It should be noted that *no* desulfurization products (monosulfides) were observed. When the above reaction was performed at room temperature in acetonitrile for 20 h or at room temperature in benzene for 4 days, no reaction was observed.

In the absence of **2a**, there was no trace of reaction (GC) after 16 h at reflux in acetonitrile.

Attempted Desulfurization of Dibenzyl Disulfide by 2a. A solution of dibenzyl disulfide (246 mg, 1.0 mmol) and **2a** (288 mg, 1.1 mmol) in 5 mL of dry acetonitrile or benzene was heated at reflux (bath 100 °C); after 14 h there was no reaction observed (GC).

Reaction of a Mixture of Two Dialkyl Disulfides with 2e. This reaction was performed as described above for the analogous reaction with **2a**, utilizing **2e** (163 mg, 1.0 mmol) in place of **2a**. In this case, $BuSSCH_2Ph$ (exchange product) and $PhCH_2SSCH_2Ph + (Me_2N)_3PS$ (desulfurization products) were formed at similar rates (GC) for reaction at room temperature in acetonitrile, 50 °C in benzene, and room temperature in benzene.

Reaction of a Mixture of Dibenzyl and Di-*p*-tolyl Trisulfides with 2a or 2e. To a solution of dibenzyl trisulfide[38] (278 mg, 1.0 mmol) and di-*p*-tolyl trisulfide[38] (278 mg, 1.0 mmol) in 6 mL of benzene was added **2a** (262 mg, 1.0 mmol). Analysis by NMR (C_6H_6) after 5 min at room temperature indicated the presence of *p*-$TolSSSCH_2Ph$ ($PhCH_2$, δ 3.75), *p*-$TolSSCH_2Ph$ ($PhCH_2$, δ 3.65), $(PhCH_2S)_2S$ ($PhCH_2$, δ 3.72), $(PhCH_2S)_2$ ($PhCH_2$, δ 3.38); presumably $(p\text{-TolS})_2S$ and $(p\text{-TolS})_2$ were also present (4-CH_3-C_6H_4, coincidental at δ 2.0). Except for the benzyl *p*-tolyl trisulfide peak for which no authentic sample was available, the identities of all peaks were confirmed by the addition of authentic samples. (Analysis by GC or GC/MS was not possible due to decomposition of the trisulfides in the GC). Reaction as above utilizing **2e** in place of **2a** gave similar results.

Reaction of a Mixture of Dibenzyl and Dipropyl Trisulfides (1j,k) with 2a or 2e. To a solution of dibenzyl trisulfide (**1j**) (28 mg, 0.1 mmol) and di-*n*-propyl trisulfide (**1k**)[38] (18 mg, 0.1 mmol) in 0.5 mL of benzene was added **2a** (26 mg, 0.1 mmol). The reaction at room temperature was monitored by both GC and NMR; after 3 h, a small amount of $PrSSSCH_2Ph$ (**1l**) had formed, after ca. 15 h, complete exchange had occurred ($PrSSSCH_2Ph$:$(PhCH_2S)_2S$ = 2:1 by NMR) without formation of any disulfides, and after 5 days the desulfurization reaction was essentially complete, resulting in a mixture of the three possible trisulfides and three possible disulfides and Ph_3PS. The identities of these components were confirmed by GC/MS and comparison (GC, NMR) with authentic samples: for benzyl *n*-propyl trisulfide (**1l**),[7a,54] NMR (C_6H_6) δ 3.80 (s, $PhCH_2$); chemical ionization (isobutane) MS, *m/e* (rel intensity) 231 (92, $M^+ + 1$), 199 (100, $M^+ + 1$-S); and for benzyl *n*-propyl disulfide,[7a] NMR (C_6H_6) δ 3.50 (s, $PhCH_2$); MS, *m/e* (rel intensity) 198 (7, M^+), 91 (100, $C_7H_7^+$); chemical ionization (isobutane) MS, *m/e* 199 (100, $M^+ + 1$). When the above reaction was repeated, utilizing 0.5 mL of acetonitrile-d_3 in place of benzene, complete exchange to $PrSSSCH_2Ph$ without formation of any disulfides occurred within 7 min at room temperature (NMR); complete desulfurization to a mixture similar to that obtained above was achieved within 23 h at room temperature. When the above two experiments were repeated, utilizing **2e** (16 mg, 0.1 mmol) in place of **2a**, NMR and GC analyses showed a mixture of exchange reaction and desulfurization products to be present after 5 min at room temperature.

In the absence of **2a** or **2e**, there was no trace of reaction or exchange after 14 days at room temperature in either acetonitrile-d_3 or benzene.

Reaction of Dibenzyl Trisulfide (1j) with 0.5 Molar Equiv of 2a or 2e. A solution of **1j** (28 mg, 0.1 mmol) and **2a** (13 mg, 0.05 mmol) in 0.5 mL of benzene showed no reaction (NMR) after 20 h at room temperature, but within 24 h at ca. 65 °C, a mixture of dibenzyl trisulfide and disulfide (ca. 1:1) plus tetrasulfide (ca. 7%) had formed. For $(PhCH_2SS)_2$, NMR (C_6H_6) δ 3.8 (s, $PhCH_2$); the identity of this peak was confirmed by the addition of authentic dibenzyl tetrasulfide.[55] When the above reaction was repeated, utilizing 0.5 mL of acetonitrile-d_3 in place of benzene, essentially identical results were obtained within 5 h at room temperature. When the above two experiments were repeated, utilizing **2e** (9.1 μL, 0.05 mmol) in place of **2a**, reaction in CD_3CN gave similar results (ca. 8% tetrasulfide) within 30 min at room temperature, but in benzene there was no significant formation of tetrasulfide; the products formed within 30 min at room temperature were 1:1 dibenzyl trisulfide and disulfide.

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada for financial support of this work. We are most grateful for helpful discussions on radiochemistry and radiochemical techniques with Professor J. J. Hogan.

Registry No. 1g, 27694-48-0; **1h**, 82891-19-8; **1i**, 82916-72-1; **1j**, 6493-73-8; **1k**, 6028-61-1; **1l**, 75030-40-9; **2a**, 603-35-0; **2b**, 1038-95-5; **2c**, 855-38-9; **2d**, 1159-54-2; **2e**, 1608-26-0; **2f**, 5815-61-2; **4a**, 82891-20-1; **4b**, 82902-14-5; **5**, 33877-16-6; **6**, 82916-73-2; $^{35}SCl_2$, 31602-27-4; ethylenediamine, 107-15-3; phenylmethanethiol, 100-53-8; 1-propanethiol, 107-03-9; (−)-sodium *O*-methyl dithiocarbonate, 37601-89-1; (−)-menthol, 2216-51-5; (±)-1-bromo-1-phenylethane, 38661-81-3; di-*p*-tolyl disulfide, 103-19-5; methyl phenyl disulfide, 14173-25-2; benzyl *p*-tolyl disulfide, 16601-19-7; methyl *p*-tolyl disulfide, 57266-34-9; benzyl phenyl disulfide, 16601-17-5; dibenzyl disulfide, 150-60-7; di-*n*-butyl disulfide, 629-45-8; benzyl *n*-butyl disulfide, 16601-16-4.

(55) Harpp, D. N.; Steliou, K.; Chan. T. H. *J. Am. Chem. Soc.* **1978**, *100*, 1222.

O-Sulfated β-Lactam Hydroxamic Acids (Monosulfactams). Novel Monocyclic β-Lactam Antibiotics of Synthetic Origin[1]

E. M. Gordon,* M. A. Ondetti, Jelka Pluscec, C. M. Cimarusti, D. P. Bonner, and R. B. Sykes

Contribution from The Squibb Institute for Medical Research, Princeton, New Jersey 08540.
Received January 27, 1982

Abstract: Monocyclic β-lactams bearing an $O\text{–}SO_3^-$ substituent at N-1 have been shown to be isolable chemical entities and represent a novel class of totally synthetic monocyclic β-lactam antibiotics. Several syntheses and the biological activity of such O-sulfated β-lactam hydroxamic acids are described.

Several years ago we set out to test the hypothesis that antimicrobial activity in β-lactam antibiotics was not rigidly dependent upon the bicyclic framework possessed by most β-lactam antibiotics. Rather, we postulated that a bicyclic ring fused azetidinone structure may be only one method of achieving suitable β-lactam activation[2] and that if sufficient ring reactivity could be induced by an alternative mechanism, within the constraints imposed by other well-documented structural requirements,[3] antimicrobial activity might be achievable. Thus, simple monocyclic β-lactams, when suitably equipped with electron-withdrawing substituents, could prove to possess significant antimicrobial ac-

(1) Dedicated to the memory of Professor David Perlman.

(2) Bioactivation of bicyclic azetidinone antibiotics may occur by "flattening", as suggested by: Rando, R. *Acc. Chem. Res.* **1975**, *8*, 281.

(3) A properly positioned anionic charge and (in most cases) a 3β-amido substituent are crucial. The importance of azetidinone nitrogen in enzyme binding has also been studied. Gordon, E. M.; Pluscec, J.; Ondetti, M. A. *Tetrahedron Lett.* **1981**, 1871.

0002-7863/82/1504-6053$01.25/0

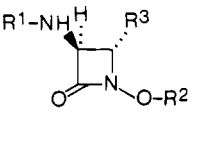
Table I. Biological Activity of O-Sulfated β-Lactam Hydroxamic Acids (Monosulfactams)

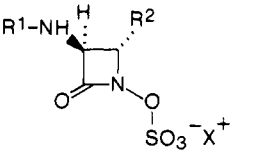
organism	SC No	compound number 4	5	8	9	29	31	37	43	Pen G K salt
Staphylococcus aureus	1276	>100	0.4	>100	3.1	1.6	0.8	100	3.1	<0.05
Staphylococcus aureus	2399	>100	0.8	>100	3.1	1.6	0.8	>100	3.1	<0.05
Staphylococcus aureus	2400	>100	0.8	>100	3.1	1.6	0.8	>100	12.5	3.1
Staphylococcus aureus	10165	>100	16	>100	12.5	6.3	0.8	>100	100	50
Streptococcus faecalis	9011	>100	50	>100	100	6.3	25	>100	100	1.6
Streptococcus agalactiae	9287	>100	0.2	>100	0.8	0.1	0.2	25	<0.05	<0.05
Micrococcus luteus	2495	>100	0.8	>100	0.4	0.4	0.4	1.6	0.8	<0.05
Escherichia coli	8294	>100	50	>100	25	0.4	25	>100	1.6	50
Escherichia coli	10857	>100	25	>100	12.5	0.2	25	25	<0.05	12.5
Escherichia coli	10896	>100	100	>100	100	0.8	50	100	1.6	>100
Escherichia coli	10909	>100	25	>100	12.5	0.2	12.5	>100	0.1	12.5
Klebsiella aerogenes	10440	>100	50	>100	25	0.8	25	>100	1.6	25
Klebsiella pneumoniae	9527	>100	50	>100	25	0.4	25	50	<0.05	50
Proteus mirabilis	8855	>100	25	>100	12.5	0.2	12.5	50	0.4	6.3
Proteus rettgeri	8479	>100	6.3	>100	6.3	<0.05	12.5	6.3	0.2	3.1
Proteus vulgaris	9416	>100	25	>100	50	0.2	25	25	<0.05	6.3
Salmonella typhosa	1195	>100	50	>100	12.5	0.2	25	25	0.2	3.1
Shigella sonnei	8449	>100	50	>100	25	0.2	25	>100	1.6	50
Enterobacter cloacae	8286	>100	>100	>100	>100	0.4	>100	>100	0.8	>100
Enterobacter aerogenes	10078	>100	>100	>100	50	0.4	>100	>100	3.1	>100
Citrobacter freundii	9518	>100	>100	>100	>100	3.1	>100	>100	3.1	>100
Ser. marcescens	9783	>100	>100	>100	>100	12.5	>100	>100	6.3	>100
Pseudomonas aeruginosa	9545	>100	100	>100	100	0.4	12.5	50	0.4	50
Pseudomonas aeruginosa	8329	>100	>100	>100	>100	3.1	100	>100	3.1	>100
Acinetobacter calcoaceticus	8333	>100	>100	>100	>100	25	100	>100	12.5	100

[a] Minimum inhibitory concentration (μg/mL), agar dilution: 10^4 cfu.

tivity.[4,5] One approach to the exploration of this idea was to investigate monocyclic azetidinone activation by heteroatom attachment at N-1. Our initial efforts focused on the introduction of an N-1 oxygen substituent. Although *N*-hydroxy β-lactams had been previously prepared by Testa[6] et al., these materials lacked 3β-amido functionalities. More recently, Miller has reported preparation of an *N*-hydroxy β-lactam containing an *N*-tert-Boc-3β-amino substituent.[7,8] With the use of this method, *N*-((benzyloxy)carbonyl)azetidinone **1** was synthesized from L-serine (Chart I). Treatment of **1** with cold trifluoroacetic acid followed by acylation with phenylacetyl chloride afforded **3** in low yield (20%). Hydrogenolysis of **3** (preferably prepared from (phenylacetyl)-L-serine[8,9]) produced the previously unreported

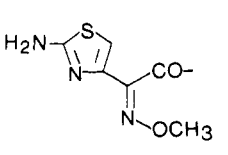
Chart I





No	R1	R2	R3
1	Boc	$-CH_2Ph$	-H
2	H	$-CH_2Ph$	-H
3	$PhCH_2CO$	$-CH_2Ph$	-H
8	$PhCH_2CO$	-H	$-CH_3$
13	$PhCH_2OCO$	$-CH_2Ph$	-H
15	$PhCH_2OCO$	-H	-H
16	$PhCH_2OCO$	$-C(CH_3)_3$ (O)	-H
20	Boc	-H	-H
41	(30)	$-CH_2Ph$	$-CH_3$
42	(40)	$-CH_2Ph$	$-CH_3$

No.	R1	R2	X
7	$PhCH_2CO$	H	K
9	$PhCH_2CO$	$-CH_3$	Pyr
14	$PhCH_2CO$	H	$(Bu)_4N$
17	$PhCH_2OCO$	-H	$(Bu)_4N$
29	(30)	-H	K
31	2-Thienyl-CH_2CO	-H	K
43	(40)	$-CH_3$	Pyr



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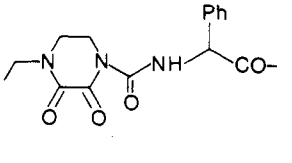

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N-hydroxy β-lactam **4** as a stable crystalline solid[10] whose structure was confirmed by an X-ray crystallographic analysis.[11] This substance exhibited no significant antibiotic activity.

Subsequent to the studies described above, we isolated a series of naturally occurring β-lactam antibiotics possessing a sulfonate residue attached to azetidinone nitrogen (–N–SO_3^-, monobactams (**6**)).[12,13] The potent antimicrobial activity of derivatives of this

(4) It has been postulated that the nocardicins, a novel series of naturally occurring monocyclic β-lactam antibiotics, may express their antimicrobial effect in vivo but not in vitro due to biotransformation to a quinone–methide intermediate. The driving force toward rearomatization should induce considerable weakening of the azetidinone lactam bond. See: Just, G.; Liak, T. J. *Can. J. Chem.* **1978**, *56*, 211. Hakimelahi, G. H.; Just, G. *Ibid.* **1979**, *57*, 1932. Boucherat, D.; Pilgrim W. R. *Tetrahedron Lett.* **1979**, 5063.

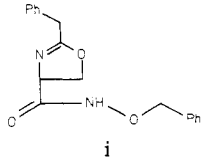
(5) The biological activity expressed by another monocyclic β-lactam β-lactam antibiotic has been attributed to its in situ conversion to a bicyclic bis(noriso)penicillin. See: Huffman, W. F.; Hall, R. F.; Grant, J. A.; Holden, K. G. *J. Med. Chem.* **1978**, *21*, 415.

(6) Nicolaus, B. J. R.; Bellosio, E.; Pogani, G.; Testa, E. *Gazz. Chim. Ital.* **1963**, *93*, 618.

(7) Mattingly, P. G.; Kerwin, J. F., Jr.; Miller, M. J. *J. Am. Chem. Soc.* **1979**, *101*, 3983.

(8) Miller, M. J.; Mattingly, P. G.; Morrison, M. A.; Kerwin, J. F., Jr. *J. Am. Chem. Soc.* **1980**, *102*, 7026.

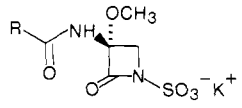
(9) However, it is noted that **3** prepared by deprotection and acylation (i.e., **1** → **2** → **3**) exhibited $[\alpha]^{26}_D$ –3.0° (*c* 0.92, MeOH), mp 126–128 °C, whereas the material obtained via (phenylacetyl)serine exhibits $[\alpha]^{26}_D$ +3.3° (*c* 0.44, MeOH), mp 130–131 °C. Miller reports $[\alpha]^{20}_D$ +9.1° (*c* 2.2, CH_3OH) for 3. We find that the coproduced oxazoline i possesses $[\alpha]^{26}_D$ +104.4° (*c* 0.675, CH_3OH). Since this material is difficult to completely remove from **3**, it is likely that the discrepancies in $[\alpha]_D$ of this substance are due to the presence of small quantities of i.



i

(10) This route could, in principle, be attended by racemization via intermediacy of an oxazolone. Since the same sequence when applied to L-threonine gives rise to a single diastereomer, we feel significant racemization is not a problem during *O*-benzylhydroxylamine coupling.

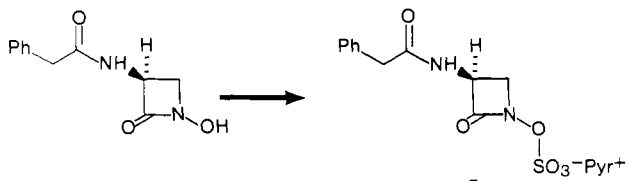
(11) The X-ray crystallographic analysis was performed by Professor J. Z. Gougoutas and M. Malley. A paper discussing the salient structural relationships of several monocyclic β-lactams will appear in due course.



6

structure[14,15] demonstrates that heteroatom attachment at β-lactam nitrogen can indeed provide a viable alternative pathway toward β-lactam activation. One explanation for the biological inactivity of **4** is the lack of substantial β-lactam reactivity. Indeed, the effect of hydroxamic acid ionization would be to deactivate the lactam bond by displacement of electron density into the ring. A second explanation is the improper placement of the essential anionic charge. It was postulated that an N-1 O-SO_3^- substituent could overcome the above obstacles by significantly increasing ring activation via its electronegativity, obviating hydroxamic acid ionization, and, simultaneously, more properly positioning an anionic charge.

To this end, sulfation of **4** (pyridine–sulfur trioxide complex/pyridine/26 °C, 2 h) afforded, after reverse-phase chromatography (HP 20-AG resin), substance **5** as a white powder



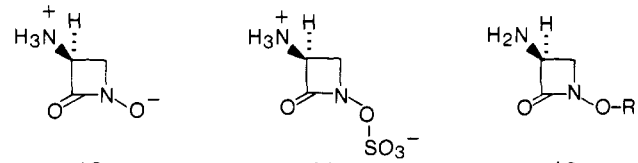
4 5

(42%), which was transformed to potassium salt **7** by passage through Dowex 50W (K^+ form) resin. Both **5** and **7**, in sharp contradistinction to **4**, have significant antibiotic activity (see Table I). To our knowledge, this is the first appearance of O-sulfated β-lactam hydroxamates in the chemical literature; indeed there are only a few reports of any O-sulfated hydroxamic acids.[16]

Following the aforementioned methodology, we synthesized biologically inactive *N*-hydroxy β-lactam **8** from L-threonine. Sulfation of **8** (pyridine–sulfur trioxide complex/pyridine/26 °C/5 h) afforded O-sulfated hydroxamate, **9**, which also showed antibiotic activity (Table I).[17]

In order to efficiently explore the chemical and biological scope of these observations, we next sought direct access to the fully elaborated, unacylated nucleus. Among these efforts were included the development of convergent synthetic approaches to **10**, **11**, and **12**.

Nucleus **10** was prepared first. Cbz-β-lactam **13** was synthesized by the reported route.[8] Attempts at chemoselective

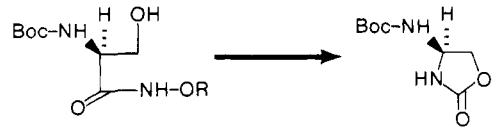


10 11 12

hydrogenolysis of **13**, which could be useful in obtaining **11** or **12**, were thwarted. No chemoselectivity was observed even under transfer-hydrogenation conditions[18] wherein controlled quantities of 1,4-cyclohexadiene were employed. Exhaustive hydrogenolysis of **13** removed both protecting groups to afford, after lyophilization, nucleus **10** as a pale yellow solid (approximately 90% pure by TLC and electrophoretic analysis). Substance **10** is zwitterionic and unstable at pH 7. Several attempts at N-acylation of this material were not promising, and attention was turned to other avenues. Our synthesis of nucleus **11** demanded chemical discrimination between nitrogen and oxygen protecting groups of a suitable β-lactam precursor. Sensitivity of the *N*-alkoxyazetidinone nucleus to acids necessitated further restriction of both protecting groups to those removable under neutral or basic conditions.

Since **7** forms an organic extractable (CH_2Cl_2) ion pair (**14**) with tetrabutylammonium hydrogen sulfate, which is returned unchanged from hydrogenolytic conditions, Cbz-*N*-hydroxy β-lactam **15** was expected to serve as a key intermediate that could be sulfated and then deprotected to give **11**. To this end, we prepared **16** but noted, as did Miller, the failure of commonly employed depivalating conditions to transform **16** to **15**.[19] However, our further investigations revealed that successful deprotection of **16** could in fact be achieved with $NaOH/H_2O_2/CH_3OH/H_2O$, or $Na_2S/H_2O/THF$,[20] to afford Cbz-*N*-hydroxy β-lactam **15** as a crystalline solid (40–50%). Sulfation followed by ion-pair extraction gave intermediate **17**.

In another approach to **15**, Boc-protected hydroxamate **19** was employed as a model to study the possibility of redox (Ph_3P/diethyl azodicarboxylate) cyclization to *N*-hydroxy β-lactam **20**. Hydrogenolysis of *N*-benzyloxy derivative **18**[7,8] afforded acyclic hydroxamic acid **19** in greater than 90% yield. Reaction of this



18 R = -CH_2Ph
19 R = -H

21

substance with triphenylphosphine/diethyl azodicarboxylate could, a priori, lead to a multitude of products, including *N*-hydroxyazetidinone **20**, Boc-L-cycloserine, a dehydroalanyl hydroxamic acid, or a Lossen rearrangement product. In the event, Lossen-type rearrangement predominated to give an intermediate isocyanate that was immediately trapped by neighboring serine hydroxyl to yield **21**.[21]

A second and considerably more efficient synthesis of **17** is predicated on the use of the commercially available antibiotic D-cycloserine[22] as a source of O-protected hydroxylamine (Scheme I). Monoacylation of D-cycloserine with carbobenzyloxy chloride afforded Cbz-cycloserine (**22**; 76%).[23] Coupling (DCC, *N*-hydroxybenzotriazole/THF) of Cbz-D-cycloserine and Cbz-L-serine produced protected hydroxamate **23** as a crystalline solid

(12) 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.; Principle, P. A.; Rathnum, M. L.; Slusarchyk, W. A.; Trejo, W. H.; Wells, J. S. *Nature (London)* **1981**, *291*, 489.

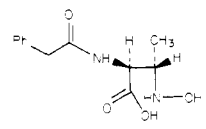
(13) Independently and simultaneously, workers at Takeda Co. reported on a similar series of natural products: Imada, A.; Kitano, K.; Kintaka, K.; Muroi, M.; Asai, M. *Nature (London)* **1981**, *289*, 590.

(14) Cimarusti, C. M.; Sykes, R. B.; Applegate, H. W.; Bonner, D. P.; Breuer, H.; Chang, H. W.; Denzel, Th.; Floyd, D. M.; Fritz, A.; Koster, W. H.; Liu, W.; Parker, W. L.; Rathnum, M. L.; Slusarchyk, W. *A.*; Treuner, U.; Young, M. Paper presented at the 182nd National Meeting of the American Chemical Society, New York, August 1981.

(15) Belgian Patent 887 428, 1981.

(16) Daniher has reported sulfation of benzohydroxamic acid to give crystalline water soluble O-sulfated hydroxamic acid salts. Boyland and Nery have reported synthesis *N*-(acetylphenyl)hydroxylamine-*O*-sulfonic acid by a similar sulfation: Dahiher, F. A. *J. Org. Chem.* **1969**, *34*, 2908. Boyland, E.; Nery, R. *J. Chem. Soc.* **1962**, 5217. Boyland, E.; Manson, D. *Biochem. J.* **1966**, *101*, 84.

(17) In one attempt at sulfation of threonine-derived *N*-hydroxy-β-lactam **8**, hydroxylamine ii was isolated as a minor product.



ii

(18) Felix, A. M.; Heimer, E. P.; Lambros, T. J.; Tzougraki, C.; Meienhofer, J. *J. Org. Chem.* **1978**, *43*, 4194.

(19) Mattingly, P. G.; Miller, M. J. *J. Org. Chem.* **1981**, *46*, 1557.

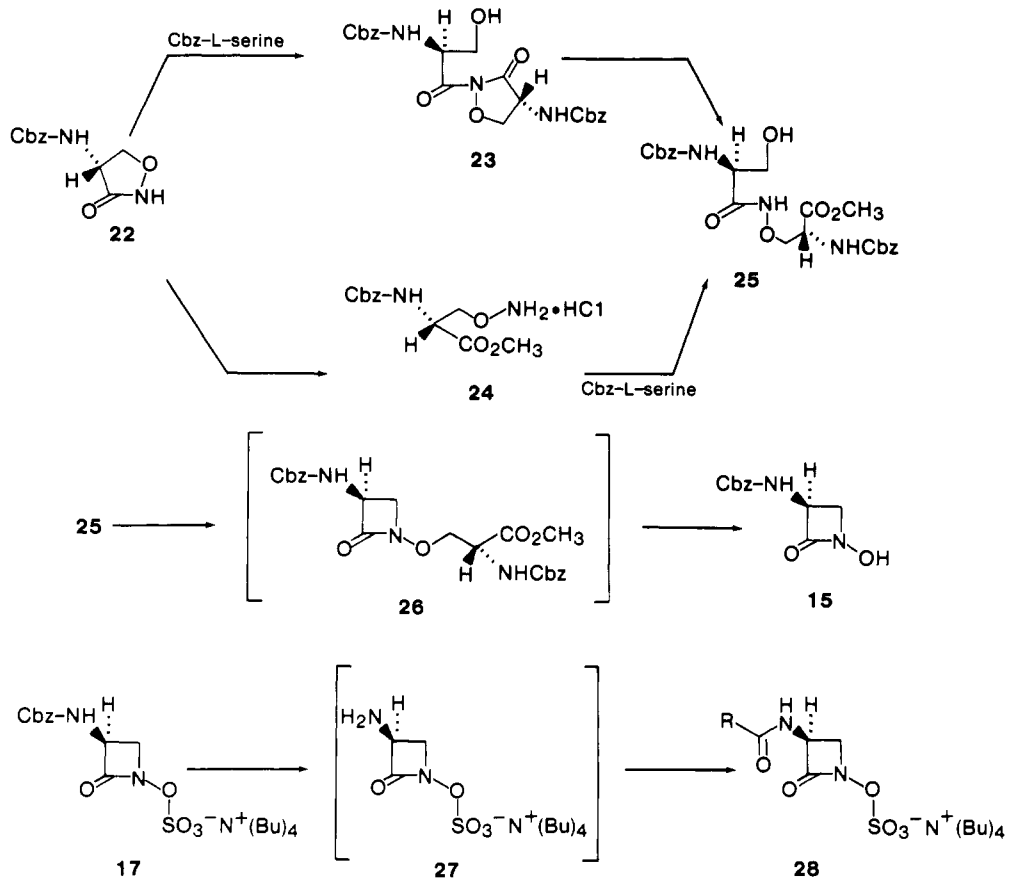
(20) Lammert, S. R.; Willis, A. I.; Chauvette, R. R.; Kokolja, S. *J. Org. Chem.* **1978**, *43*, 1243.

(21) Okada, Y.; Tsuda, Y.; Yagyu, M. *Chem. Pharm. Bull.* **1980**, *28*, 2254.

(22) Purchased from Sigma Co.

(23) Stammer, C. H. *J. Med. Chem.* **1970**, *13*, 1013.

Scheme I

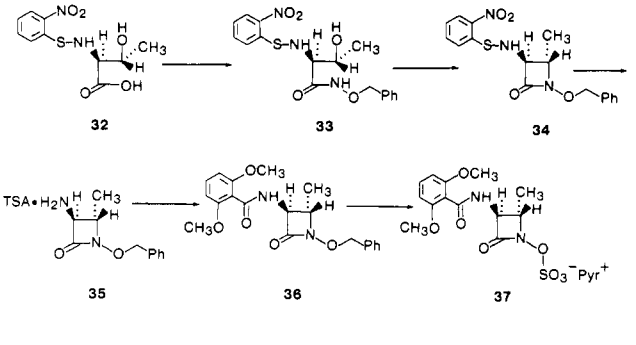


(85%). Methanolysis of **23** ($NaOCH_3/CH_3OH$) provided acyclic hydroxamate **25**. Alternatively, and preferably, methanolysis of **22** (HCl/CH_3OH) gave α-Cbz-β-aminoxy-D-alanine methyl ester hydrochloride (**24**; 88%), which, when coupled to Cbz-L-serine ((1-ethyl-3-(3-dimethylamino)propyl)carbodiimide/H_2O/pH 4.2), also produced **25** (82%). Cyclodehydration of hydroxamate **25** (Ph_3P/diethyl azodicarboxylate/THF) then yielded β-lactam **26**. Rather than perform a difficult purification of **26**, the crude reaction mixture was treated with DBU to initiate β elimination of Cbz-dehydroalanine methyl ester. In this way, **15** was easily separated from triphenylphosphine, bis(carbethoxy)hydrazine, and the dehydroalanine ester by acid–base extraction. The net result is a one-vessel transformation of **25** to crystalline **15** in 62% yield *without* chromatography. The optical rotation of this β-lactam was identical with that obtained via pivaloyl cleavage, confirming the stereochemical integrity of C-3.

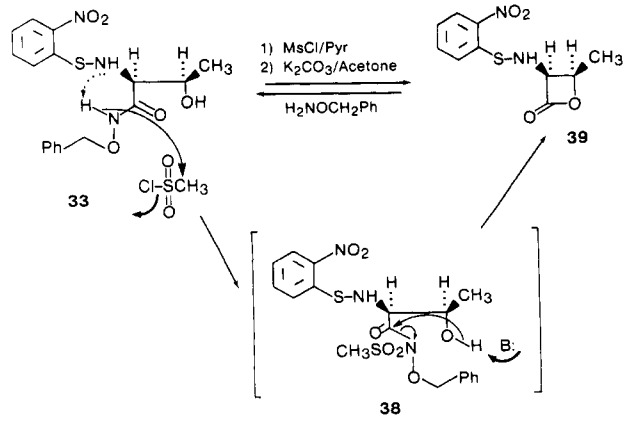
In practice, hydrogenolysis of **17** (DMF, 10% Pd/C) followed by in situ acylation of **27** (DCC/HBT) did produce a number of side-chain analogues (**28**) such as **29** and **31**, albeit in low yield. These materials were highly bioactive (see Table I).

To provide a more practical avenue to this class, our attention returned to utilization of nucleus **2**, a putative intermediate in the transformation of **1** to **3**. The low yields in this conversion were expected to be due to instability of the *N*(benzyloxy)azetidinone in trifluoroacetic acid, rather than to difficulties in acylation. This hypothesis proved correct and is borne out by the following experiments (Scheme II). Coupling (DCC/HBT/THF) of *N*-(*o*-nitrophenylsulfenyl)-L-threonine[24] and *O*-benzylhydroxylamine afforded hydroxamate **33**. Mesylation (MsCl/pyridine) followed by cyclization (K_2CO_3/acetone) yielded key intermediate **34** (24% isolated)[25] along with the intriguing crystalline β-lactone **39** (23%) (see Scheme III).

Scheme II



Scheme III



Since ring opening of **39** with *O*-benzylhydroxylamine cleanly returns the original hydroxamate (and not the corresponding allothreonine isomer), a plausible mechanism for its formation is given in Scheme III. The somewhat basic sulfenamide nitrogen

(24) Prepared by the method of: Zervas, L.; Borovas, D.; Gazis, E. *J. Am. Chem. Soc.* **1963**, *85*, 3660.

(25) For use of this reaction sequence in synthesis of monobactams, see: Floyd, D. M.; Fritz, A. W.; Cimarusti, C. M. *J. Org. Chem.* **1982**, *47*, 176.

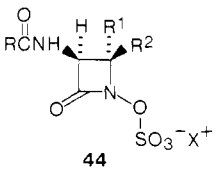
is implicated as an intramolecular base leading to N-mesylation. N-Mesylation or β-lactone formation is not observed in the identical system where *N*-Cbz or *N*-Boc protection is employed.[26]

The facile cleavage of sulfenamides by soft nucleophiles under acidic catalysis was then exploited to obtain nucleus **35**. Treatment of β-lactam **34** with equimolar amounts of *p*-thiocresol and *p*-TSA cleanly afforded **35** as a white crystalline powder (80%). Thus, this intermediate is accessible from L-threonine in four steps.[27]

Acylation of **35** proceeded uneventfully. This protected nucleus reacted smoothly with acid chlorides such, as 2,6-dimethoxybenzoyl chloride to give **36** (91%). Carboxylic acids (corresponding to Chart I, **30** and **40**) were also coupled with DCC/HBT/diisopropylethylamine/DMF. In this way **41** and **42** were synthesized. Hydrogenolysis of the above materials with 10% Pd/C (H_2) or freshly prepared palladium black (1,4-cyclohexadiene, EtOH, 1.5 h)[28] yielded the corresponding *N*-hydroxy analogues in high yield. In most cases these were immediately sulfated (pyridine–sulfur trioxide/pyridine) and purified by reverse-phase chromatography to give materials such as **37** and **43**. All of these substances display potent antimicrobial activity.

Conclusion

In summary, we have demonstrated that simple monocyclic β-lactams bearing an $-O-SO_3$ substituent at N-1 are isolable chemical entities and represent a novel class of totally synthetic monocyclic β-lactam antibiotics (**44**). The term



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"monosulfactams" is proposed to describe such monocyclic O-sulfated β-lactam hydroxamic acids, which are readily synthesized by the newly developed methodology described herein.

Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus are uncorrected. Proton nuclear magnetic resonance spectra were recorded on Varian Associates Model T-60 and XL100-15 spectrometers. Chemical shifts are reported as δ values (ppm) relative to tetramethylsilane as internal standard. ^{13}C NMR spectra were obtained on a Jelco FX60Q spectrometer and are reported in δ values as parts per million relative to internal tetramethylsilane. Infrared spectra were determined on Perkin-elmer Models 621 and 257 recording spectrophotometers. Optical rotations were obtained on a Perkin-Elmer 141 spectrophotometer. Analytical and preparative thin-layer chromatography (PLC) was carried out with E. Merck F-254 silica gel plates. Column chromatography was performed with Mallinckrodt SilicAR CC-7 or Merck silica gel 60. HP 20-AG is the analytical grade of a macroreticular polystyrene–divinylbenzene copolymer available from Mitsubishi Chemical Industries, Ltd.

1-(Benzyloxy)-3-((phenylacetyl)amino)-2-azetidinone (3) from 3-((*tert*-Butoxycarbonyl)amino)-1-(benzyloxy)-2-azetidinone (1). To a cold solution (0 °C) of **1** prepared according to Miller[7,8] in dry methylene chloride (10 mL) was added trifluoroacetic acid (10 mL). The reaction mixture was stirred for 0.5 h, toluene (100 mL) was added, and the mixture was concentrated to an oil. The toluene chase was repeated twice more.

The resulting oil was dissolved in methylene chloride (30 mL) and triethylamine added (0.536 mL) followed by phenylacetyl chloride (0.291 mL, 2.2 equiv, 0.341 g). After being stirred for 1 h, the mixture was poured into ethyl acetate (100 mL), washed successively with 10% $NaHCO_3$, 10% $KHSO_4$, and brine, and then dried over sodium sulfate. Upon concentration to an oil, crystals formed spontaneously (0.120 g, 20%). Four recrystallizations from ethyl acetate/hexane in the cold afforded an analytical sample: mp 126–128 °C; IR (KBr) 1770, 1655, 1545 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.11 (dd, 1 H), 3.53 (s, 2 H, superimposed on t, 1 H), 4.61 (m, 1 H), 2.93 (s, 2 H), 6.56 (m, 1 H), 7.28 (s, 5 H), 7.36 (s, 5 H); ^{13}C NMR ($CDCl_3$) δ 43.0 (t), 52.2 (d), 54.0 (t), 77.7 (t), 162.7 (s), 171.5 (s) (aromatics omitted); $[\alpha]^{26}_D$ −3.04° (*c* 0.92, CH_3OH). Anal. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.84; N, 9.02. Found: C, 69.17; H, 5.76; N, 8.92.

1-(Benzyloxy)-3-((phenylacetyl)amino)-2-azetidinone (3) was prepared from *N*-(phenylacetyl)serine essentially by the method of Miller[8] (triphenylphosphine/diethyl azodicarboxylate/THF). The product obtained in 34% yield following chromatography was recrystallized from ethyl acetate/hexane: mp 130–131 °C; $[\alpha]^{26}_D$ +3.37° (*c* 0.44, CH_3OH); IR and ^1H NMR spectra same as above.

This material was usually accompanied by small amounts of oxazoline i (white needles): mp 99–100 °C; IR (KBr) 1670, 1658, 1628 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.56 (s, 2 H), 4.50 (s, 2 H superimposed on 1 H, t), 4.90 (s, 2 H), 7.26 (s, 5 H), 7.36 (s, 5 H), 9.21 (br s, 1 H); mass spectrum, *m/e* 310 (M^+); ^{13}C NMR ($CDCl_3$) δ 34.3 (t), 67.2 (d), 69.9 (t), 78.1 (t), (aromatic omitted), 168.4, 169.3; $[\alpha]^{26}_D$ +104.4° (*c* 0.675, CH_3OH). Anal. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.86; N, 9.03. Found: C, 69.79; H, 6.10; N, 9.19.

Preparation of *N*-Hydroxy β-Lactam 4. A solution of **3** (1.10 g, 3.55 mM) in absolute ethanol (250 mL) containing 10% Pd/C was hydrogenated under atmospheric pressure at 26 °C for 1 h. The reaction mixture was filtered and the catalyst washed well with ethanol. The combined filtrate and washings were concentrated under reduced pressure to a solid residue (0.77 g, >99%). Recrystallization from methanol/chloroform afforded an analytical sample: mp 145–6 °C dec; IR (KBr) 1760, 1718, 1678 cm^{-1}; TLC R_f 0.64, $CHCl_3/CH_3OH$/88% formic acid (70:30:2); ^1H NMR (100 MHz, Me_2SO-d_6) δ 3.28 (dd, 1 H, *J* = 5, 2 Hz), 3.44 (s, 2 H), 3.70 (dd, 1 H, *J* = 5, 5 Hz), 4.68 (m, 1 H), 7.26 (s, 5 H), 8.76 (d, 1 H, *J* = 8 Hz); ^{13}C NMR (CD_3OD) δ 43.3 (t), 53.2 (d), 55.0 (t), 164.7 (s), 174.3 (s); negative ferric chloride test for hydroxamic acids; $[\alpha]^{26}_D$ −96.4° (*c* 0.25, CH_3OH). Anal. Calcd for $C_{11}H_{12}N_2O_3 \cdot 0.25H_2O$: C, 58.78; H, 5.60; N, 12.46. Found: C, 59.06; H, 5.37; N, 12.51.

Monosulfactam 5 Pyridinium Salt. To a solution of *N*-hydroxyazetidinone **4** (0.150 g, 0.68 mM) in distilled pyridine containing 4-Å molecular sieves was added pyridine–sulfur trioxide complex (0.216 g, 1.36 mM) at 26 °C. After being stirred for 2 h, the reaction mixture was concentrated under reduced pressure, vacuum-dried, and then purified on HP 20-AG resin (25 mL). Elution with water and then 5% acetone/water, followed by lyophilization of the Rydon positive fractions, afforded **5** as a white, hygroscopic powder (0.110 g, 43%): IR (Nujol) 1772, 1652 cm^{-1}; ^1H NMR (100 MHz $CDCl_3/CD_3OD$) δ 3.55 (s, 2 H), 3.80 (dd, 1 H, *J* = 5, 2 Hz), 4.07 (dd, 1 H, *J* = 5, 5 Hz), 4.95 (m, 1 H), 7.24 (s, 5 H), 7.8–8.8 (due to pyridinium ion); ^{13}C NMR (D_2O, dioxane standard) δ 42.7 (t, Ph–CH_2–), 53.1 (d, –NH–CH–), 54.4 (t, –CH_2–N–OSO_3^-), 128–148 (aromatic), 165.3 (s), 175.7 (s); $[\alpha]^{26}_D$ +5.9° (*c* 0.64, H_2O); electrophoresis (250 *V*, pH 4.5 phosphate buffer, 1 h, visualized with UV and Rydon spray) +3.3 cm; TLC (all on E. Merck F254 silica gel) R_f 0.37 $CHCl_3/CH_3OH$/formic acid (70:30:2), 0.58 *n*-BuOH/CH_3CO_2H/H_2O (60:20:20), 0.69 $CH_3OH/CHCl_3$/formic acid (70:30:2), 0.56 *n*-BuOH/CH_3CO_2H/H_2O (60:20:20). Anal. Calcd for $C_{16}H_{17}N_3O_6S \cdot 0.5H_2O$: C, 49.47; H, 4.67; N, 10.81; S, 8.25. Found: C, 49.15; H, 4.74; N, 10.71; S, 8.34.

Monosulfactam 7 Potassium Salt. A solution of pyridinium salt **5** (1.5 g, 3.96 mM) in doubly distilled water was applied to a column of Dowex W2 (K^+ form) ion-exchange resin (150 mL). Elution with water (1.5 L) gave five fractions. After lyophilization, fraction 1 contained 1.33 g of white fluffy potassium salt (100%): IR (Nujol) 1772, 1650 cm^{-1}; ^1H NMR (100 MHz, D_2O) δ 3.65 (s, 2 H), 3.80 (dd, 1 H, *J* = 5, 2 Hz), 4.12 (dd, 1 H, *J* = 5, 5 Hz), 4.86 (dd, 1 H, *J* = 5, 2 Hz), 7.24 (s, 5 H); ^{13}C NMR (D_2O, dioxane standard) δ 42.8 (t), 53.1 (d), 54.5 (t); $[\alpha]^{26}_D$ +7.1° (*c* 0.7, H_2O); TLC, R_f as for **5**, 96% pure by spectrodensitometry at 215 nm.

Monosulfactam 14 Tetrabutylammonium Salt. To an aqueous (5 mL) solution of potassium salt **7** (93 mg, 0.275 mM) was added tetrabutylammonium hydrogen sulfate (102 mg, 0.302 mM). The solution was shaken for a few minutes, then saturated with NaCl, and extracted with methylene chloride (4 × 10 mL). The combined extracts were dried over sodium sulfate and concentrated under reduced pressure to an oil (112 mg, 83%): IR ($CHCl_3$) 1781, 1672 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.98 (m, 12 H), 1.52 (m, 16 H), 3.22 (m, 8 H), 3.57 (s, 2 H), 3.69 (dd, 1 H, *J* = 5, 2), 4.12 (dd, 1 H, *J* = 5, 5 Hz), 4.90 (m, 1 H), 6.82 (d, 1 H, *J* = 7 Hz), 7.26 (s, 5 H); 97% pure by TLC and electrophoretic spectrodensitometry at 215 nm. Anal. Calcd for $C_{11}H_{11}N_2O_6S \cdot C_{16}H_{36}N$: C, 59.85; H, 8.74; N, 7.75; S, 5.91. Found: C, 60.25; H, 9.40; N, 7.13; S, 5.51.

***N*-(Phenylacetyl)-L-threonine.** L-Threonine (35.7 g, 0.3 M) was dissolved in 1 N NaOH (1 L) and chilled to −5 to −10 °C. To the cold, mechanically stirred solution was added dropwise phenylacetyl chloride (46.3 g, 39.6 mL). The reaction mixture was stirred overnight as the temperature rose to 26 °C. The mixture was washed with ether, acidified

(26) Personal communication from Dr. D. M. Floyd.
(27) Yield reported for this sequence is not optimized.
(28) "Organic Syntheses"; Wiley: New York, 1979; Vol. 59, p 159.

to pH 2 with HCl, and extracted with ethyl acetate (2×). The combined extracts were dried over sodium sulfate and concentrated under reduced pressure until white crystalline solids formed. Ether was added to the mixture and the crystals were collected (34.8 g, 49%): mp 161–163 °C; IR (KBr) 1670 br, 1640 cm^{-1}.

Preparation of *N*-Hydroxy β-Lactam 8. *N*-Phenylacetyl)-L-threonine (9.5 g, 40 mM) was suspended in water (approximately 50 mL), and a solution of *O*-benzylhydroxyamine hydrochloride (7.04 g, 44 mM) in water (50 mL) was added. The pH of the stirred mixture was adjusted to 4.2 with 1 N KOH, and a solution of WSC [8.43 g, 44 mM, 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide hydrochloride] in water (50 mL) was added. The pH was maintained at 4.2 with 1 N HCl. After 30 min, an oily precipitate was present in the reaction vessel. The product was partitioned between ethyl acetate and brine, and the organic layer was then dried over sodium sulfate and concentrated to white solids (8.7 g, 63%), which were used directly.

To a cold (0 °C) solution of the above (7.5 g, 22 mM) in dry THF (200 mL) was added diethyl azodicarboxylate (4.2 g, 3.8 mL, 24.2 mM), followed by triphenylphosphine (6.43 g, 24.2 mM). The reaction mixture was stirred overnight at 26 °C under nitrogen. The solvent was then removed and the residue chromatographed on silica gel (ether/hexane) to afford the product (2.0 g, white solids, 28%). Recrystallization from chloroform/hexane afforded a purified sample: mp 97–99 °C; IR (KBr) 1755, 1648 cm^{-1}; ^{1}H NMR (100 MHz, $CDCl_3$) δ 1.25 (d, 3 H, J = 6 Hz), 3.42 (dd, 1 H, J = 6, 2 Hz), 3.55 (s, 2 H), 4.12 (dd, 1 H, J = 5, 2 Hz), 4.94 (s, 2 H), 6.18 (m, 1 H), 7.36 (m, 10 H).

A solution of the above β-lactam (0.5 g, 1.54 mM) in ethanol (15 mL) containing 10% Pd/C catalyst (0.25 g) was hydrogenated at 26 °C for 1 h. The reaction mixture was filtered, the catalyst was washed with ethanol, and the combined filtrates were evaporated to an oily residue. Trituration with ether afforded **8** as amorphous solids (0.340 g, 95%): IR (KBr) 1765 br, 1730 sh, 1655 cm^{-1}; ^{1}H NMR (100 MHz, CD_3OD) δ 1.37 (d, 2 H, J = 6 Hz), 3.53 (s, 2 H), 3.74 (d of q, 1 H, J = 6, 2 Hz), 4.24 (d, 1 H, J = 2 Hz), 7.27 (s, 5 H); mass spectrum, m/e 234 (M^+); TLC R_f 0.70 $CHCl_3/CH_3OH/HCO_2H$ (70:30:2), 0.72 *n*-BuOH/HOAc/H_2O (60:20:20), 100% pure by spectrodensitometry at 215 nm. Anal. Calcd for $C_{12}H_{14}N_2O_3$: C, 61.52; H, 6.02; N, 11.96. Found: C, 61.06; H, 6.03; N, 11.80.

Monosulfactam 9 Pyridinium Salt. To a solution of **8** (0.225 g, 0.96 mM) in dry pyridine (9 mL) was added 4A molecular sieves (1 mL), followed by pyridine–sulfur trioxide complex (0.61 g, 3.84 mM). The reaction mixture was stirred under nitrogen for 5 h at 26 °C and then filtered and concentrated under reduced pressure. Purification on HP-20 resin (water/acetone) afforded the product as a very hygroscopic white solid (0.130 g, 30%): IR (KBr) 1774, 1660 cm^{-1}; ^{1}H NMR (100 MHz, D_2O/DSS) δ 1.45 (d, 3 H, J = 6 Hz), 3.65 (s, 2 H), 4.19 (d of q, 1 H, J = 6, 2 Hz), 4.46 (d, 1 H, J = 2 Hz), 7.16 (s, 5 H), 7.8–8.8 (m, 5 H); TLC R_f 0.43 $CHCl_3/CH_3OH/HCO_2H$ (70:30:2), 0.59 *n*-BuOH/HOAc/H_2O (60:20:20), 0.69 $CH_3OH/CHCl_3/HCO_2H$ 70:30:2), 87% pure by ultraviolet spectrodensitometry at 215 nm, positive reaction with 4,4′-bis(dimethylamino)diphenylcarbinol and Rydon reagent. Anal. Calcd for $C_{12}H_{14}N_2O_5S\cdot H_2O$: C, 49.62; H, 5.14; N, 10.21; S, 7.79. Found: C, 50.37; H, 5.07; N, 10.32; S, 7.73.

In one attempt to sulfate *N*-hydroxy β-lactam **8**, the product was chromatographed on HP 20-AG, passed through a Dowex 50W (K^+ form) resin column, and finally rechromatographed on HP 20-AG. *N*-Hydroxy acid ii was isolated from this process in low yield after recrystallization from water: mp 164–165 °C dec; IR (KBr) 1720, 1625 cm^{-1}; ^{1}H NMR (100 MHz, Me_2SO) δ 0.93 (d, 3 H, J = 7 Hz), 3.26 (m, 1 H), 3.55 (s, 2 H), 4.54 (dd, 1 H, J = 5, 8 Hz), 7.27 (s, 5 H), 8.05 (d, 1 H, J = 8 Hz); mass spectrum, m/e 253 (M + 1).

Nucleus 10. 3-(((Benzyloxy)carbonyl)amino)-1-(benzyloxy)-2-azetidinone (**13**) was prepared by the method of Miller.[7,8] A solution of **13** (1.1 g, 3.37 mM) in ethyl acetate (50 mL) containing 10% Pd/C (0.5 g) was hydrogenated at atmospheric pressure for 2 h. The reaction mixture was filtered and the filtrate concentrated to a solid. After trituration with ethyl acetate, the residue was dissolved in water, washed with ethyl acetate, and lyophilized. Zwitterion **10** was obtained (0.158 g, 46%) as a white powder, which gradually yellowed: IR (Nujol) 1735, 1455 cm^{-1}; ^{1}H NMR (100 MHz) δ 3.48 (dd, 1 H, J = 6, 2 Hz, H_β), 3.83 (dd, 1 H, J = 5, 6 Hz, H_α), 4.22 (dd, 1 H, J = 5, 2 Hz, H_3); ^{13}C NMR (D_2O, dioxane standard) δ 51.4, 54.7; TLC 87% pure by ultraviolet spectrodensitometry. Anal. Calcd for $C_3H_6N_2O_2$: C, 35.29; H, 5.92; N, 27.44. Found: 35.81; H, 5.59; N, 25.11.

3-(((Benzyloxy)carbonyl)amino)-1-((pivaloyl)oxy)-2-azetidinone (16). This material was obtained in a like manner to Miller.[19] Recrystallization from ethyl acetate/hexane afforded white needles: mp 114–115 °C; IR (KBr) 1803, 1772, 1718, 1532 cm^{-1}; ^{1}H NMR (100 MHz, $CDCl_3$) δ 1.28 (s, 9 H), 3.62 (dd, 1 H, J = 6, 2 Hz), 3.98 (dd, 1 H, J = 6, 5 Hz), 4.89 (m, 1 H), 5.13 (s, 2 H), 5.32 (m, 1 H), 7.34 (s, 5 H); $[\alpha]^{26}_D$ +11.0° (*c* 0.58 CH_3OH). Anal. Calcd for $C_{16}H_{20}N_2O_5$: C, 59.99; H, 6.29; N, 8.75. Found: C, 59.52; H, 6.01; N, 8.69.

***N*-Hydroxy β-Lactam 15.** (**A**) To a cold (0 °C) solution of azetidinone **16** (0.160 g, 0.5 mM) in THF (5 mL) and water (2.5 mL) was added a solution of $Na_2S\cdot 9H_2O$ (0.120 g, 0.5 mM) in water (2.5 mL). The reaction mixture was stirred at 0 °C for 1 h and then poured into 10% $KHSO_4$ (25 mL) and extracted with ethyl acetate (3 × 50 mL). The combined extracts were dried over sodium sulfate and concentrated under reduced pressure to an oily residue, which crystallized as white solids (37 mg, 41%). Recrystallization from acetone/hexane (2×) afforded an analytical sample: mp 128–131 °C; $[\alpha]^{26}_D$ −4.0° (CH_3OH, *c* 0.25); IR (KBr) 1770, 1717 cm^{-1}; ^{1}H NMR (100 MHz, CD_3OD/$CDCl_3$) δ 3.48 (m, 1 H), 3.84 (dd, 1 H, J = 6, 4 Hz), 4.60 (m, 1 H), 5.10 (s, 2 H), 7.36 (s, 5 H); ^{13}C NMR (CD_3OD) δ 54.3, 55.3, 67.8. Anal. Calcd for $C_{11}H_{12}N_2O_4$: C, 55.92; H, 5.12; N, 11.86. Found: C, 55.64; H, 5.10; N, 11.73.

(**B**) To a cold (0 °C) suspension of **16** (3.2 g, 10 mM) in methanol (25 mL) were added a mixture of 1 N NaOH (10 mL) and 30% H_2O_2 (3.05 mL) in water (10 mL). The reaction mixture was stirred at 0 °C and after about 10 min became a clear solution. After 1 h, the volume was concentrated by one-half and the mixture poured into aqueous saturated $NaHCO_3$ (50 mL). The aqueous layer was washed with ethyl acetate (2 × 75 mL) and then acidified to pH 2 with 10% $KHSO_4$, saturated with salt, and extracted with ethyl acetate (4 × 100 mL). The combined organic extracts were dried over sodium sulfate and concentrated to a pale yellow gummy solid (2.3 g). Precipitation from a chloroform solution with hexane, followed by ether trituration, afforded pale yellow solids similar to the above product.

***N*-((Benzyloxy)carbonyl)-D-cycloserine (22).** This material was prepared according to the procedure of Stammer et al.[23] (76%): mp 123–127 °C; IR (KBr) 1735 br, 1540 cm^{-1}; ^{13}C NMR (CD_3OD) δ 54.5 (α-C), 67.9 ($PhCH_2O$–), 73.8 (β-C), 128.8, 129.0, 129.4, 137.8, 171.8.

α-((Benzyloxy)carbonyl)-β-aminoxy-D-alanine Methyl Ester Hydrochloride (24). Acetyl chloride (7.1 mL) was added dropwise to chilled (0–5 °C), stirred methanol (100 mL) to form an approximately 1 N solution of methanolic HCl. After 30 min, D-cycloserine (5.0 g) was added, and the suspension was stirred over 12 h while the temperature rose to 26 °C. The volatiles were removed by evaporation, and the residue was triturated with ether to yield a white crystalline mass (5.7 g, 88%) after drying in vacuo: mp 110–112 °C; IR (KBr) 1740, 1680 cm^{-1}; ^{1}H NMR (100 MHz, Me_2SO) δ 3.69 (s, 3 H), 4.28 (m, 2 H), 4.50 (m, 1 H), 5.08 (s, 2 H), 7.36 (s, 5 H).

Protected Hydroxamate 25. (**A**) To a suspension of Cbz-L-serine (3.46 g, 14.5 mM) in water (15 mL) was added an aqueous (15 mL) solution of **24** (4.49 g, 14.5 mM). The mixture was vigorously stirred (air stirrer), while adjusted to pH 4.2 with 1 N KOH. A solution of 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide (WSC) (14.5 mM) in water (10 mL) was added portionwise over 5 min, while the pH was maintained at 4.2 by addition of 1 N HCl. After an additional 20 min of stirring, the reaction mixture was saturated with NaCl and extracted with ethyl acetate (5×). The combined ethyl acetate extracts were dried over Na_2SO_4 and concentrated over reduced pressure to a viscous oil (5.8 g, 81.9%). The product was suitable for immediate use. In another run, a sample was purified by preparative TLC (3:1 $EtOAc/CH_2Cl_2$) to give a pure white foam: IR ($CHCl_3$) 1700 br cm^{-1}; ^{1}H NMR (100 MHz, $CDCl_3$) δ 3.65 (s, 3 H), 4.13 (m, 4 H), 4.56 (br m, 2 H), 5.08 (s, 2 H), 5.10 (s, 2 H), 5.92 (d, 1 H, J = 7 Hz), 6.54 (br m, 1 H), 7.30 (s, 10 H), 9.72 (br s, 1 H); ^{13}C NMR (CD_3OD) δ 52.8, 54.4, 56.2, 62.6, 67.7, 76.2, 128.6, 129.2, 137.5, 158.1, 170.1, 171.4.

(**B**) **Via 23.** To a stirred solution of Cbz-D-cycloserine (4.32 g, 20 mM) in THF (200 mL) were added Cbz-L-serine (4.38 g, 20 mM), *N*-hydroxybenzotriazole (3.06 g, 20 mM), and dicyclohexylcarbodiimide (4.12 g, 20 mM). After 12 h of stirring at 26 °C, the mixture was filtered and concentrated under reduced pressure. The residue was redissolved in ethyl acetate (250 mL), washed with aqueous sodium bicarbonate (3 × 100 mL), and 10% $KHSO_4$ (3 × 100 mL), and then dried over sodium sulfate and concentrated to a white solid residue (7.1 g, 85%). Recrystallization of a portion from warm methanol afforded an analytical sample of **23**: mp 168–169 °C; IR (KBr) 1772, 1720 br, 1670 cm^{-1}; ^{1}H NMR (100 MHz, Me_2SO) δ 3.50–4.46 (complex m, 3 H), 4.72 (m, 3 H), 5.01 (s, 2 H), 5.04 (s, 2 H), 7.32 (s, 10 H), 7.54 (d, 1 H, J = 8 Hz), 8.06 (d, 1 H, 7 Hz); ^{13}C NMR (Me_2SO) δ 48.2, 53.2, 62.8, 65.8, 78.0, 127.7, 128.4, 136.7, 156.0, 156.1, 171.2, 171.8; $[\alpha]^{26}_D$ +34.3° (*c* 0.65, Me_2SO); mass spectrum, m/e 601 (M^+ + 2 Me_3Si), 673 (M^+ + 3Me_3Si). Anal. Calcd for $C_{22}H_{23}N_3O_8$: C, 57.76; H, 5.06; N, 9.18. Found: C, 57.50; H, 4.95; N, 9.16.

A stirred, methanolic solution (25 mL) of **23** (0.310 g, 0.78 mM) was cooled to −10 °C, whereupon a solution of sodium methoxide (43 mg, 0.78 mM) in methanol (1 mL) was injected. After being stirred at −10 °C for 20 min, the mixture was poured into 10% aqueous $KHSO_4$ and extracted with ethyl acetate (2×). The combined extracts were dried and concentrated under reduced pressure to a viscous clear oil. PLC (3:1 $EtOAc/CH_2Cl_2$) afforded **25** as a clear oil, identical with the material previously prepared.

***N*-Hydroxyazetidinone 15 Directly from Hydroxamate 25.** To a cold (0–5 °C) solution of **25** (6.08 g, 12.44 mM) in distilled THF (100 mL) was added triphenylphosphine (3.6 g, 13.7 mM), followed by diethyl azodicarboxylate (2.15 mL, 2.38 g, 13.68 mM). The reaction mixture was allowed to stir for 12 h under nitrogen, whereupon TLC indicated that cyclization had occurred. To the above reaction mixture was added DBU (7.0 mL, 49.6 mM). After 30 min, TLC indicated the absence of the above proximate product. THF was removed by evaporation, and the resulting residue was partitioned between ethyl acetate and saturated $NaHCO_3$. The aqueous layer was washed once with ethyl acetate, then adjusted to pH 2 with saturated $KHSO_4$, and finally extracted with ethyl acetate (5×). The combined extracts were dried and concentrated to a crystalline solid (1.8 g, 62%) identical with material prepared by the above methods.

O-Sulfated Azetidinone 17. To a solution of **15** (1.1 g, 4.65 mM) in dry pyridine (45 mL) containing 4A molecular sieves (approximately 1 mL) was added pyridine–sulfur trioxide complex (1.48 g, 9.30 mM). After 2 h of stirring at 26 °C under nitrogen, the pyridine was removed under reduced pressure and the residue partitioned between pH 4.3 buffer (0.5 M KH_2PO_4, 50 mL) and ethyl acetate (50 mL). The aqueous layer was washed once more with ethyl acetate (50 mL), then treated with tetrabutylammonium hydrogen sulfate (1.57 g, 4.65 mM), and extracted with methylene chloride (3 × 50 mL). The combined organic extracts were dried over sodium sulfate and concentrated to a viscous yellow oil (1.81 g, 67%). The material was purified on SilicAR CC-4 with CH_2Cl_2/MeOH (1% to 8%) as elutant to afford 0.7 g of crystal clear, viscous oil: IR ($CHCl_3$) 1785, 1675 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (m, 12 H), 1.50 (m, 16 H), 3.22 (m, 8 H), 3.58 (s, 2 H), 3.73 (m, 1 H), 4.13 (dd, 1 H, J = 5, 5 Hz), 7.0 (d, 1 H, J = 7 Hz), 7.26 (s, 5 H); TLC R_f 0.77 $EtOAc/CH_3OH$ (4:1), visualization with Rydon reagent.

Preparation of Monosulfactam 29. A solution of **17** (0.70 g, 1.20 mM) in DMF (15 mL) was hydrogenated for 6.5 h over 10% Pd/C catalyst (0.35 g). After filtration to remove catalyst, side-chain **30** (0.251 g, 0.125 mM) and DCC (0.25 g, 1.25 mM), followed by hydroxybenzotriazole (0.191 g, 1.25 mM), were added to the mixture, and it was stirred overnight at 26 °C. The reaction mixture was concentrated under high vacuum (T = 40 °C), diluted with acetone (25 mL), and then filtered. The solids were washed with a small amount of acetone, and the combined filtrate was treated with a solution of potassium perfluorobutanesulfonate (0.425 g, 1.25 mM) in acetone (2 mL). The resulting precipitate was collected by filtration (0.250 g). Purification by HP 20-AG chromatography with water–acetone (0–5%) as elutant gave the product as a fluffy white powder after lyophilization (0.045 g, approximately 7%): IR (Nujol) 1777, 1660, 1635 cm^{-1}; ^1H NMR (100 MHz, D_2O) δ 3.95 (dd, 1 H, J = 5, 2 Hz), 4.04 (s, 3 H), 4.25 (dd, 1 H, J = 5, 5 Hz) 6.10 (dd, 1 H, J = 5 , 2 Hz), 7.08 (s, 1 H); 93% pure by spectrodensitometry after TLC.

Hydroxamic Acid 19. A solution of *O*-benzyl-α-(*N*-*tert*-Boc)-L-serine hydroxamate (1.5 g, 4.83 mM, prepared according to Miller[8]) in ethanol (75 mL) containing 10% Pd/C (0.5 g) was hydrogenated at atmospheric pressure (26 °C for 1 h). The catalyst was filtered and washed with ethanol. The combined filtrate and washings were evaporated to a white foam, which crystallized from CH_3OH/EtOH to give 0.9 g (90%) of **19**: mp 106–112 °C; IR (KBr) 1725, 1665 cm^{-1}; ^1H NMR ($CD_3OD/CDCl_3$) δ 1.46 (t, 1 H, J = 5 Hz); ^{13}C NMR (CD_3OD) δ 28.6 (q), 55.9 (t), 63.0 (d), 80.9 (s), 157.3 (s), 169.9 (s). Anal. Calcd for $C_8H_{16}N_2O_5$: C, 43.63; H, 7.32; N, 12.72. Found: C, 44.01, H, 7.43; N, 12.91.

Rearrangement of 19 to 21. To a cold (0 °C) solution of **19** (0.220 g, 1 mM) and triphenylphosphine (0.288 g, 1.1 mM) in THF (10 mL) was added diethyl azodicarboxylate (0.191 g, 0.173 mL, 1.1 mM). The reaction mixture was stirred for over 8 h while the temperature rose to 26 °C. The reaction mixture was concentrated in vacuo and chromatographed on silica gel (70:10:2 $CHCl_3/CH_3OH/HCO_2H$) to yield **21** as a white crystalline solid (0.124 g, 61%): mp 184–187 °C; IR (KBr) 1765, 1740, 1685 cm^{-1}; ^1H NMR (100 MHz, $CD_3OD/CDCl_3$) δ 1.44 (s, 9 H), 4.18 (dd, 1 H, J = 4, 10 Hz), 4.59 (dd, 1 H, J = 8, 10), 5.47 (m, 1 H); ^{13}C NMR (CD_3OD) δ 28.6 (q), 61.7 (t), 71.4 (d), 80.9 (s); mass spectrum, m/e 346 (M^+ + $2Me_3Si$); $[\alpha]^{26}_D$ −97.7° (c 0.350, CH_3OH); negative ferric chloride test. Anal. Calcd for $C_8H_{14}N_2O_4$: C, 47.51; H, 6.98; N, 13.86. Found: C, 47.39; H, 6.97; N, 13.50.

***N*-((*o*-Nitrophenyl)sulfenyl)-L-threonine 32.** Following the procedure of Zervas et al.,[24] L-threonine (11.9 g, 100 mM) was added to dioxane (125 mL) and 2 N NaOH (50 mL). To the vigorously stirred solution was added *O*-nitrobenzenesulfenyl chloride (20.9 g, 110 mM) in ten equal portions over 15 min, while 2 N NaOH (60 mL) was slowly added dropwise. After an additional 5 min, the reaction mixture was diluted with water (400 mL) and acidified to pH 2.5 with 10% $KHSO_4$ (or 1 N H_2SO_4). The organic layer was immediately extracted with ethyl acetate (3 × 200 mL), and the combined extracts were dried over sodium sulfate and the concentrated to an oil. The product crystallized on scratching (20.0 g, 73%). For success in the next step it was found advisable to recrystallize the product. Recrystallization of 17 g from acetone/hexane afforded 9.5 g of bright yellow crystals, mp 145–148 °C, which was stored in the freezer: ^{13}C NMR (acetone-d_6) 20.0, 68.3, 70.0, 124.9, 125.1, 125.5, 134.0, 173.1.

Hydroxamate 33. Nps-L-threonine (39.0 g, 143 mM) and *O*-benzylhydroxamine hydrochloride (22.92 g, 143 mM) were suspended in water (500 mL), and with vigorous stirring the pH was adjusted to 4.2 with 1 N NaOH. A solution of 1-ethyl-3-(3-(dimethylamino)propyl)-carbodiimide hydrochloride in water (100 mL) was added portionwise, while the pH was controlled at 4.2 with addition of 10% $KHSO_4$. The addition lasted 5 min, and stirring and pH control was continued for an additional 30 min, whereupon a heavy granular precipitate was present. The reaction mixture was extracted with ethyl acetate (4 × 300 mL), and the combined extracts were dried over sodium sulfate and concentrated to a yellow oil (approximately 50 g). Chromatography on Silic*AR* CC-7 (2 kg, CH_2Cl_2 → 50% CH_2Cl_2/EtOAc) afforded the product as a yellow foam (19.5 g, 36%). A portion was crystallized and recrystallized from acetone/hexane to provide an analytical sample: mp 130–133 °C; IR (KBr) 1655, 1505 cm^{-1}; ^1H NMR (100 MHz, $CD_3OD/CDCl_3$) δ 1.23 (d, 3 H, J = 7 Hz), 3.18 (m, 1 H), 4.0 (d of q, 1 H, J = 8, 6 Hz), 4.87 (s, 2 H), 7.35 (s, 5 H), 7.18–8.30 (m, 4 H); ^{13}C NMR (acetone-d_6) δ 19.4, 68.6 (lg peak, α and β carbons superimposed), 77.9, 125.2, 125.4, 125.7, 128.6, 129.4, 134.3; $[\alpha]^{26}_D$ −2.2° (c 0.5, CH_3OH). Anal. Calcd for $C_{17}H_{19}N_3O_5S$: C, 54.10; H, 5.07; N, 11.13; S, 8.49. Found: C, 53.54; H, 4.87; N, 11.11; S, 8.47.

Preparation of β-Lactam 34. To a cold solution (0 °C) of **33** (9.4 g, 25 mM) in pyridine (34 mL) was added mesyl chloride (8.58 g, 5.85 mol, 75 mL) all at once. After 2 h at 0 °C, TLC indicated the absence of starting material. The mixture was poured into ice water (100 mL) and extracted with ethyl acetate (5 × 100 mL). The extracts were washed with ice-cold 10% $KHSO_4$ (4 × 100 mL), dried over sodium sulfate, and concentrated under reduced pressure *without* heat. This afforded 9.6 g of a dark residue which was used directly.

A solution of crude mesylate (9.6 g) in acetone (125 mL) was added dropwise over 35 min to a refluxing mixture of anhydrous potassium carbonate (10 g) and acetone (approximately 600 mL). After 2.5 h, TLC indicated the reaction was complete. The mixture was cooled to 26 °C, filtered, and evaporated to a dark foam. Chromatography on SilicAR CC-7 (9:1 CH_2Cl_2/hexane → CH_2Cl_2) afforded β-lactam **34** as a clear yellow oil (2.15 g, 24%). Crystallization and recrystallization from $CHCl_3$/hexane produced an analytical sample: mp 97–100 °C; IR (KBr) 1748 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$), δ 1.19 (d, 3 H, J = 6 Hz), 3.25 (d, 1 H, J = 6 Hz, NH), 3.48 (d of g, 1 H, J = 1, 6 Hz), 3.74 (d of d, 1 H, J = 1, 6 Hz), 4.95 (s, 2 H), 7.34 (s, 5 H), 7.2–8.4 (m, 4 H); ^{13}C NMR (acetone-d_6) δ 15.4 (q), 61.6 (d), 69.6 (d), 77.8 (t), 124.8 (d), 125.2 (d), 125.5 (d), 128.4 (d), 128.7 (d), 129.2 (d), 129.6 (d), 134.1 (d), 135.7 (s), 142.6 (s), 145.7 (s), 162.6 (s). Anal. Calcd for $C_{17}H_{17}N_3O_4S$: C, 56.81; H, 4.76; N, 11.69; S, 8.92. Found: C, 56.6; H, 4.85; N, 11.45; S, 8.64.

β-Lactone **39** was also isolated (2.95 g, 23%) and recrystallized from EtOAc/hexane: mp 134–135 °C; IR (KBr) 1800 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.61 (d, 3 H, J = 6 Hz), 3.43 (d, 1 H, J = 8 Hz, NH), 4.81 (complex multiplet, 2 H), 7.2–8.4 (m, 4 H); ^{13}C NMR (acetone-d_6) δ 14.6 (q), 71.3 (d), 75.5 (d), 124.5, 125.5 (d), 134.4 (s); $[\alpha]^{26}_D$ −41.0° (c 0.5, CH_3OH). Anal. Calcd for $C_{10}H_{10}N_2O_4S$: C, 47.23; H, 3.96; N, 11.01; S, 12.61. Found: C, 47.18; H, 3.92; N, 10.87; S, 12.17.

Reconversion of β-Lactone 39 to Hydroxamate 33. To a cold (−5 to 0 °C) solution of β-lactone **39** (0.144 g, 0.65 mM) in CH_2Cl_2 (2 mL) was added a solution of *O*-benzylhydroxylamine (0.080 g, 0.65 mM) in CH_2Cl_2 (0.5 mL). After 30 min of stirring at −5 °C, 2 equiv more of *O*-benzylhydroxylamine was added and the mixture stirred at 26 °C for 12 h. At this point the product had precipitated and was collected by filtration. A rapid wash with ether followed by air drying afforded **33**: mp 140–141 °C; identical with previously prepared material by mixture melting point, IR, ^1H NMR, ^{13}C, NMR, and TLC.

β-Lactam Tosylate Salt 35. To a stirred solution of **34** (1.07 g, 3 mM) in CH_2Cl_2 (20 mL) were added *p*-toluenesulfonic acid (0.57 g, 3 mM) and *p*-thiocresol (0.74 g, 6 mM). The reaction mixture was, stirred under nitrogen for 2 h, whereupon TLC indicated the absence of starting material. The solvents were removed in vacuo, and the residue was triturated with ether (4 × 25 mL) to afford the product as cream-colored

solids (0.90 g, 80%): IR (KBr) 1775 cm^{-1}; ^1H NMR (100 MHz, Me_2SO) δ 1.25 (d, 3 H, J = 6 Hz), 2.28 (s, 3 H), 3.36 (br, 2 H), 3.93 (d of q, 1 H, J = 6, 1 Hz), 4.02 (d, 1 H, J = 1 Hz), 4.98 (s, 2 H), 7.11 (d, 2 H, J = 9 Hz), 7.42 (s, 5 H), 7.51 (d, 2 H, J = 8 Hz).

(2*S*-*trans*)-3-[(2,6-Dimethoxybenzoyl)amino]-2-methyl-4-oxo-1-azetidinyl Sulfate, Pyridine Salt (1:1) (37). To a cold (-10 °C) solution of β-lactam salt **35** (0.95 g, 2.5 mM) in methylene chloride (50 mL) were added 2,6-dimethoxybenzoyl chloride (0.60 g, 3 mM) and 4-(dimethylamino)pyridine (0.61 g, 5 mM). The reaction was stirred under nitrogen and allowed to rise to 26 °C over 5 h. The reaction mixture was concentrated to an oil and partitioned between ethyl acetate and aqueous potassium hydrogen sulfate solution. The organic layer was washed with aqueous sodium bicarbonate and brine, then dried over sodium sulfate, and concentrated to a yellow foam (0.843 g, 91.5%): ^1H NMR ($CDCl_3$) δ 1.36 (d, 3 H), 3.66 (m, 1 H), 3.75 (s, 6 H), 4.25 (dd, 1 H, J = 6, 1 Hz), 5.00 (s, 2 H), 7.33 (s, 5 H), 6.50-7.85 (4 H).

To a stirred solution of **36** (0.848 g, 2.28 mM) in absolute ethanol (20 mL) under nitrogen were added 1,4-cyclohexadiene (8 mL) and freshly prepared palladium black (approximately 0.85 g, prepared according to "Organic Syntheses".[28] After 1 h, TLC indicated the absence of starting material, and the reaction mixture was filtered and evaporated to give the *N*-hydroxy β-lactam as a white solid (0.605 g, 94.8%): IR (KBr) 1772, 1657 cm^{-1}; ^1H NMR (CD_3OD) 1.48 (d, 2 H, J = 6 Hz), 3.81 (s, 6 H, overlapping with m, 1 H), 4.33 (d, 1 H, J = 1 Hz), 6.5-7.5 (m, 3 H).

To a solution of the above (0.60 g, 2.14 mM) in dry pyridine (20 mL) under nitrogen were added 4A molecular sieves (approximately 3 mL) and pyridine-sulfur trioxide complex (1.35 g, 8.5 mM). After 3 h, the reaction mixture was filtered, and the filtrate was concentrated and applied to an HP 20-AG resin column (acetone/water). The desired fractions were lyophilized to afford **37** (0.192 g, 20%) as a white powder: IR (KBr) 1776, 1653 cm^{-1}; ^1H NMR (100 MHz, D_2O) δ 1.56 (d, 3 H, J = 6 Hz), 3.83 (s, 6 H), 4.32 (m, 2 H), 6.6-9.0 (m, 8 H, aromatic). Anal. Calcd for $C_{18}H_{21}N_3O_8S\cdot0.5H_2O$: C, 48.21; H, 4.94; N, 9.37; S, 7.15. Found: C, 48.23; H, 4.94; N, 9.37; S, 7.10.

β-Lactam 42. A suspension of acid **40** (0.879 g, 2.75 mM), *N*-hydroxybenzotriazole (0.42 g, 2.75 mM), and DCC (0.56 g, 2.75 mM) in DMF (15 mL) was stirred at 26 °C for 1 h, at which point a solution of **35** (0.95 g, 2.5 mM) and diisopropylethylamine (0.44 mL, 2.5 mM) in DMF (5 mL) was added. The reaction mixture was stirred at room temperature overnight, then poured into water (100 mL), and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with water (3 × 100 mL) and aqueous sodium bicarbonate solution (1 × 100 mL) and then dried over sodium sulfate and concentrated under reduced pressure to a yellow semisolid residue. PLC (EtOAc) afforded the desired product as a yellow foam (0.599, 47%), which recrystallized from $CHCl_3$/isopropyl ether: mp 100-105 °C; IR (KBr) 1768, 1712, 1672 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.12 (d, 3 H, J = 6 Hz), 1.16 (t, 3 H, J = 4 Hz), 3.54 (m, 6 H), 4.02 (m, 2 H), 4.31 (dd, 1 H, J = 1, 6 Hz), 4.91 (s, 2 H), 5.44 (d, 1 H, J = 6 Hz), 7.32 (s), 7.37 (s).

β-Lactam 41. In a similar manner **35** (0.95 g, 2.5 mM) was reacted with acid **30** (0.55 g, 2.75 mM) to give, after chromatography, **41** as a yellow foam (0.643 g, 46%), which crystallized from $CHCl_3$/isopropyl ether: mp 90-105 °C slow dec; IR (KBr) 1765, 1667 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.12 (d, 3 H, J = 6 Hz), 3.68 (d of q, 1 H, J = 6, 1 Hz), 3.92 (s, 3 H), 4.56 (dd, 1 H, J = 1, 6 Hz), 4.98 (s, 2 H), 5.55 (br, 2 H), 6.76 (s, 1 H), 6.78 (s, imp ?), 7.37 (s, 5 H), 8.12 (d, 1 H).

[2*S*-[2α,3β(*R)]]-3-[(((((4-Ethyl-2,3-dioxo-1-piperazinyl)carbonyl)amino)phenylacetyl)amino]-2-methyl-4-oxo-1-azetidinyl Sulfate, Pyridine Salt (1:1) (43).** An ethanolic solution (25 mL) of **42** (0.270 g, 0.53 mM) containing 10% Pd/C (130 mg) was hydrogenated at atmospheric pressure for 2 h. The reaction mixture was filtered and concentrated to a white sticky solid (0.220 g, 99%), which was used directly. To a solution of the above (0.220 g, 0.53 mM) in pyridine (7 mL) were added 4A molecular sieves (approximately 1 mL) and pyridine-sulfur trioxide complex (0.33 g, 2.1 mM). After being stirred under nitrogen at 26 °C for 4.5 h, the reaction mixture was filtered and concentrated to an oil. Chromatography on HP 20-AG resin H_2O/acetone) followed by lyophilization of the appropriate fractions afforded the desired product as a white powder (0.080 g, 25%): IR (KBr) 1780, 1723, 1677 cm^{-1}; ^1H NMR (100 MHz, D_2O) δ 1.19 (t, 3 H, J = 7 Hz), 1.44 (d, 3 H, J = 6 Hz), 3.52 (q, 2 H, J = 7 Hz), 3.68 (m, 3 H), 4.01 (m, 4 H), 4.54 (d, 1 H, J = 2 Hz), 5.46 (s, 1 H), 7.48 (s, 5 H), 8.10-9.0 (m, 5 H); TLC R_f 0.63 $CHCl_3/CD_3OD/HCO_2H$ (70:30:2), 0.42 *n*-BuOH/HOAc/H_2O (60:20:20), 96-99% pure by spectrodensitometry. Anal. Calcd for $C_{24}H_{28}N_6O_9S\cdot2.2H_2O$: C, 46.78; H, 5.19; N, 13.63. Found: C, 46.36; H, 4.74; N, 13.42.

Acknowledgment. We thank the Squibb Institute Analytical Department for assistance during the course of this research and Judith Melnik for help in the preparation of the manuscript.

Registry No. 1, 71405-00-0; **2**, 82933-24-2; **3**, 75624-37-2; **4**, 82933-25-3; **5**, 82933-27-5; **7**, 82933-28-6; **8**, 82933-31-1; **8** benzyl ether, 82933-33-3; **9**, 82933-35-5; **10**, 82933-36-6; **13**, 71404-99-4; **14**, 82933-30-0; **15**, 82933-37-7; **16**, 76530-06-8; **17**, 82933-42-4; **18**, 26048-92-0; **19**, 82933-43-5; **21**, 82933-44-6; **22**, 28832-02-2; **23**, 82933-40-2; **24**, 82933-38-8; **25**, 82933-39-9; **29**, 82951-09-5; **30**, 82933-61-7; **32**, 7685-70-3; **33**, 82933-45-7; **33** mesylate, 82933-47-9; **34**, 82933-46-8; **35**, 82933-50-4; **36**, 82933-53-7; **36**-ol, 82933-54-8; **37**, 82933-52-6; **39**, 82933-48-0; **40**, 82933-56-0; **41**, 82933-57-1; **42**, 82933-55-9; **43**, 82933-59-3; **42**-ol, 82933-60-6; i, 75624-38-3; ii, 82951-08-4; L-*N*-(phenylacetyl)serine, 2752-53-6; *N*-(phenylacetyl)-L-threonine, 2798-50-7; *N*-(phenylacetyl)-L-threonine *O*-benzylhydroxyamide, 82933-32-2; phenylacetyl chloride, 103-80-0; L-threonine, 72-19-5; *O*-benzylhydroxylamine hydrochloride, 2687-43-6; *o*-nitrobenzenesulfenyl chloride, 7669-54-7; 2,6-dimethoxybenzoyl chloride, 1989-53-3; Cbz-L-serine, 1145-80-8; Pen G K salt, 113-98-4.

Chemistry of Singlet Oxygen. 38. Temperature Effect on the Photooxidation of Sulfides[1]

Chee-liang Gu and C. S. Foote*

Contribution from the Department of Chemistry, University of California, Los Angeles, Los Angeles, California 90024. *Received February 16, 1982*

Abstract: The reactivity of diethyl sulfide with singlet oxygen has been determined at room temperature (23-24 °C) and at -78 °C in various solvents. Although the consumption of sulfide is much faster at -78 °C, the rate of removal of singlet oxygen by sulfide is relatively independent of solvent and temperature. A comparison of the rate of product formation with the rate of singlet oxygen removal shows that over 97% quenching is observed in aprotic and about 10% in protic solvents at room temperature. At -78 °C, the quenching process is suppressed in both protic and aprotic solvents. Surprisingly, 2,5-diphenylfuran showed a similar but much smaller effect of solvent and temperature.

Sulfides have been shown to have very large and surprising effects of solvent and temperature on their reactions with singlet oxygen. Foote and Peters[2,3] found that in protic solvents the reaction rates do not vary much with temperature but that in

0002-7863/82/1504-6060$01.25/0