueous HCl. The resulting solution was extracted with ethyl acetate (2 × 100 mL), and combined extracts were washed with 1 N HCl until acidic, followed by saturated $NaHCO_3$ and finally brine. Drying over $MgSO_4$ and concentrating in vacuo afforded 8.58 g (92%) of the desired mesylate **13** which was homogeneous by TLC and spectral analysis: mp 117–117.5 °C (EtOAc); $[\alpha]_D$ −6.8° (*c* 1, MeOH); ^{1}H NMR (C_3D_6O) 4.42 (3 H, m), 3.72 (3 H, s), 3.11 (3 H, s), 1.43 (9 H, s); ^{13}C NMR (C_3D_6O) 166.0, 155.5, 79.7, 69.1, 69.7, 52.3, 36.9, 28.1; IR (Nujol) 3320, 3260, 1665, 1528, 1362, 1350, 1285, 1190, 1160, 850 cm^{-1}. Anal. Calcd for $C_{10}H_{20}N_2O_7S$: C, 38.45, H, 6.45; N, 8.97; S, 10.27. Found: C, 38.46; H, 6.58; N, 8.88; S, 10.40.

Mesylate 14. After 38.0 g of crude hydroxamate **11**, obtained from 170 mmol of threonine, was dissolved in 250 mL of dry pyridine and cooled to 0 °C, 17.9 mL (222 mmol) of methanesulfonyl chloride was added over a 10-min period. The mixture was then stirred for 2 h and poured into 1300 mL of iced 1 N HCl. The solution was then adjusted to pH 4 with concentrated HCl, and the mixture was extracted with ethyl acetate (3 × 300 mL). The combined organic layers were washed with 200 mL of saturated $NaHCO_3$ and 200 mL of brine, dried over $MgSO_4$, and concentrated to about 150 mL. The concentrate was then seeded with the desired product to initiate crystallization and diluted with 150 mL of hexane. After the mixture was stored at 5 °C for 16 h, it was filtered to yield 38 g (78%) of analytically pure mesylate **14**: mp 131–132 °C; $[\alpha]_D$ −6.8° (*c* 1.5, MeOH); ^{1}H NMR (C_3D_6O) 5.06 (1 H, m), 4.30 (1 H, m), 3.70 (3 H, s), 3.05 (3 H, s), 1.48–1.31 (12 H, s + d); ^{13}C NMR (C_3D_6O) 165.8, 155.5, 79.4, 78.4, 63.3, 56.3, 37.5, 27.6, 17.7; IR (Nujol) 3305, 3210, 1660, 1525, 1300, 1250, 1185, 1160, 930, 900, 830 cm^{-1}. Anal. Calcd for $C_{11}H_{22}N_2O_7S$: C, 40.48; H, 6.80; N, 8.59; S, 9.83. Found: C, 40.53; H, 6.79; N, 8.49; S, 9.56.

Mesylate 15. A solution of 20.0 g (91.3 mmol) of hydroxamate **12** in 95 mL of pyridine was treated with 8.4 mL (105 mmol) of methanesulfonyl chloride at −5 °C (dropwise addition). The reaction mixture was stirred at 0 °C for 2 h and then poured, with rapid stirring, into 600 mL of ice-cooled water. The resulting precipitated product was removed by filtration, and the aqueous solution was adjusted to pH 4 with 6 N HCl. The solution was then saturated with NaCl and extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed sequentially with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated to yield additional product. Combining the two solids gave 23.8 g (80%) of the desired mesylate **15**: mp 124–126 °C dec (EtOAc); $[\alpha]_D$ −3.3° (*c* 3.3, MeOH); ^{1}H NMR ($CDCl_3$) 4.92 (1 H, br q, J = 6 Hz), 4.34 (1 H, m), 3.84 (3 H, s), 3.08 (3 H, s), 1.54 and 1.48 (12 H, s + d); ^{13}C NMR (CD_3OD) 167.8, 157.2, 81.3, 78.6, 64.5, 57.2, 38.4, 28.6, 18.2; IR (KBr) 3320, 3240, 2980, 1665, 1540, 1360, 1300, 1245, 1175, 1045, 895, 810 cm^{-1}. Anal. Calcd for $C_{11}H_{22}N_2O_7S$: C, 40.36; H, 7.08; N, 8.55; S, 9.78. Found: C, 40.35; H, 6.72; N, 8.46; S, 10.07.

(*S*)-1-Methoxy-3-[(*tert*-butoxycarbonyl)amino]-2-azetidinone (16). A solution of 1.69 g (5.41 mmol) of mesylate **13** in 10 mL of acetone was added to a refluxing slurry of powdered K_2CO_3 (2.29 g, 16.2 mmol) in 90 mL of acetone and stirred for 1 h. Upon cooling, the thick slurry was filtered through Celite, and the solids were washed with 100 mL of ethyl acetate. The resulting solution was concentrated and rediluted with 100 mL of ethyl acetate. After being washed sequentially with 25-mL portions of 1 N HCl, saturated $NaHCO_3$, and brine, the organic solution was dried over $MgSO_4$ and concentrated to afford 1.10 g (94%) of the desired azetidinone **16**: mp 91.5–92 °C (EtOAc, heptane); $[\alpha]_D$ −10.5°C (*c* 1, MeOH); ^{1}H NMR (C_3D_6O) 4.61 (1 H, m), 3.87 (1 H, t, J = 4.5 Hz), 3.76 (3 H, s), 3.56 (1 H, dd, J = 2.6, 4.5 Hz), 1.41 (9 H, s); ^{13}C NMR (C_3D_6O) 162.5, 154.9, 79.0, 61.9, 53.3, 50.7, 27.6; IR (Nujol) 3355, 3290, 1780, 1680, 1535, 1340, 1275, 1260, 1165, 1000 cm^{-1}. Anal. Calcd for $C_9H_{16}N_2O_4$: C, 49.99; H, 7.46; N, 12.96. Found: C, 49.81; H, 7.56; N, 12.92.

(3*S*)-*trans*-1-Methoxy-3-[(*tert*-butoxycarbonyl)amino]-4-methyl-2-azetidinone (17). The cyclization of 6.5 g (20 mmol) of mesylate **14** in 300 mL of acetone as described above afforded, after concentration and trituration with hexane, 4.0 g (87%) of the desired product **17**: mp 83–84.5 °C (hexane–EtOAc); $[\alpha]_D$ −34.0° (*c* 1.7, MeOH); ^{1}H NMR (C_3D_6O) 3.91 (2 H, m), 3.77 (3 H, s), 1.82 (12 H, s + d); ^{13}C NMR (C_3D_6O) 161.8, 155.1, 79.1, 62.9, 60.3, 27.7, 15.9; IR (Nujol) 3340, 1790, 1680, 1530, 1370, 1330, 1255, 1160, 1020, 870 cm^{-1}. Anal. Calcd for $C_{10}H_{18}N_2O_4$: C, 52.16; H, 7.88; N, 12.17. Found: C, 51,84; H, 7.68; N, 12.13.

(3*S*)-*cis*-1-Methoxy-3-[(*tert*-butoxycarbonyl)amino]-4-methyl-2-azetidinone (18). In 100 mL of water containing 5.54 g (40 mmol) of K_2CO_3, 150 mL of 1,2-dichloroethane was added. The mixture was then brought to reflux, and a suspension containing 3.26 g (10 mmol) of mesylate **15** and 339 mg (1 mmol) of TBAHS in 50 mL of 1,2-dichloroethane was added. After 25 min the mixture was cooled and diluted with 100 mL of methylene chloride, and the phases were separated. The aqueous phase was washed with an additional 50 mL of methylene chloride, and the combined organic phases were dried over $MgSO_4$, filtered, and concentrated to afford 1.91 g (83%) of crystalline product **18**. This cyclization was also conducted with K_2CO_3 in acetone at reflux for 3 h. A workup as described in the above examples gave a greater than 95% yield of **18**: mp 107–109 °C (EtOAc–pentane); $[\alpha]_D$ +49.8° (*c* 3.05, MeOH); ^{1}H NMR ($CDCl_3$) 5.69 (1 H, br d, J = 8 Hz, exchangeable), 4.74 (1 H, dd, J = 8, 5 Hz), 4.15 (1 H, dq, J = 5, 6 Hz), 3.85 (3 H, s), 1.48 (9 H, s), 1.29 (3 H, d, J = 6 Hz); ^{13}C NMR ($CDCl_3$) 161.7, 155.2, 80.2, 63.7, 58.9, 56.2, 28.0, 12.8; IR (KBr) 1785, 1690, 1535, 1345, 1280, 1170, 1045, 1005, 965, 865 cm^{-1}. Anal. Calcd for $C_{10}H_{18}N_2O_4$: C, 52.16; H, 7.88; N, 12.16. Found: C, 52.43; H, 8.04; N, 12.25.

(*S*)-3-[(*tert*-Butoxycarbonyl)amino]-2-azetidinone (9). After condensation of 40 mL of anhydrous ammonia at ca. −40 °C, 258 mg (11.2 mmol) of sodium was added in several small pieces. The resulting blue solution was stirred for 10 min, and 1.10 g (5.1 mmol) of the methoxylated azetidinone **16** added as a solution in 10 mL of THF over a 2-min period. Following this addition, the blue color discharged, and the colorless mixture was stirred for 10 min, whereupon 1.34 g (25 mmol) of NH_4Cl was added. The ammonia was then allowed to distill off, and 50 mL of THF was added to the white slurry. After filtration and washing of the solids with an additional 25 mL of THF, the combined organics were concentrated to give 970 mg (>100%) of product which was essentially pure by TLC analysis. Recrystallization from ethyl acetate gave 638 mg (67%) of pure **9**: mp 171.5–172.5°C; $[\alpha]_D$ −19.8° (*c* 1, MeOH); ^{1}H NMR (C_3D_6O) 4.82 (1 H, br m), 3.55 (1 H, t, J = 5 Hz), 3.27 (1 H, dd, J = 5, 3 Hz), 1.42 (9 H, s); ^{13}C NMR ($CDCl_3$) 168.6, 158.9, 80.4, 58.9, 44.9, 28.2; IR ($CHCl_3$) 3820, 2980, 1770, 1710, 1505, 1370, 1245, 1160 cm^{-1}; IR (Nujol) 1760, 1730, 1690 cm^{-1}. Anal. Calcd for $C_8H_{14}N_2O_3$: C, 51.60; H, 7.58; N, 15.04. Found: C, 51.49; H, 7.80; N, 14.76.

(3*S*)-*trans*-3-[(*tert*-Butoxycarbonyl)amino]-4-methyl-2-azetidinone (19). Azetidinone **17** (13.8 g, 60 mmol) was dissolved

(21) Elliot, D. F. *J. Chem. Soc.* **1950**, 62.

in 30 mL of THF and added slowly to a solution of 3.18 g (138 mmol) of sodium in 200 mL of liquid ammonia at −45 °C. After the mixture was stirred for an additional 5 min, 16.05 g (300 mmol) of NH_4Cl was added, and the resulting colorless mixtue was stirred for 5 min. Subsequently, 150 mL of methylene chloride was added, and the ammonia was distilled off under a stream of nitrogen followed by the addition of 50 mL of water. The phases were then separated, and the aqueous phase was washed with an additional 50 mL of methylene chloride. The combined organic phases were dried over Na_2SO_4 and concentrated. The crude product was then crystallized by dissolving it in 20 mL of ethyl acetate, adding 50 mL of hexane, and cooling at 5 °C overnight. Filtration afforded 10.8 g (87%) of pure **19**: mp; 135–137°C; $[\alpha]_D$ −68.4° (*c* 2.8, MeOH); ^1H NMR (C_3D_6O) 4.20 (1 H, dd, J = 8.5, 2 Hz), 3.67 (1 H, dq, J = 6.5, 2 Hz), 1.44 (9 H, s), 1.35 (3 H, d, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$) 167.4, 155.0, 80.3, 64.8, 54.1, 28.2, 19.2; IR ($CHCl_3$) 3400, 2980, 1765, 1710, 1495, 1450, 1370, 1350, 1325 cm^{-1}. Anal. Calcd for $C_9H_{16}N_2O_3$: C, 53.98; H, 8.06; N, 13.99. Found: C, 53.72; H, 8.26; N, 13.89.

(3*S*)-*cis*-3-[(*tert*-Butoxycarbonyl)amino]-4-methyl-2-azetidinone (20). After condensation of 500 mL of ammonia at −78 °C, 20 g (87 mmol) of the methoxylated azetidinone **18** was added, and the resulting solution treated with 4.64 g (200 mmol) of sodium (added in small portions). The blue solution was stirred for an additional 5 min after the sodium addition was complete, and then 11.7 g (220 mmol) of NH_4Cl was added. The ammonia was then removed under a stream of nitrogen (warm water bath), and the resulting solid was resuspended in about 1 L of ethyl acetate, filtered, and washed with water. The solution was dried over Na_2SO_4 and concentrated to yield 16.3 g (94%) of the desired product: mp 183–185 °C (EtOAc); $[\alpha]_D$ +34.0° (*c* 2.94, MeOH); ^1H NMR ($CDCl_3$) 6.87 (1 H, br s), 5.80 (1 H, br d, J = 8 Hz), 4.96 (1 H, dd, J = 5, 8 Hz), 3.94 (1 H, dq, J = 5, 6 Hz), 1.45 (9 H, s), 1.27 (3 H, d, J = 6 Hz); ^{13}C NMR (CD_3OD) 170.3, 157.5, 80.7, 61.1, 51.3, 28.6, 15.8; IR ($CHCl_3$) 3430, 3400, 2980, 1765, 1715, 1505, 1375, 1165 cm^{-1}. Anal. Calcd for $C_9H_{16}N_2O_3$: C, 53.98; H, 8.06; N, 13.98. Found: C, 53.58; H, 8.07; N, 13.97.

Preparation of DMF·SO_3 Complex. In general, 1–2 M solutions of the complex in DMF were prepared as follows. A volume of anhydrous DMF was cooled to 0 °C under nitrogen, and trimethylsilyl chlorosulfonate was added at a moderate rate. After the addition was complete, the reaction vessel was evacuated at 10^{-1} torr for 30 min, with stirring, to remove trimethylsilyl chloride. The resulting solution of DMF·SO_3 complex in DMF was then titrated for active SO_3 by using published procedures.[22] These solutions were stable for at least several months when stored with rigorous exclusion of moisture at 5 °C.

(*S*)-3-[(Benzoxycarbonyl)amino]-2-oxoazetidine-1-sulfonic Acid Tetra-*n*-butylammonium Salt (25). A solution of **24**[3] (220 mg, 1.0 mmol) in 3 mL of methylene chloride was cooled at 0 °C, and 1.5 mL of 1 M DMF·SO_3 complex in DMF solution was added. The reaction was then stirred for 20 min, poured into 50 mL of 0.5 N KH_2PO_4, and extracted with 25 mL of methylene chloride. The resulting aqueous layer was then treated with 340 mg (1.0 mmol) of TBAHS and extracted with methylene chloride (3 × 25 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated. Trituration of the residue with diethyl ether gave a white, crystalline solid. Filtration and washing with additional diethyl ether followed by vacuum drying gave 500 mg (92%) of sulfonated azetidinone **25**: mp 114–116 °C; $[\alpha]_D$ −9.5° (*c* 1, MeOH); ^1H NMR ($CDCl_3$) 7.35 (5 H, s); 5.09 (2 H, s), 4.80 (1 H, m), 3.85 (1 H, m), 3.62–2.95 (8 H, m), 1.95–0.80 (28 H, envelope); ^{13}C NMR ($CDCl_3$) 162.9, 155.4, 136.0, 128.3, 127.9, 127.8, 66.8, 58.4, 56.1, 48.8, 23.7, 19.5, 13.5; IR ($CDCl_3$) 3420, 2960, 2880, 1760, 1720, 1520, 1250, 1055 cm^{-1}. Anal. Calcd for $C_{27}H_{47}N_3O_6S$: C, 59.86; H, 8.75; H, 7.76; S, 5.92. Found: C, 59.24; H, 8.70; N, 7.62; S, 5.89.

(*S*)-3-[(*tert*-Butoxycarbonyl)amino]-2-oxoazetidine-1-sulfonic Acid Tetra-*n*-butylammonium Salt (26). A solution of 558 mg (3.0 mmol) of the azetidinone **9** in 5 mL of pyridine was heated, under nitrogen, to 80 °C, and 1.02 g (9.0 mmol) of pyridine–sulfur trioxide complex added. The mixture, which quickly became homogeneous, was stirred for 30 min and then poured into 100 mL of 0.5 N KH_2PO_4. The resulting solution was extracted with methylene chloride (2 × 25 mL), and the combined organic extracts were back-washed with an additional 25 mL of phosphate solution. The combined aqueous layer were then treated with 1.02 g (3.0 mmol) of TBAHS and extracted with methylene chloride (1 × 50 and 2 × 25 mL). After the organic extract was dried over Na_2SO_4, it was concentrated to yield 1.39 g (91%) of the desired tetra-*n*-butylammonium salt **26** which was essentially pure by TLC analysis (EtOAc–MeOH, 4:1; silica gel 60). All attempts to crystallize this material were unsuccessful: ^1H NMR ($CDCl_3$) 5.37 (1 H, br d, exchangeable), 4.70 (1 H, m), 3.81 (1 H, t, J = 6 Hz, actually a dd), 3.55–2.88 (9 H, m), 1.95–0.60 (37 H, m with s at 1.42 and 0.98); ^{13}C NMR ($CDCl_3$) 163.0, 154.3, 57.8, 55.4, 48.4, 27.6, 23.2, 18.9, 13.0; IR (Film) 3300, 2960, 2880, 1765, 1705, 1520, 1485, 1370, 1260, 1165, 1040, 920, 730 cm^{-1}.

(3*S*)-*trans*-3-[(*tert*-Butoxycarbonyl)amino]-4-methyl-2-oxoazetidine-1-sulfonic Acid Tetra-*n*-butylammonium Salt (27). Azetidinone **19** (8.0 g, 40 mmol) was dissolved in 40 mL of pyridine and heated at 90 °C, and 19.1 g (120 mmol) of Pyr·SO_3 was added under a stream of nitrogen. The mixture was stirred at 90 °C for 45 min and then poured into 1 L of 0.5 N KH_2PO_4 solution. The aqueous solution was then extracted with 200 mL of methylene chloride and the resulting organic layer back-extracted with an additional 100 mL of phosphate solution. Treatment of the combined aqueous phases with 13.6 g (40 mmol) of TBAHS followed by methylene chloride extraction (3 × 200 mL) and drying over Na_2SO_4 gave, after concentration, 18.7 g (90%) of a semicrystalline product, **27**: mp 142–144 °C (EtOAc); $[\alpha]_D$ −12.5 (*c* 1.2, MeOH); ^1H NMR ($CDCl_3$) 5.18 (1 H, d, J = 7.5 Hz, exchangeable), 4.34–3.62 (2 H, m), 3.62–3.50 (8 H, m), 1.95–0.65 (40 H, m and s at 1.45 and 1.0); ^{13}C NMR ($CDCl_3$) 162.9, 154.5, 79.7, 62.3, 58.6, 58.0, 27.8, 23.4, 19.2, 17.7, 13.3; IR (film) 3490, 3300, 2975, 2965, 2935, 1765, 1710, 1520, 1485, 1460, 1370, 1330, 1250, 1160, 1045, 885, 735 cm^{-1}. Anal. Calcd for $C_{25}H_{51}N_3O_6S$: C, 57.55; H, 9.85; N, 8.05; S, 6.15. Found: C, 57.20; H, 9.65; N, 7.92; S, 6.01.

(3*S*)-*cis*-3-[(*tert*-Butoxycarbonyl)amino]-4-methyl-2-oxoazetidine-1-sulfonic Acid Tetra-*n*-butylammonium Salt (28). A solution of azetidinone **20** (25 g, 125 mmol) in 150 mL of pyridine was heated under nitrogen to 90 °C, and 59.62 g (375 mmol) of Pyr·SO_3 was added. The resulting solution was heated at 90 °C for an additional 45 min and poured into 4 L of 1 M aqueous KH_2PO_4. The reaction was then worked up in a manner identical with that for the above examples to afford 55.7 g (85%) of semisolid product **28**. Attempts to recrystallize this material from ethyl acetate were unsuccessful: ^1H NMR ($CDCl_3$) 4.95 (1 H, m), 4.17 (1 H, m), 3.5 to 3.0 (8 H, m), 1.95–0.70 (40 H, envelope); ^{13}C NMR ($CDCl_3$) 162.7, 154.7, 79.9, 58.2, 55.1, 27.8, 23.6, 19.3, 13.9, 13.3; IR ($CDCl_3$) 3430, 2960, 1760, 1715, 1510, 1490, 1375, 1255, 1160 1055 cm^{-1}.

(*S*)-3-Amino-2-oxoazetidine-1-sulfonic Acid (29). The crude product **26** from the 3-mmol sulfonation described above was dissolved in 10 mL of 97% formic acid and stirred for 4.5 h at room temperature. Approximately 30 mL of methylene chloride was then added to the resulting slurry, and the mixture was filtered. Washing with additional methylene chloride and drying afforded 310 mg (61% based on azetidinone **9** used in the sulfonation step) of pure product **29**: mp >200 °C dec; $[\alpha]_D$ −45.0° (*c* 2, H_2O); ^1H NMR (D_2O, 100 MHz) 4.76 (1 H, dd, partially obscured by HOD, observed d, J = 2.9 Hz), 4.06 (1 H, dd, J = 5.8, 6.9 Hz), 3.79 (1 H, dd, J = 2.9, 6.9 Hz); ^{13}C NMR (D_2O) 161.5, 54.6, 46.6; IR (KBr) 3430, 3120, 1785, 1610, 1515, 1330, 1240, 1195, 1045, 735, 640, 580, 535 cm^{-1}. Anal. Calcd for $C_3H_6N_2O_4S$: C, 21.68; H, 3.64; N, 16.86; S, 19.30. Found: C, 21.65; H, 3.66; N, 16.84; S, 19.18.

(3*S*)-*trans*-3-Amino-4-methyl-2-oxoazetidine-1-sulfonic Acid (30). The crude sulfonated azetidinone **27** (18.7 g, 35.9 mmol) was dissolved in 110 mL of 97% formic acid and stirred at room temperature. After about 5 min a white precipitate formed, and the reaction was continued for 4.5 h. The slurry was then diluted with 110 mL of methylene chloride and filtered. The white powder was washed with additional methylene chloride and dried in vacuo to yield 6.02 g (93%) of analytically pure **30**: mp >218 °C dec; $[\alpha]_D$ −41.1° (*c* 1, H_2O); ^1H NMR (D_2O, 100 MHz) 4.80 (2 H, m with s at 4.31), 1.58 (3 H, d, J = 5.9 Hz); ^{13}C NMR (D_2O, dioxane standard) 161.3, 60.1, 57.5, 17.5; IR (KBr) 3120,

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2950, 1775, 1620, 1520, 1395, 1340, 1310, 1270, 1220, 1195, 1160, 1120, 1045, 750, 715, 630, 600, 570, 550 cm^{-1}. Anal. Calcd for $C_4H_8N_2O_4S$: C, 26.66; H, 4.44; N, 15.55; S, 17.77. Found: C, 26.62; H, 4.72; N, 15.47; S, 17.49.

(3*S*)-*cis*-3-Amino-4-methyl-2-oxoazetidine-1-sulfonic Acid (31). The crude product **28** (55.7 g, 106 mmol) from the above example was dissolved in 300 mL of 97% formic acid and stirred for 3 h. Filtration of the resulting slurry afforded 6.7 g of pure product. The mother liquor was then concentrated to ca. 150 mL and diluted with an equal volume of toluene. After the mixture was cooled at −20 °C for several hours an additional 1.7 g of product was obtained by filtration to afford a total of 8.4 g (44%) of the desired zwitterion **31**. Further attempts to recover additional material were unsuccessful: mp >200 °C dec; $[\alpha]_D$ −62° (*c* 3.15, H_2O); ^1H NMR (D_2O, 100 MHz) 4.8–4.1 (2 H, m obscured by HOD peak), 1.50 (3 H, d, J = 6.5 Hz); ^{13}C NMR (D_2O, dioxane standard) 160.5, 56.0, 53.8, 12.5; IR (KBr) 3420 (br), 3180 (br), 3010, 2950, 1765, 1525, 1315, 1280, 1230, 1050, 640 cm^{-1}. Anal. Calcd for $C_4H_8N_2O_4S$: C, 26.66; H, 4.44; N, 15.55; S, 17.77. Found: C, 26.63; H, 4.74; N, 15.30; S, 17.47.

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Registry No. **9**, 72229-74-4; **10**, 83511-25-5; **11**, 83511-26-6; **12**, 80543-39-1; **13**, 83511-27-7; **14**, 83511-28-8; **15**, 80575-79-7; **16**, 72229-73-3; **17**, 83542-13-6; **18**, 80543-40-4; **19**, 80582-03-2; **20**, 80582-06-5; **24**, 80082-81-1; **25**, 80082-47-9; **26**, 83511-30-2; **27**, 80082-60-6; **28**, 80582-08-7; **29**, 79720-18-6; **30**, 80082-65-1; **31**, 80582-09-8; L-serine, 56-45-1; methoxyamine hydrochloride, 593-56-6; L-threonine, 72-19-5; *allo*-threonine, 2676-21-3.

Sythesis of Aminomethyl Crown Ethers

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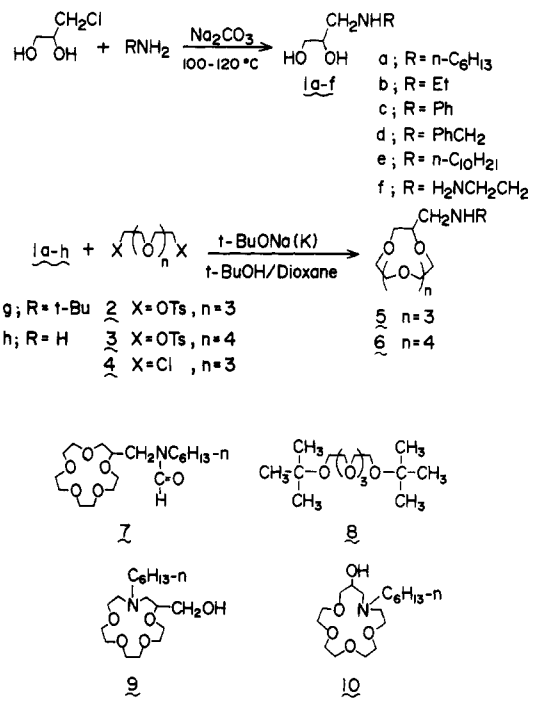
Various N-substituted or unsubstituted aminomethyl crown ethers, which possess a reactive amino group, were prepared in good yields by the reaction between 3-amino-1,2-propanediols or aminomethyl oligoethylene glycols and oligoethylene glycol ditosylates or dichlorides. The scope of the reaction was investigated and the complexing ability of these new crown ether derivatives with sodium and potassium ions in methanol was measured by potentiometric titration.

Recently, the syntheses and applications of many linear and network polymers including macrocyclic polyethers in the backbone or as a pendant group have been reported.[1,2] Although most of them are obtained from benzo crown compounds by utilizing the functional groups introduced in their benzene ring, some crown polymers are prepared from hydroxy crown ethers[3,4] or diaza crown ethers.[5-7]

We have previously reported some facile syntheses of crown ethers bearing functional groups such as chloromethyl,[8] hydroxymethyl,[9] and bromomethyl,[10] which are useful intermediates for the syntheses of immobilized crown compounds, lariat ethers,[11-13] bis crown ethers,[3,14] etc.

Scheme I



Crown compounds having amino groups can also be utilized for the above objectives. Montanari et al. have synthesized [(ethylamino)nonyl]-18-crown-6 and have reported that the immobilized crown ethers derived from it showed good activity as phase-transfer catalysts.[15-17]

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