MONOBACTAMS: RING ACTIVATING N-1-SUBSTITUENTS IN MONOCYCLIC β-LACTAM ANTIBIOTICS

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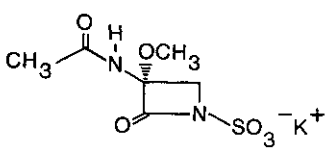
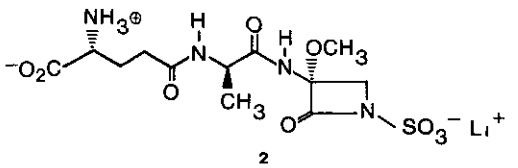
Abstract —— Several alternatives to the sulfonate residue in the naturally-occurring monobactams, 3-acylamino-2-oxoazetidine-1-sulfonates, provide new monobactams having potent activity against aerobic gram-negative bacteria. The monobactams compared here include: (a) those where the anionic activating group (sulfonate or phosphonate(-inate)) is attached to the β-lactam nitrogen, and (b) those where an oxygen atom is interposed between the acidic group and the β-lactam nitrogen, i.e. sulfate and phosphate(-onate) groups. Chemical and biological relationships between these classes of monobactams are presented.

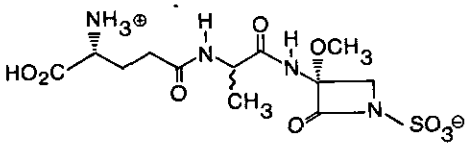
In 1981, researchers at the Squibb Institute reported the isolation of SQ 26,180 (1) and SQ 26,445 (2) from bacterial fermentation broths of Chromobacterium violaceum and a Gluconobacter species, respectively[1]. These β-lactam antibiotics exhibited modest antibacterial activity, resulting from a unique structural feature: a monocyclic β-lactam activated by an N-1 sulfonate group. The Squibb group suggested the term "monobactams" for this class of antibiotics characterized by the 2-oxoazetidine-1-sulfonic acid moiety. Simultaneously, investigators at the Takeda laboratories reported the isolation of sulfazecin (3) and isosulfazecin (4) from the bacterium Pseudomonas acidophila[2]. The structures assigned to SQ 26,445 and sulfazecin are identical.



1
SQ 26,180

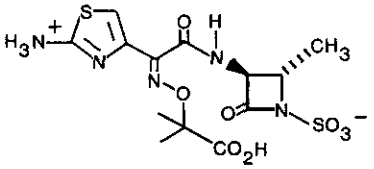


2
SQ 26,445



3 (S) - ala SULFAZECIN
4 (R) - ala ISOSULFAZECIN

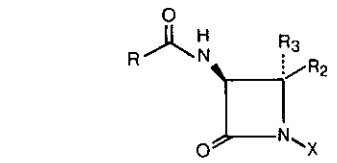
Differences in the biological activity of SQ 26,180 and SQ 26,445, whose structures vary in the acyl side chain, indicated that chemical modification might lead to enhanced biological activity. *Among possibilities for structural modification* of the naturally-occurring monobactams, with retention of the basic 2-oxoazetidine-1-sulfonate nucleus, were: (a) removal of the methoxyl group at C-3, (b) side chain alteration at C-3, and (c) substitution at the 4-position. Replacement of methoxyl by hydrogen gave compounds with enhanced chemical stability but diminished β-lactamase stability. Modification of the acyl side chain[3,4,5] improved intrinsic activity, but stability to β-lactamases was lacking. Addition of a methyl group at the C-4 position, either in the α or β configuration, however, afforded compounds with a high degree of β-lactamase stability[5]. One lead compound identified from these structure-activity relationships was the clinically useful monobactam, aztreonam (5). Efficacy has been demonstrated against a broad range of resistant aerobic gram-negative bacteria including Pseudomonas aeruginosa[5].

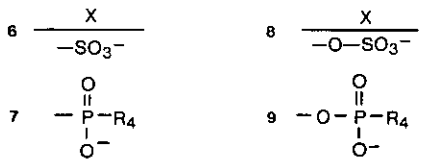


5
AZTREONAM
SQ 26,776

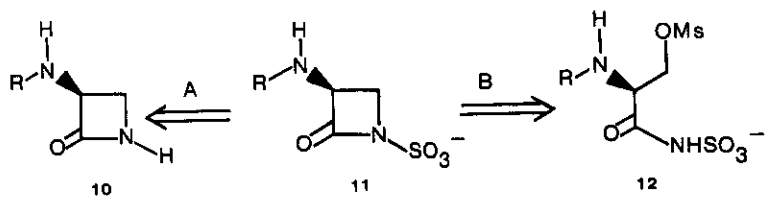
The sulfonate moiety in monobactams activates the β-lactam ring and provides an anionic charge for binding at the active site of enzymes involved in bacterial cell wall biosynthesis. Other N-1 residues that might serve this dual purpose were investigated. Tetracoordinate sulfur *(VI) and phosphorus (V) have similar bond lengths and* tetrahedral geometry; therefore, azetidinone-1-phosphonic(inic) acids (7) were potential compounds for comparison with sulfonated monobactams.

The availability of 1-hydroxy-azetidinones provided potential intermediates for the synthesis of analogous sulfates (8) and phosphates (9). In these derivatives, the effect of moving the anionic charge farther from the ring, while inductively activating the β-lactam toward nucleophilic attack, could be assessed.

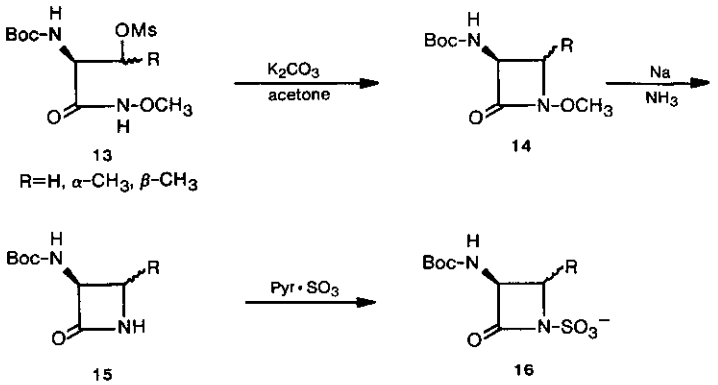




Two synthetic approaches to N-sulfonated monobactams have been reported from our laboratories: sulfonation of 3-acylamino-2-azetidinones (path A)[6] and ring closure of sulfonated amino acid amides (path B)[4]. In the former method (Scheme 2) the azetidinones are obtained from mesylates (13) derived from hydroxamates of L-serine, L-threonine or L-allothreonine. Base induced ring closure to N-1 methoxylated azetidinone (14) followed by reductive removal of the methoxyl group with sodium in liquid ammonia provides the azetidinone (15). Sulfonation can be accomplished using a variety of reagents including pyridine·SO_3 and DMF·SO_3 complexes.

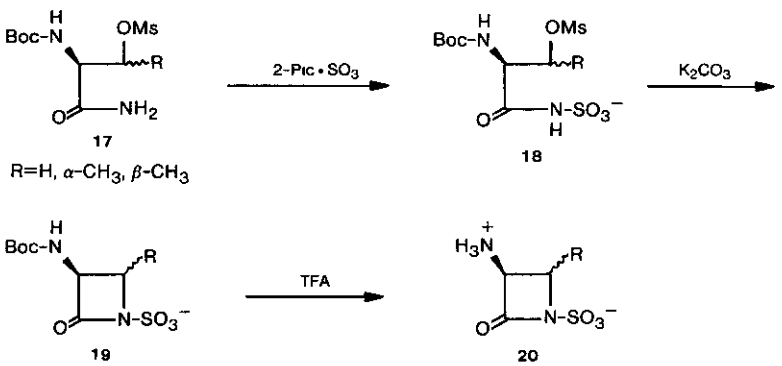


Scheme 1



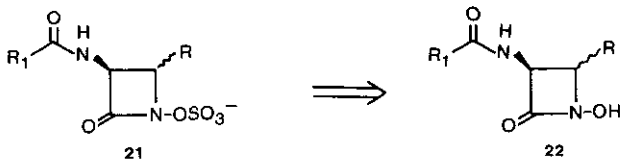
Scheme 2

In the second method (Scheme 3) amino acid amides (17), derived from L-serine, L-threonine or L-allothreonine, are sulfonated with 2-picoline•SO_3 complex to give the mesylated acylsulfamates (18), which undergo ring closure to (19) in the presence of K_2CO_3. Subsequent deprotection under acidic conditions provides zwitterions (20) in overall yields of 52-58% from the starting amino acids. Overall yields of zwitterions (20) from the amino acids via Scheme 2 were 23-45%. Neither method requires chromatographic purification.



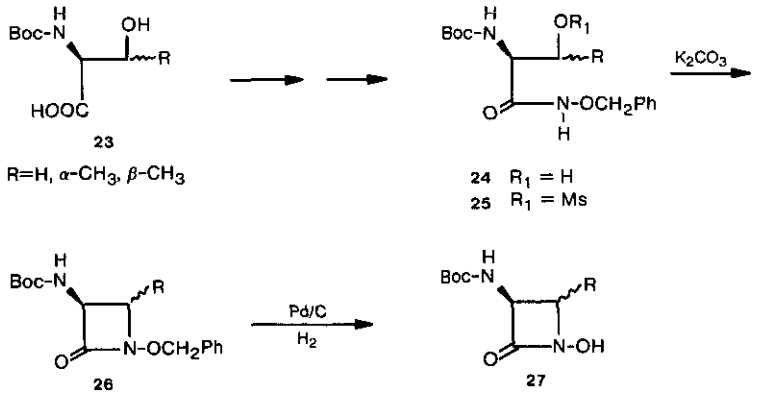
Scheme 3

The preparation of azetidinone-1-sulfates (21) was facilitated by the recent availability of 1-hydroxy-2-azetidinones (22)[7]. Gordon et al.[8] at Squibb first reported sulfation of N-1 hydroxyazetidinones (22) to (21) in 1982. Initial work in this area was hindered by the instability of C-4 unsubstituted compounds (21), requiring development of appropriate protecting groups. When the greater stability of C-4 methylated compounds (21) became apparent, more conventional protecting groups were used, which facilitated rapid preparation of numerous analogs.



Scheme 4

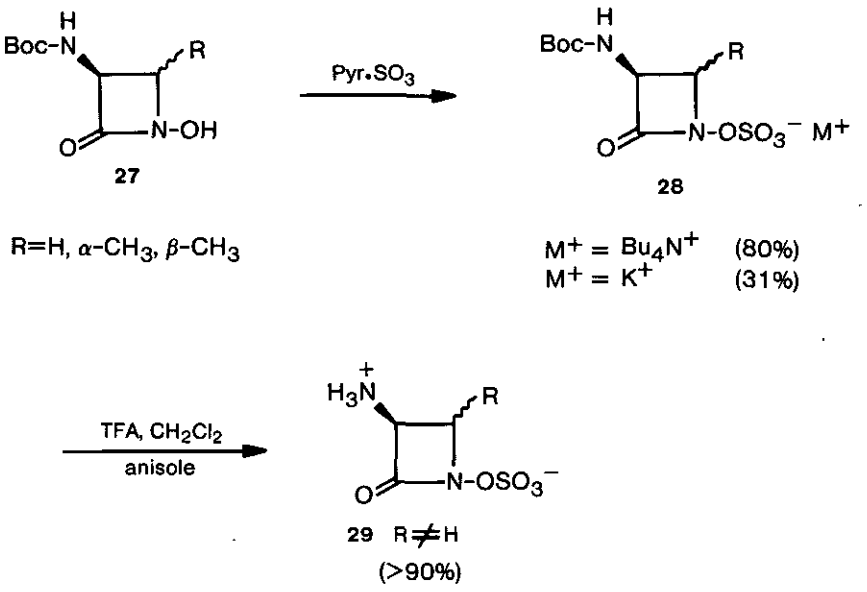
Intermediates (23), derived from serine, threonine, and allothreonine were initially converted by Miller et al.[7] to hydroxamate intermediates (24). Ring closure using Mitsunobu conditions and hydrogenolysis of the benzyl protecting group gave the N-hydroxy-azetidinone (27). By applying methodology of Floyd et al.[6] and Gordon et al.[8], we have recently prepared the 1-hydroxy BOC azetidinones (27) in about 25% overall yield from BOC derivatives of L-serine, L-threonine, and L-allothreonine via the mesylate cyclization route (Scheme 5). All intermediates crystallize from reaction mixtures, and no chromatography is required.



Scheme 5

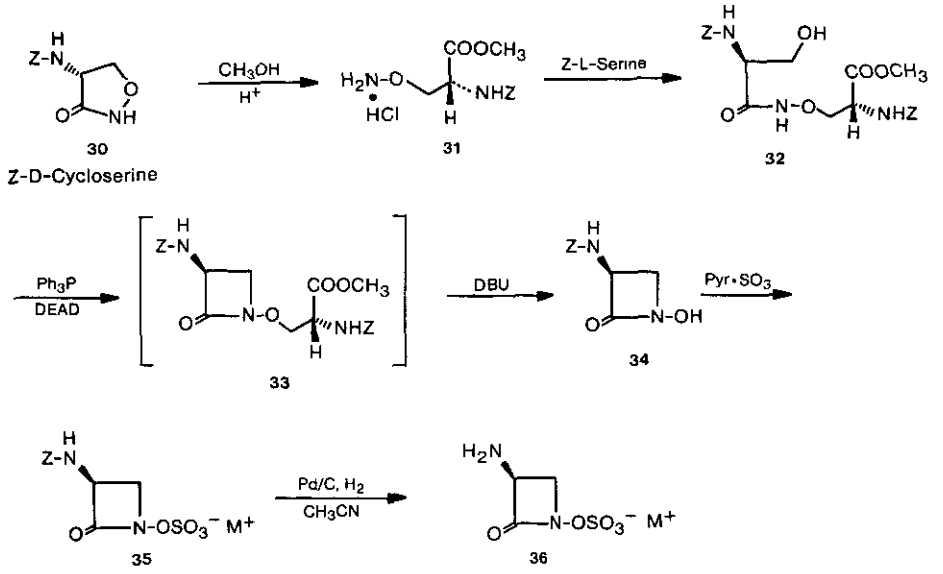
Sulfonation of azetidinones (27) with excess pyridine•SO_3 complex in pyridine at room temperature is complete in about 0.5-1.5 hr, and the desired products are isolated in about 80% yield as tetrabutylammonium salts. Conversion to the corresponding potassium form followed by purification by reverse phase chromatography gives analytically pure potassium salts (28) in about 30% yield. Treatment of 4α- or 4β-methyl potassium salts (28) with trifluoroacetic acid

in the presence of anisole provides the desired zwitterions (29) in greater than 90% yield. Attempted deprotection of the 4-unsubstituted azetidinone (28), under similar conditions, results in decomposition.



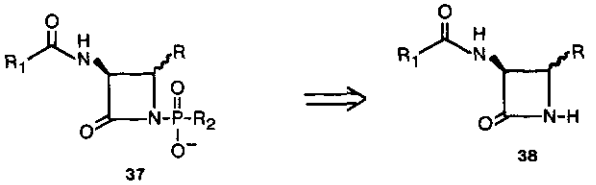
Scheme 6

Because BOC derivative (28) (R=H) was unstable to acidic conditions necessary for deprotection, Z-protection of the 3-amino group was employed. 1-Hydroxy-Z-azetidinone (34) could be prepared as described by Gordon et al.[8] Methanolysis of Z-protected D-cycloserine gave O-protected hydroxylamine (31), which was condensed with Z-L-serine to give (32). Triphenylphosphine-diethylazodicarboxylate mediated cyclization afforded crude azetidinone (33) which, on treatment with DBU, undergoes β-elimination to Z-dehydroalanine methyl ester and (34). No chromatography is required, and Z-L-serine is converted to (34) in 51% yield. Sulfonation (61%) of (34) followed by rapid hydrogenolysis (>90%) in CH_3CN gave (36).

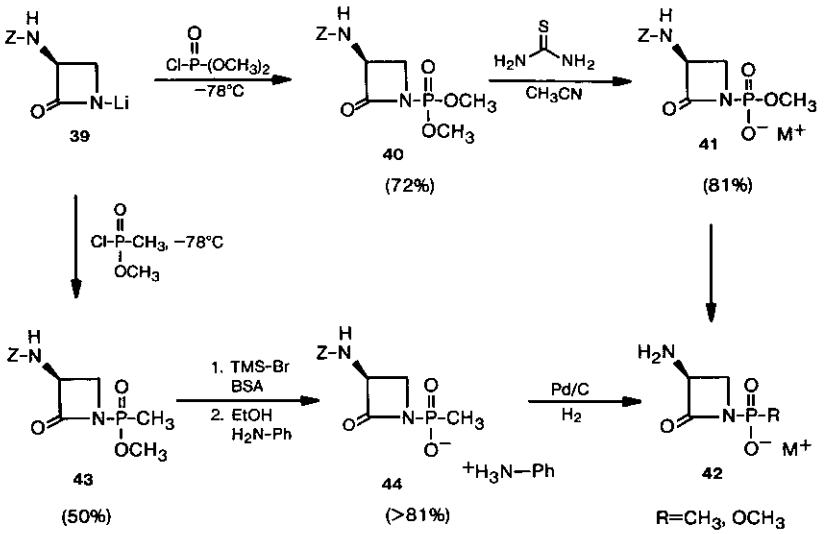


Scheme 7

Synthesis of N-1 phosphonate activated 2-oxoazetidines (37) from (38) has been accomplished by Koster et al.[9] using a variety of methods involving phosphonylation(-inylation) of azetidinones (Scheme 8). For example, treatment of the lithium anion (39), generated from the corresponding azetidinone with n-butyl lithium in THF at -78°C, with dimethyl chlorophosphate provides (40). Monodemethylation to (41) occurs on subsequent treatment with thiourea in refluxing acetonitrile. Alternatively, demethylation of N-1 phosphinates can be performed using bromotrimethylsilane, in the presence of bis(trimethylsilyl)acetamide as an acid scavenger. Subsequent alcoholysis of the intermediate silyl ester gives phosphinate (44), exemplified in the sequence (39) to (44). Catalytic hydrogenation of intermediates (41) and (44) affords 3-aminoazetidinone-1-phosphonic(-inic) acids.

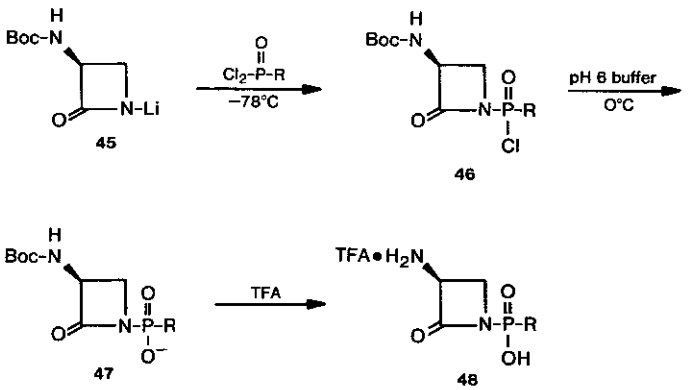


Scheme 8



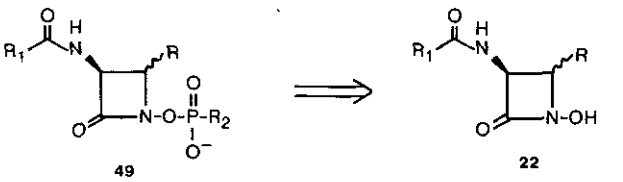
Scheme 9

An alternative approach (Scheme 10) to N-1 2-oxoazetidine-1-phosphonates circumvents the dealkylation step. Phosphorylation of the lithium anion of the azetidinone with alkyl dichlorophosphates, followed by immediate hydrolysis of the intermediate phosphonyl(-inyl) chlorides (46) in aqueous buffer, affords phosphonates(-inates) (47). Overall yields in this sequence are 35-40%. Hydrolysis of phosphonyl chlorides (46) to (47) is in marked contrast to the hydrolysis of 1-chlorosulfonyl-2-oxoazetidines, which results in N-S bond cleavage to give N-1 unsubstituted 2-oxoazetidines as reported by Graf[10]. Removal of the BOC protecting group from (47) is accomplished using trifluoroacetic acid.



Scheme 10

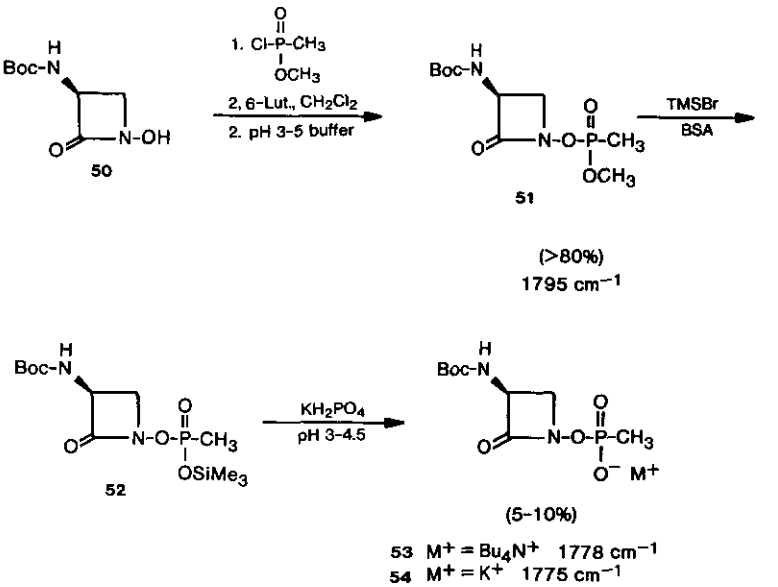
Synthesis of N-1 O-phosphorus activated 2-azetidinones (49) utilized 1-hydroxy-2-azetidinone intermediates (22), also used in the preparation of N-1 O-sulfates. In contrast to phosphonylation of the azetidinone nitrogen (vide supra), phosphonylation of (22) could be accomplished under mildly basic conditions.



49 22

Scheme 11

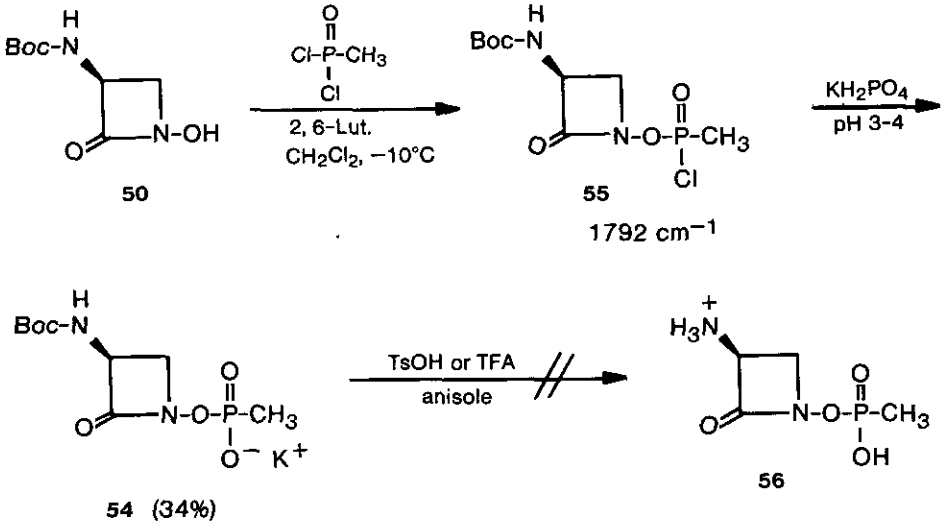
Treatment of the 1-hydroxyazetidinone (50) with chloromethylphosphonic acid methyl ester and 2,6-lutidine at -10°C followed by workup with buffer afforded the unstable methyl phosphonate (51) (1795 cm^{-1}, CH_3CN, β-lactam C=O). Decomposition of (51) occurred on silica gel chromatography and on standing in solvents such as CH_3CN or CH_2Cl_2 at ambient temperature. Demethylation was achieved using bromotrimethylsilane and bis(trimethylsilyl)trifluoroacetamide followed by buffered hydrolysis, which provided tetrabutylammonium salt (53) (1778 cm^{-1}, CH_3CN, β-lactam C=O) and subsequently, pure potassium salt (53) (1775 cm^{-1}, Nujol, β-lactam C=O), albeit in low yield (5-10%).



50 51 52

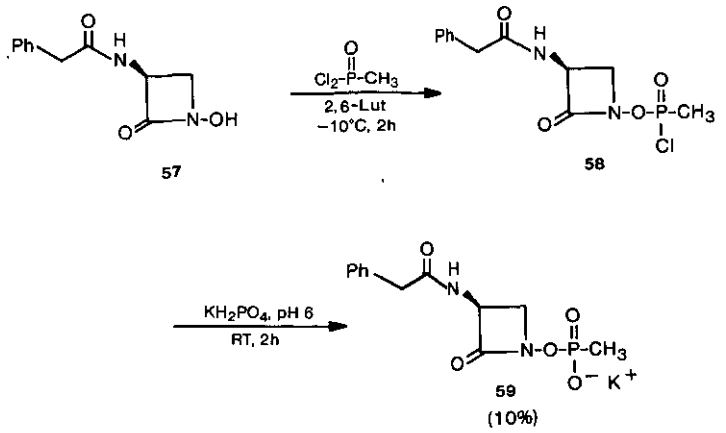
Scheme 12

A more efficacious preparation of (54) involved treatment of (50) with methylphosphonic dichloride and 2,6-lutidine in CH_2Cl_2 at -10°C. Subsequent hydrolysis of unstable intermediate (55) (1792 cm^{-1}, CH_2Cl_2, β-lactam C=O) at pH 3-4 gave pure (54) in 34% yield. Attempts to remove the BOC protecting group from (54) using acidic conditions, as in the case of N-1 sulfate (28) (R=H), however, resulted in decomposition. Amine protection with the Z-group, therefore, had to be used, and 1-hydroxy-2-oxoazetidine (34) was converted to the Z analog of (54) (50%), which, on hydrogenolysis of its tetrabutylammonium salt provided the relatively unstable free amine form of (56).

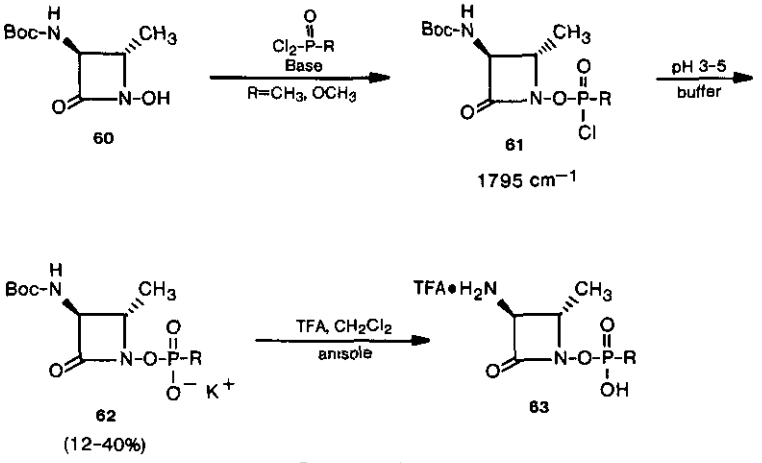


Scheme 13

To circumvent the instability problems encountered in amine deprotection and acylation, 4-unsubstituted N-1 O-phosphorus activated azetidinones, at times, were prepared directly by phosphorylation of appropriate 3-acylamino-1-hydroxyazetidinones. For example, potassium salt (59) was prepared by this direct method, although in low yield (10%).



Scheme 14

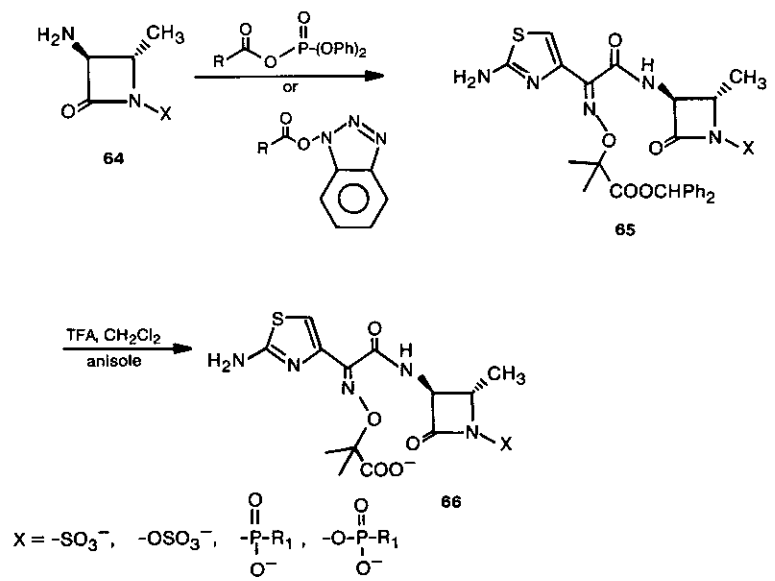


Scheme 15

In contrast to the acid instability of 4-unsubstituted N-1 O-phosphorus activated azetidinones like (54), the corresponding 4α- and 4β-methyl analogs could be deprotected under acidic conditions, paralleling our experience with the N-1 sulfate series. As exemplified in the 4α-methyl series in Scheme 15, phosphorylations with methylphosphonic(-oric) dichlorides in the presence of 2,6-lutidine or triethylamine at low temperatures gave unstable chloro intermediates (61), which were hydrolyzed at pH 3-5 to give stable potassium salts (62). Removal of the BOC group under acidic conditions at -10°C for 1 hr gave the amino acid salts (63) in good yields. The

phosphorylation step using methylphosphoric dichloride required temperatures of -60°C to -30°C for 1.5 hr, and was followed by buffered hydrolysis at ambient temperature providing (62) ($R=OCH_3$) in a maximum yield of only 12%. Phosphorylations with methylphosphonic dichloride, in contrast, were carried out at -10°C to -5°C for 1 hr and provided potassium salts in the 4α- and 4β-methyl series in yields ranging 26-40%. The low yield of phosphates like (62) ($R=OCH_3$) as compared to phosphonates (62) ($R=CH_3$) is attributed to decomposition during hydrolysis of (61) ($R=OCH_3$) compared to (61) ($R=CH_3$).

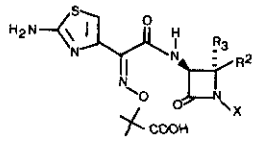
Acylations of monobactams were performed using activated esters of desired acyl side chains under aqueous or non-aqueous conditions, as exemplified in Scheme 16. In general, yields in acylations of monobactams where X is $-SO_3^{\ominus}$ or $-\overset{O}{\overset{\|}{P}}(O^{\ominus})-R$ were considerably higher than those where X is $-OSO_3^{\ominus}$ or $-O-\overset{O}{\overset{\|}{P}}(O^{\ominus})-R$. The benzhydryl group in (65) was removed with dilute trifluoroacetic acid in the presence of anisole. Although 4-unsubstituted N-1 O-sulfonate and N-1 O-phosphorus activated azetidinones are unstable under acidic conditions, 4-unsubstituted compounds (65) ($X=-OSO_3^{\ominus}$) and (65) ($X=-O-\overset{O}{\overset{\|}{P}}(O^{\ominus})-R$) could be deprotected with dilute trifluoroacetic acid under carefully controlled conditions.



Scheme 16

A comparison of intrinsic activity of several N-1 sulfonated and N-1 sulfated monobactams, including aztreonam (SQ 26,776), against a number of sensitive gram-positive and gram-negative organisms is given in Table 1. Little or no activity is observed against the gram-positive Staphylococcus strains, but all compounds exhibit a broad spectrum of activity against aerobic gram-negative organisms, including Pseudomonas aeruginosa. For corresponding analogs between classes, activities are essentially equivalent, and 4-methyl substitution in either the α or β configuration enhances activity.

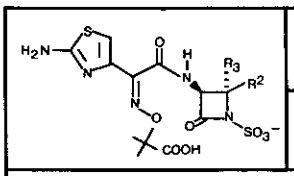
Table 1.
Influence of C-4 Substitution on Intrinsic Activity of 2-Oxoazetidine-1-Sulfonates and 1-Sulfates



	X	SO_3^-			OSO_3^-		
	R_2	H	H	CH_3	H	H	CH_3
	R_3	H	CH_3	H	H	CH_3	H
MIC (μg/ml) Agar Dil. 10^4 CFU							
Organism	**SC#**	**81,402**	**26,776**	**26,917**	**28,488**	**28,511**	**28,577**
Staph. aureus	1276	>100	>100	>100	>100	>100	50
Staph. aureus	2400	>100	>100	>100	>100	>100	100
E. coli	8294	0.4	0.4	0.2	0.8	0.8	0.8
E. coli	10,857	0.2	0.1	0.1	0.4	0.1	0.1
K. aerogenes	10,440	0.4	0.4	0.4	0.4	0.2	0.4
Prot. mirabilis	3855	<0.05	<0.05	<0.05	0.1	<0.05	<0.05
Prot. vulgaris	9416	0.1	<0.05	<0.05	0.2	<0.05	<0.05
Ent. cloacae	8236	0.2	0.2	0.4	0.4	0.1	0.4
Ser. marcescens	9783	0.8	0.2	0.2	0.8	0.1	0.2
Ps. aeruginosa	9545	0.8	0.4	0.4	1.6	0.8	0.8
Ps. aeruginosa	8329	3.1	6.3	1.6	3.1	1.6	1.6

Table 2 shows a number of N-1 sulfated monobactams in an abbreviated representation of our secondary screen that is designed to assess stability of compounds to β-lactamase-producing organisms at high (10^6 CFU) and low (10^4 CFU) inoculum level. Additionally, compounds are compared against three pairs of β-lactamase-producing (TEM+, P99+, K1+) and non-β-lactamase-producing (TEM−, P99−, K1−) strains of bacteria. A striking feature of the N-1 sulfonates is the increase in stability to β-lactamases on substitution of methyl groups for hydrogen at C-4.

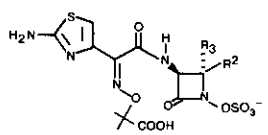
Table 2.
Effect of C-4 Substitution on Activity of 2-Oxoazetidine-1-Sulfonates Against β-Lactamase Producing Organisms



		R_2	H		H		CH_3	
		R_3	H		CH_3		H	
MIC (μg/ml) Agar Dil. Inocula (CFU)			10^4	10^6	10^4	10^6	10^4	10^6
Organism	**SC#**	**SQ#**	**81,402**		**26,776**		**26,917**	
E. coli TEM+	10,404		3.1	25	<0.05	0.2	0.2	0.2
E. coli TEM−	10,439		0.4	0.4	0.1	0.1	0.2	0.4
Ent. cloacae P99+	10,435		>100	>100	25	50	12.5	50
Ent. cloacae P99−	10,441		0.1	0.4	0.1	0.1	0.1	0.4
K. aerogenes K1+	10,436		>100	>100	25	>100	1.6	3.1
K. aerogenes K1−	10,440		0.1	0.2	< 0.05	0.1	0.2	0.4
K. pneumo.	11,066		25	>100	0.4	0.8	0.4	0.8
C. freundii	10,204		0.4	100	0.1	25	0.2	25
Prot. rettgeri	8,217		<0.05	0.1	<0.05	1.6	<0.05	<0.05
Prot. vulgaris	10,951B		<0.05	6.3	<0.05	<0.05	<0.05	<0.05
Ser. marcescens	9,782		1.6	1.6	0.1	0.4	0.2	0.8
Ps. aeruginosa	8,329		3.1	12.5	1.6	6.3	3.1	6.3
Ps. aeruginosa	9,545		0.8	0.8	0.4	0.4	0.4	0.8

The secondary screen of a number of N-1 sulfates is shown in Table 3. In contrast to the sulfonates, susceptibility to β-lactamases is similar for the 4-unsubstituted and 4α-methyl sulfates. All sulfates are significantly active against Pseudomonas aeruginosa. As a class, the N-sulfated monobactams are less lactamase stable than the N-sulfonates.

Table 3.
Effect of C-4 Substitution on Activity of 2-Oxoazetidine-1-Sulfates Against β-Lactamase Producing Organisms

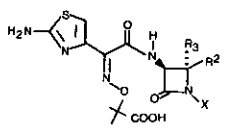


		R_2	H		H		CH_3	
		R_3	H		CH_3		H	
MIC (μg/ml) Agar Dil. Inocula (CFU)			10^4	10^6	10^4	10^6	10^4	10^6
Organism	**SC#**	**SQ#**	**28,488**		**28,511**		**28,577**	
E. coli TEM+	10,404		50	>100	25	>100	1.6	6.3
E. coli TEM−	10,439		0.4	1.6	0.2	0.8	0.4	0.4
Ent. cloacae P99+	10,435		>100	>100	>100	>100	100	>100
Ent. cloacae P99−	10,441		0.4	50	0.2	0.4	0.2	0.8
K. aerogenes K1+	10,436		>100	>100	>100	>100	>100	>100
K. aerogenes K1−	10,440		0 4	0.8	0.2	0.8	0.2	0.4
K. pneumo.	11,066		>100	>100	100	>100	6.3	50
C. freundii	10,204		1.6	100	0.8	25	0.4	12.5
Prot. rettgeri	8,217		<0.05	0.4	<0.05	0.2	<0 05	0.2
Prot. vulgaris	10,951B		0.4	3.1	0.1	0 8	<0.05	0.2
Ser. marcescens	9,782		6.3	6.3	0.4	1.6	0.4	0.8
Ps. aeruginosa	8,329		1.6	12.5	3.1	6.3	0.8	6.3
Ps. aeruginosa	9,545		3.1	3.1	—	—	0.8	0.8

In Table 4 the intrinsic activity of several N-phosphorus and N-O-phosphorus activated monobactams is shown. None of the compounds exhibits activity against gram-positive organisms, and only the N-O-phosphorus class is significantly active against Pseudomonas aeruginosa. The N-phosphorus compounds are intrinsically less active than the N-O-phosphorus compounds, and although 4-methyl substitution results in high intrinsic activity in the N-O-phosphorus series, 4β-methyl substitution in the N-phosphorus series results in dramatic lowering of activity.

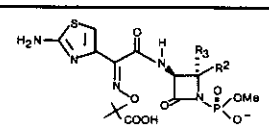
The good stability of two significantly active N-phosphorus compounds to β-lactamases is reflected in Table 5, especially in the case of the 4α-methyl compound SQ 27,327. By comparison, the N-O-phosphorus compounds in Table 6 are less lactamase stable, the β-methyl derivative SQ 28,235, being more stable than the α-methyl analog SQ 28,112 or the 4-unsubstituted compound SQ 28,870. The N-O-phosphorus compounds have significant activity against Pseudomonas aeruginosa.

Table 4.
Influence of C-4 Substitution on Intrinsic Activity of 2-Oxoazetidine-1-Phosphonates and 1-Phosphates



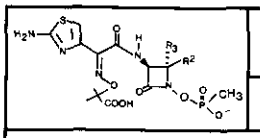
	X	$-P(=O)(OCH_3)O^-$			$-O-P(=O)(CH_3)O^-$		
	R_2	H	H	CH_3	H	H	CH_3
	R_3	H	CH_3	H	H	CH_3	H
MIC (μg/ml) Agar Dil. 10^4 CFU							
Organism	**SC#**	**27,159**	**27,327**	**27,490**	**28,870**	**28,112**	**28,235**
Staph. aureus	1276	>100	>100	>100	>100	>100	>100
Staph. aureus	2400	>100	>100	>100	>100	>100	>100
E. coli	8294	6.3	3.1	>100	3.1	1.6	1.6
E. coli	10,857	0.8	0.8	50	0.8	<0.05	0.4
K. aerogenes	10,440	6.3	3.1	>100	3.1	0.8	3.1
Prot. mirabilis	3855	1.6	0.8	100	0.4	0.4	6.3
Prot. vulgaris	9416	1.6	0.4	25	0.8	<0.05	<0.05
Ent. cloacae	8236	1.6	1.6	>100	0.8	0.2	0.8
Ser. marcescens	9783	6.3	3.1	>100	1.6	0.4	1.6
Ps. aeruginosa	9545	25	12.5	>100	3.1	1.6	1.6
Ps. aeruginosa	8329	>100	>100	>100	3.1	1.6	3.1

Table 5.
Effect of C-4 Substitution on Activity of 2-Oxoazetidine-1-Phosphonates Against β-Lactamase Producing Organisms



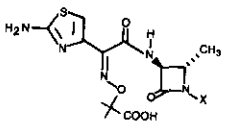
	R_2	H		H	
	R_3	H		CH_3	
MIC (μg/ml) Agar Dil. Inocula (CFU)		10^4	10^6	10^4	10^6
Organism	**SC#**	**27,159**		**27,327**	
E. coli TEM+	10,404	0.8	3.1	0.4	0.8
E. coli TEM−	10,439	1.6	1.6	0.8	0.8
Ent. cloacae P99+	10,435	>100	>100	6.3	50
Ent. cloacae P99−	10,441	1.6	3.1	0.8	1.6
K. aerogenes K1+	10,436	6.3	25	0.4	0.4
K. aerogenes K1−	10,440	0.8	1.6	0.4	0.8
K. pneumo.	11,066	1.6	3.1	1.6	1.6
C. freundii	10,204	0.8	>100	0.4	3.1
Prot. rettgeri	8,217	0.4	0.8	0.2	0.2
Prot. vulgaris	10,951B	0.8	3.1	0.4	0.4
Ser. marcescens	9,782	1.6	3.1	1.6	3.1
Ps. aeruginosa	8,329	>100	>100	>100	>100
Ps. aeruginosa	9,545	25	12.5	6.3	6.3

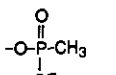
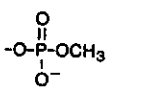
Table 6.
Effect of C-4 Substitution on Activity of 2-Oxoazetidine-1-O-Phosphonates Against β-Lactamase Producing Organisms



		R_2	H		H		CH_3	
		R_3	H		CH_3		H	
MIC (μg/ml) Agar Dil. Inocula (CFU)			10^4	10^6	10^4	10^6	10^4	10^6
Organism	**SC#**	**SQ#**	**28,870**		**28,112**		**28,235**	
E. coli TEM+	10,404		12.5	50	0.8	3.1	0.4	1.6
E. coli TEM−	10,439		0.8	1.6	0.8	1.6	0.8	1.6
Ent. cloacae P99+	10,435		>100	>100	100	>100	100	100
Ent. cloacae P99−	10,441		0.8	3.1	0.4	25	0.4	1.6
K. aerogenes K1+	10,436		>100	>100	>100	>100	50	100
K. aerogenes K1−	10,440		0.4	1.6	0.8	1.6	0.8	1.6
K. pneumo.	11,066		100	>100	3.1	25	3.1	3.1
C. freundii	10,204		0.8	3.1	0.8	50	0.4	25
Prot. rettgeri	8,217		0.1	0.8	<0.05	0.4	<0.05	0.4
Prot. vulgaris	10,951B		0.4	3.1	0.4	1.6	0.1	0.8
Ser. marcescens	9,782		3.1	12.5	0.8	3.1	1.6	3.1
Ps. aeruginosa	8,329		3.1	6.3	3.1	12.5	6.3	12.5
Ps aeruginosa	9,545		3.1	3.1	0.8	1.6	1.6	0.8

Table 7.
Comparison of a 2-Oxoazetidine-1-O-Phosphonate and its 1-O-Phosphate Analog Against β-Lactamase Producing Organisms

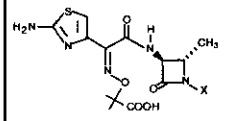


		X				
MIC (μg/ml) Agar Dil. Inocula (CFU)			10^4	10^6	10^4	10^6
Organism	**SC#**	**SQ#**	**28,112**		**28,225**	
E. coli TEM+	10,404		0.8	3.1	6.3	>100
E. coli TEM−	10,439		0.8	1.6	0.4	0.8
Ent. cloacae P99+	10,435		100	>100	100	>100
Ent. cloacae P99−	10,441		0.4	25	0.2	0.4
K. aerogenes K1+	10,436		>100	>100	>100	>100
K. aerogenes K1−	10,440		0.8	1.6	0.2	0.8
K. pneumo.	11,066		3.1	25	25	>100
C. freundii	10,204		0.8	50	0.4	100
Prot. rettgeri	8,217		<0.05	0.4	<0.05	0.2
Prot. vulgaris	10,951B		0.4	1.6	0.1	6.3
Ser marcescens	9,782		0.8	3.1	0.4	1.6
Ps. aeruginosa	8,329		3.1	12.5	3.1	12.5
Ps aeruginosa	9,545		0.8	1.6	1.6	1.6

Increasing the oxidation state of phosphorus in the O-phosphorus activated series (Table 7) results in a decrease in lactamase stability; however, activity against Pseudomonas aeruginosa is undiminished.

A comparison of various 4α-methyl N-1 activated monocyclic azetidinones, including aztreonam (SQ 26,776), is given in Table 8. The O-activated derivatives, SQ 28,511 and SQ 28,112, although possessing good intrinsic activity, lack the β-lactamase stability of aztreonam. The N-phosphonic acid, SQ 27,327, exhibits the best lactamase stability, but has less intrinsic activity, particularly against Pseudomonas aeruginosa. Overall, the C-4 substituted monobactam N-1 sulfonates provide the most favorable combination of intrinsic antimicrobial activity and β-lactamase stability.

Table 8.
Comparison of Aztreonam and N-1 Congeners Against β-Lactamase Producing Organisms

		X	$-SO_3^-$		$-OSO_3^-$		$-P(=O)(O^-)-OCH_3$		$-O-P(=O)(O^-)-CH_3$	
MIC (μg/ml) Agar Dil. Inocula (CFU)			10^4	10^6	10^4	10^6	10^4	10^6	10^4	10^6
Organism	**SC#**	**SQ#**	**26,776**		**28,511**		**27,327**		**28,112**	
E coli TEM+	10,404		<0.05	0.2	25	>100	0.4	0 8	0.8	3.1
E. coli TEM−	10,439		0 1	0.1	0.2	0.8	0 8	0.8	0 8	1 6
Ent. cloacae P99+	10,435		25	50	>100	>100	6.3	50	100	>100
Ent. cloacae P99−	10,441		0.1	0.1	0.2	0.4	0.8	1 6	0.4	25
K. aerogenes K1+	10,436		25	>100	>100	>100	0.4	0.4	>100	>100
K. aerogenes K1−	10,440		*<0.05*	*0 1*	*0.2*	*0.8*	*0.4*	*0.8*	*0.8*	*1.6*
K. pneumo	11,066		0.4	0.8	100	>100	1.6	1.6	3.1	25
C. freundii	10,204		0.1	0.2	0.8	25	0.4	3.1	0.8	50
Prot. rettgeri	8,217		<0.05	1.6	<0.05	0.2	0.2	0.2	<0.05	0 4
Prot. vulgaris	10,951B		<0.05	<0.05	0.1	0.8	0.4	0 4	0 4	1.6
Ser. marcescens	9,782		0.1	0.4	0.4	1.6	1.6	3 1	0 8	3.1
Ps. aeruginosa	8,329		1.6	6.3	3.1	6.3	>100	>100	3.1	12.5
Ps. aeruginosa	9,545		0.4	0 4	—	—	6.3	6.3	0.8	1.6

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