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Regioselective Activation of Aminothiazole(iminoxyacetic acid)acetic Acid: An Efficient Synthesis of the Monobactam Aztreonam

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Abstract:

An efficient synthesis of the monobactam aztreonam [[2*S*-[2α,3*β*(*Z*)]]-3[[(2-amino-4-thiazolyl)[(1-carboxy-1-methylethoxy)imino]acetyl]amino]-2-methyl-4-oxo-1-azetidinesulfonic acid] (1) by acylation of α-aminoazetidinone 22 with the regioselectively activated aminothiazoleiminoxyacetic diacid 15 or 18 is described. Reaction of benzhydryl ester 10 with *N*-hydroxybenzotriazole and dicyclohexylcarbodiimide followed by ester deprotection formed the monoacid amide 15. Alternatively, chemoselective transient silylation of the diacid 9 followed by activation with *N*-hydroxysuccinimide formed active ester 18. Acylation of α-aminoazetidinone 22 with amide 15 or ester 18 produced aztreonam (1) in 75−85% yield.

Introduction

The monobactam aztreonam (**1**, Azactam), a synthetic monocyclic *β*-lactam antibiotic,[1] currently is in use for the treatment of Gram-negative bacterial infections.[2a] Phenyl mannitol broths containing aztreonam have found application in the improved detection of methicillin-resistant *Staphylococcus aureus*.[2b] More recently, an in vitro synergistic additive effect of aztreonam with other antibiotics, for example, ciprofloxacin and levofloxacin, against *Pseudomonas aeruginosa* has been observed.[2c] Aztreonam (**1**) incorporates the unique activating group $-SO_3^-$ on the *β*-lactam ring nitrogen. This activating group was first observed in natural monobactams isolated from New Jersey Pine Barrens soil samples.[3] The synthetic monobactam tigemonam employs the more labile activating group $-OSO_3^-$ on the azetidinone ring nitrogen[4,5] (Figure 1).

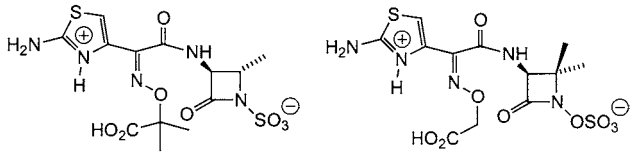
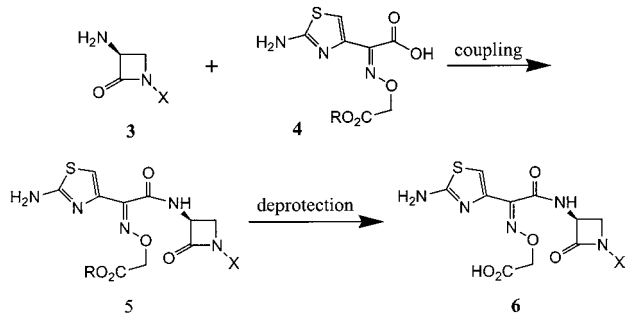


Figure 1. **Structures of aztreonam and tigemonam.**

Scheme 1. **Typical synthesis of monobactams 6**



A typical synthesis of monobactams **6** is delineated in Scheme 1. Coupling of α-aminoazetidinones **3** with monoacid esters **4** forms the intermediate **5**, which then is deprotected to provide the monobactams **6**. The benzhydryl ester protecting group commonly is used in the synthesis of monobactams and other *β*-lactam antibiotics.[6] This typically requires the use of a strong acid, for example, TFA, MSA, or $AlCl_3$, for deprotection.[6b] The relative instability of the activated azetidinones to strong acids and the desire for a more economical and efficient synthesis prompted us to explore alternative constructions.

We envisaged the use of an unprotected, regioselectively activated aminothiazoleiminoxy acid **7** as shown in Scheme 2.

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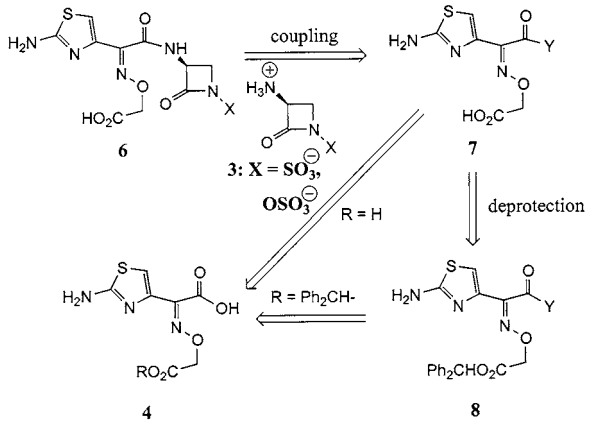
Scheme 2. **Proposed retrosynthesis of monobactams 6**

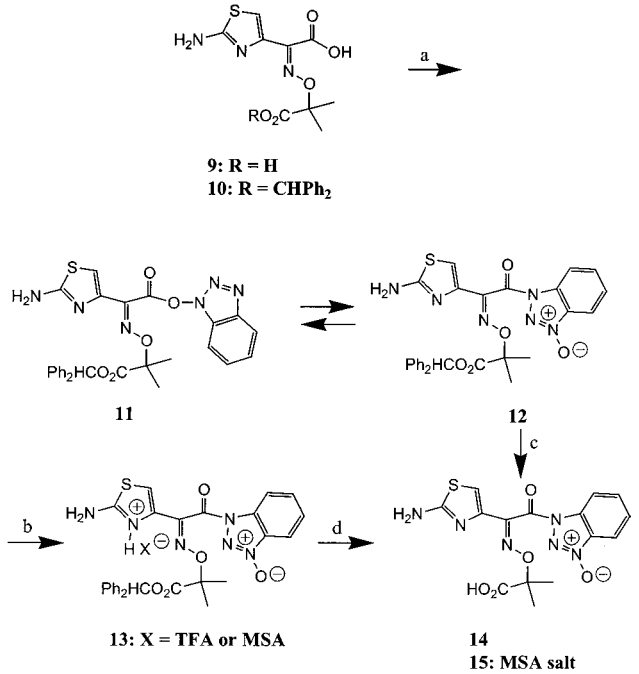


Activation of the monoacid **4** (R = $-CHPh_2$) to **8** (Y = activating group) followed by the chemoselective deprotection of the benzhydryl ester group could form the desired activated acid **7**. Alternatively, it might be possible to prepare acid **7** directly from the diacid **4** (R = H). Finally, the coupling of activated acid **7** with azetidinone **3** would produce the monobactam **6**. These routes would avoid exposure of the azetidinone nucleus to strongly acidic deprotection conditions and offer the possibility of better economics and atom efficiency. The diacid route was particularly attractive since the need for benzhydryl protection (and subsequent deprotection) would be obviated, as the diacid would be easily available from, for example, the diethyl ester. This work describes our efforts to prepare suitable monoacid activated derivatives and their application in the efficient synthesis of aztreonam (**1**).

Essential requirements for a suitable activating group would be its stability to hydrolysis and its resistance to nucleophilic attack by the iminoxycarboxylic acid function (to form a cyclic anhydride) under the N-acylation reaction conditions. *N*-Hydroxybenzotriazole (HOBT) is often used for activation in racemization-free peptide bond-formation reactions.[7] Its reaction with a carboxylic acid in the presence of dicyclohexylcarbodiimide (DCC) forms the active OBT-ester (cf. **11**, Scheme 3) as the kinetic product which is used in situ for amidation reactions. Protection of the amino group in the thiazoleiminoxy acids is not required in these coupling reactions. Generally, on standing the OBT-ester rearranges to the more stable and isolable NBT-amide (cf. **12**), which also can undergo amidation reactions.[8] The NBT-amide of the acid **7** thus seemed a possible target.

Relative to the OBT-ester, the corresponding OSu-ester, prepared by reaction of an acid with *N*-hydroxysuccinimide (HOSu), is more stable and isolable and presented another opportunity.[9]

Scheme 3. **Synthesis of monoacid active amide 14**[a]



[a] Reaction conditions and yields: a. HOBT, DCC, CH_3CN, 20 °C. or MesOBT, TEA, CH_3CN, 20 °C. b. TFA or MSA, CH_3CN, 20 °C, 18 h; 65−80%. c. TFA, anisole; MSA; 90%. d. MSA, anisole, CH_2Cl_2, 0 °C, 6 h; 90%.

Results and Discussion

Synthesis of the Active Amide 14. The NBT-amide **14** was prepared by the reaction of monoacid ester **10** with HOBT and DCC followed by the deprotection of the benzhydryl group (Scheme 3).

Reaction of acid **10** with HOBT (DCC, DMF) at 0 °C selectively formed the OBT-ester **11** in 70% yield. However, the OBT-ester proved too fragile to survive the strongly acidic conditions used for the removal of the benzhydryl group. Efforts next were focused on the NBT-amide. At 20 °C, partial isomerization to the NBT-amide occurred to produce a 2:3 mixture of **11** and **12**.[8d] In CH_2Cl_2, a ratio of ∼3:7 was obtained starting from either **11** or **12**, and in CH_3CN a ratio of ∼1:4 was observed. Thus, the OBT-ester is the kinetic product, and the NBT-amide is the preferred, thermodynamic product.

It proved possible to isolate the TFA or MSA salts **13** of the NBT-amide **12** by crystallization from the equilibrium mixture of **11** and **12**, prepared from **10** in CH_3CN by the use of DCC (82% yield) or MsOBT[10] (68% yield). Subsequent deprotection of the MSA salt **13** with additional MSA in CH_3CN gave the unprotected NBT-amide **15** in 90% yield. Although this active amide could be stored at −20 °C for one month without noticeable decomposition, above 5 °C gradual decomposition was observed. This led to a detailed study of the corresponding more stable O-Su ester.

Preparation of the OSu Active Ester 18. Reaction of monoacid ester **10** with *N*-hydroxysuccinimide (DCC, DMF, 25 °C) formed the OSu-ester **16** in 98% yield (Scheme 4).

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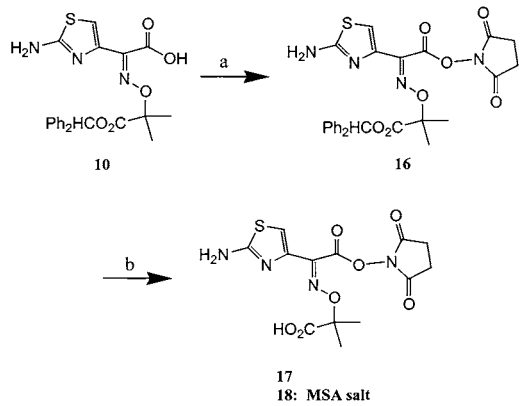
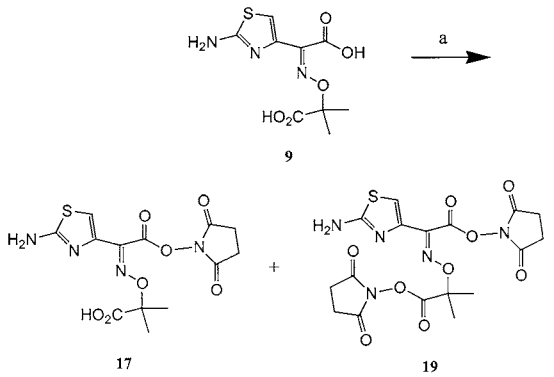
(10) (a) Itoh, M.; Nojima, H.; Notani, J.; Hagiwara, D.; Takai, K. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 3320−3329. (b) MsOBT has been found to be shock-sensitive and impact-sensitive. Safe preparation and use of MsOBT will be described: Prasad, J. S. et al., manuscript in preparation.

Scheme 4. **Synthesis of OSu-ester MSA salt 18, from acid 10**[a]



[a] Reaction conditions and yields: a. HOSu, DCC, DMF, 20 °C; 98%. b. MSA or TFA, anisole, CH_2Cl_2, 0 °C, 6 h; 84%.

Scheme 5. **Synthesis of OSu-ester 17 from diacid 9**[a]



[a] Reaction conditions: a. HOSu, DCC, 0 °C.

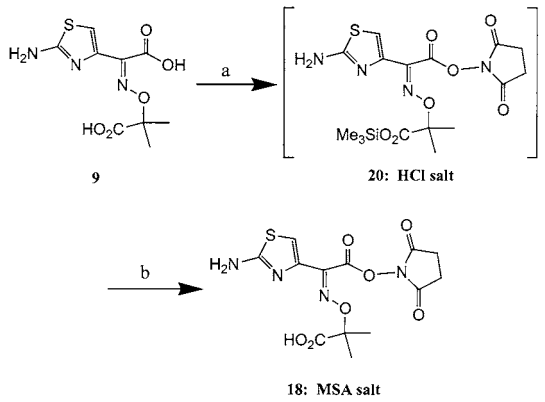
The crude ester was subjected to deprotection with MSA (anisole, 0 °C, 2 h), and then methyl ethyl ketone was added to crystallize the MSA salt **18** in 84% yield. This intermediate had good stability when stored at 5 °C.

As mentioned previously, diacid **9** would be particularly attractive as a starting material for a number of reasons. Attempts to selectively form the monoacid OSu-ester **18** from the diacid **9** with HOSu and DCC were unsuccessful. A mixture (4:1) of **17** and the corresponding di-OSu ester **19** was formed (Scheme 5). Comparable results were obtained with HOBT.

Surprisingly, however, reaction of diacid **9** with 1 equiv of Me_3SiCl followed by in situ reaction with HOSu and DCC formed **20** in high yield (Scheme 6). Subsequent treatment with a tertiary amine followed by MSA gave the targeted MSA salt **18**.

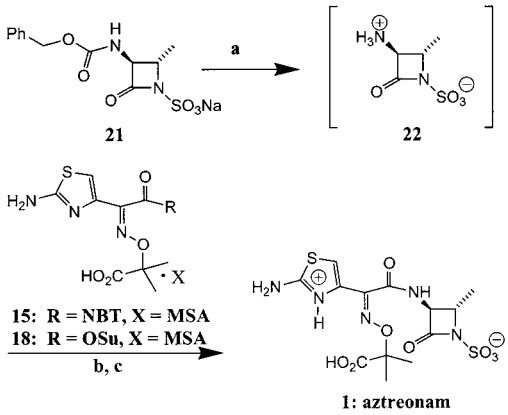
Thus, reaction of diacid **9** with Me_3SiCl followed by HOSu and DCC produced the diester **20**. Treatment of **20** with Et_3N, filtration of DCU and Et_3N-HCl, and addition of MeOH and MSA resulted in crystallization of the MSA salt **18** in 80% yield. Diester **19** was also present (~1%) in the recrystallized batches of monoester **18**. This process was scaled up to produce 51 kg (yield ~75%) of **18** in a single batch in our pilot plant. Unlike the amino acid ester **17**, the salt **18** was stable at 20 °C for several weeks and was unchanged over 1 year at 5 °C.

Scheme 6. **Synthesis of OSu-ester MSA salt 18, from diacid 9**[a]



[a] Reaction conditions and yields: a. i. TMSCl, DMF, 50 °C. ii. HOSu, DCC, 0 °C. b. i. Et_3N. ii. MeOH, MSA, 5 °C, 0.5 h; 80%.

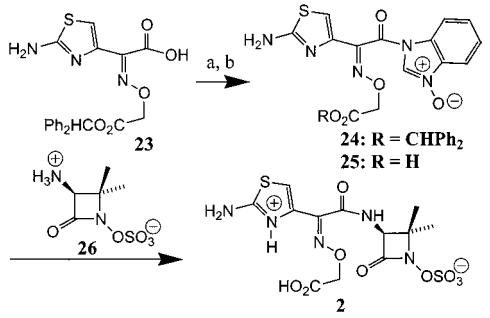
Scheme 7. **Synthesis of aztreonam (1)**[a]



[a] Reaction conditions and yields: a. Pd−C, H_2, MeOH/H_2O, HCl. b. i. **15**, aq EtOH, Et_3N, 20 °C, 3 h. ii. HCl; 81%. c. i. **18**, aq EtOH, 0 °C, Et_3N, 3 h. ii. HCl; 86%.

Synthesis of Aztreonam (1). Acylations of zwitterion **22** with the active amide **15** and the OSu-ester **18** were carried out in aqueous CH_3CN, acetone, and EtOH in the presence of Et_3N (Scheme 7). The aztreonam zwitterion **1** was precipitated with HCl; initial yields of the product varied from 50 to 80%. Aqueous EtOH was preferred since the product could be easily precipitated with acid from this solvent as a nicely filterable solid. Lower yields were primarily the result of competitive hydrolysis of the activating group. Careful control of the pH during the acylation reaction (pH 8−8.5) minimized this side reaction. Thus, reaction of isolated zwitterion **22** with active amide **15** (aq EtOH, Et_3N, 20 °C, 3 h) followed by acidification with HCl gave aztreonam (**1**) in 81% yield. Furthermore, a telescoped process was developed, starting with the carbobenzyloxy azetidinone **21**.[1e] Thus, hydrogenolysis (H_2, aqueous MeOH) of azetidinone **21** to zwitterion **22** followed by filtration to remove the catalyst and in situ acylation with the OSu-ester **18** produced aztreonam (**1**) in 86% yield. The acylation was thoroughly investigated prior to introduction into the pilot plant. After the initial charge of the active ester **18** (1.05 mol equiv), the content of aminoazetidinone **22** was monitored by HPLC (UV wavelength 210 nm). The reaction slowed considerably after 75 min. It required two (3 and 4 mol % each) additional charges of the active ester **18** for

Scheme 8. **Synthesis of tigemonam (2)**[a]



[a] Reaction conditions and yields: a. HOBT, DCC, DMF, 20 °C; 62%. b. TFA, anisole, CH_2Cl_2, 0 °C; 86%. c. CH_2Cl_2, Bu_3N, −20 °C; TFA; 69%.

complete consumption of the aminoazetidinone. This protocol simplified the purification process and gave the product in reproducible, high yields. The process was scaled up to 12 kg output of aztreonam **1** in our pilot plant, and in total, over 70 kg of the product were prepared by this method.[11]

Synthesis of Tigemonam (2). A similar approach was used for the synthesis of the orally active monobactam tigemonam (**2**, Scheme 8).[12] The reaction of acid **23** with HOBT (DCC, DMF, 20 °C) formed the active amide **24** in 62% yield. Chemoselective deprotection (TFA, anisole, CH_2Cl_2) of the benzhydryl ester in **24** gave the desired acid **25** in 86% yield. Coupling (Bu_3N, CH_2Cl_2) of the α-aminoazetidinone **26** with active amide **25** produced tigemonam (**2**) in 69% yield.

In conclusion we have developed efficient processes for the syntheses of the regioselectively activated aminothiazole monoacid amide **15** and the ester **18**. Acylation of amide **15** with α-aminoazetidinone **22** furnished aztreonam (**1**). This strategy avoids exposure of the monobactam to the strongly acidic deprotection conditions for removal of the benzhydryl group in the last step of the aztreonam synthesis. The more economical synthon monoacid OSu-ester **18** was prepared by chemoselective transient silylation of the diacid **9** followed by esterification with HOSu, obviating the use of the bulky and expensive benzhydryl ester. Coupling of the OSu-ester **18** with the in situ generated zwitterion **22** provided an alternative efficient synthesis of aztreonam (**1**). This process was implemented to prepare 70 kg of the drug substance.

Experimental Section

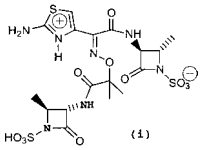
All new compounds described in the Experimental Section were fully characterized. Analytical and spectral data for these compounds are for lab batches. HPLC analysis results are described as area % (AP).

(*Z*)-2-[[[1-(2-Amino-4-thiazolyl)-2-(3-oxido-1H-benzotriazol-1-yl)-2-oxoethylidene]amino]oxy]-2-methylpropanoic Acid, Diphenylmethyl Ester, Methanesulfonate (1:1) Salt (13). Monoacid ester **10**[1e] (100.0 g, 0.228 mol) was charged into a three-necked flask fitted with a mechanical stirrer, thermometer, and an addition funnel. A solution of DCC (49.3 g, 0.239 mol) in CH_3CN (90.0 mL) was added in one portion. HOBT (monohydrate, 34.9 g, and 0.228 mol) was added in small portions with slight cooling so as to maintain the internal temperature at 20−24 °C. After 3 h, DCU was removed by suction filtration, and the cake was washed with CH_3CN (3 × 35.0 mL). A solution of MSA (24.0 g, 0.250 mol) in CH_3CN (45.0 mL) was added slowly to the filtrate over 60−90 min, keeping the internal temperature at ∼20 °C. Precipitation of the product starts during the addition. The mixture was stirred for 15 h to complete precipitation of the product. The solid was filtered, washed with EtOAc (3 × 75 mL), and dried under vacuum at 25 °C to a constant weight to give 120 g (yield ∼80%) of **13**, HPLC AP (240 nm) 99.[13] ^{1}H NMR (DMSO-d_6, 270 MHz) δ 1.48 (s, 6H), 2.45 (s, 3H), 3.7−4.5 (broad for $(NH_3)^+$, 6.81 (s, 1H), 7.25−7.38 (m, 10 H), 7.79 (t, 1H, J = 7.6 Hz, 8.2 Hz), 8.03 (t, 1H, J = 8.2 and 7.6 Hz), 8.13 (d, 1H, J = 8.2 Hz), 8.47 (d, 1H, J = 7.6 Hz). Anal. Calcd for $C_{28}H_{24}N_6O_5S\cdot 0.9CH_3SO_3H\cdot 0.5H_2O$: C, 53.23; H, 4.42; N, 12.89; S, 9.34; H_2O, 1.38. Found: C, 52.86; H, 4.56; N, 12.96; S, 8.96; H_2O, 0.95 (K.F.).

(*Z*)-2-[[[1-(2-Amino-4-thiazolyl)-2-(3-oxido-1H-benzotriazol-1-yl)-2-oxoethylidene]amino]oxy]-2-methylpropanoic Acid, Methanesulfonate (1:1) Salt (15). A solution of anisole (38.9 g, 0.36 mol) in CH_2Cl_2 was cooled to 0 °C, and MSA (51.9 g, 0.54 mol) was added, maintaining the temperature at 0 °C. Ester **13** (117.5 g, 0.18 mol) was introduced in small portions over 30 min, and stirring was continued at 0 °C. After 5 h TLC (silica gel: EtOAc−AcOH−H_2O = 20:1:1, visualized by UV light and Rydon's spray; R_f of ester **13** = 0.89, **14** = 0.70, diacid **9** = 0.0) indicated completeness of the reaction. The mixture was diluted with acetone (60.0 mL) at 0 °C, and EtOAc (1.5 L) was added slowly over 1 h (Caution! Fast addition of EtOAc causes formation of a sticky solid). After stirring for an additional hour, the solid was filtered with suction, washed with cold EtOAc, and dried under vacuum at 25 °C to a constant weight to furnish 79.3 g (yield ∼90%) of salt **15**, AP (234 nm) 99.[13] ^{1}H NMR (DMSO−d_6, 270 MHz) δ 1.40 (s, 6H), 2.47 (s, 3H), 4.1−4.9 (broad for OH and $(NH_3)^+$, 7.32 (s, 1H), 7.80 (t, 1H, J = 7.6 Hz), 8.04 (t, 1H, J = 8.2 and 7.6 Hz), 8.13 (d, 1H, J = 8.2 Hz), 8.43 (d, 1H, J = 7.6 Hz).

2-[(2-Amino-thiazol-4-yl)-2(2,5-dioxo-pyrrolidin-1-yl-oxycarbonyl)-methyleneaminooxy]-2-methyl-propionic Acid Benzhydryl Ester (16). Dimethylformamide (1.3 L) was charged into a three-necked flask, fitted with a mechanical stirrer, thermometer, and an addition funnel. Monoacid ester

(11) The bisacylation product (**i**) was formed by reaction of the azetidinone **22** with diester **19** and was present (AP 0.1−0.2) in the recrystallized batches of aztreonam **1**.



(i)

(12) Singh, J. unpublished work. Synthesis of tigemonam **2** was not optimized by this method.

(13) HPLC method: Column: Bondapak C18, 3.9 mm × 300 mm, 10 μ irreg., no. 27324 (Waters). Solvent: 0.01 M TBA−HSO_4/CH_3CN = 32:68; for **12** (UV detection at 240 nm; R_t **12** = 3.73 min, **11** = 5.66 min, and **10** = 2.12 min) and 60:40 for **14** (UV light 234 nm, R_t **14** = 3.16 min and **9** = 1.74 min).

10 (300.0 g, 0.683 mol) and *N*-hydroxysuccinimide (78.6 g, 0.683 mol) were added. A solution of DCC (147.0 g, 0.716 mol) in DMF (200 mL) was added slowly at such a rate that the internal temperature did not rise above 30 °C. After 2 h TLC (silica gel: EtOAc−AcOH−H_2O = 8:1:1, visualized by UV light. R_f of **10** = 0.55) indicated completion of the reaction. The mixture was cooled to 0 °C and stirred for 1 h. DCU was removed by suction filtration, and the cake was washed with ice-cold DMF ((250 mL). The filtrate was cooled to 0 °C, and MeOH (1.8 L) was added, keeping the temperature below 10 °C. Water (1.8 L) was added slowly at 10 °C; when turbidity appeared, the addition was stopped to allow induction of crystallization. After completion of the addition of H_2O, the mixture was cooled to 0 °C and stirred for 1 h. The product was filtered and washed with ice-cold MeOH/H_2O (1:1, 3 × 200 mL) and dried under vacuum at 25 °C to a constant weight to yield 360.0 g (∼98%, corrected yield 84% vs a standard that was prepared by recrystallization)[14] of diester **16**. ^{1}H NMR (DMSO-d_6, 270 MHz) δ 1.56 (s, 6H), 2.90 (s, 4H), 6.82 (s, 1H), 7.08 (s, 1H), 7.20−7.41 (m, 10H), 7.45 (s, 2H). ^{13}C NMR (DMSO-d_6, 68 MHz) δ 23.40, 25.60, 76.96, 82.90, 112.10, 126.29, 127.59, 128.34, 140.23, 140.40, 143.37, 158.26, 169.29, 169.66, 171.30.

2-Amino-4-[(1-carboxy-1-methyl-ethoxyimino)−(2,5-dioxo-pyrrolidin-1-yloxycarbonyl)-methyl]-thiazol-3-ium Methanesulfonate (18). Intermediate **18** was prepared by two methods.

*Method A: By Selective Deprotection of Benzhydryl Ester **16**.* Anisole (100 mL) and CH_2Cl_2 (1.0 L) were charged into a three-necked flask fitted with a mechanical stirrer, thermometer, and an addition funnel. The solution was cooled to 0 °C, and MSA (100 mL) was added slowly; the temperature rose to 5 °C. Diester **16** (200.0 g, 0.448 mol) was added portionwise, keeping the temperature at 0−3 °C. After 1 h TLC (silica gel: EtOAc, visualized by UV light. R_f of **16** = 0.8) indicated completeness of the reaction. Methyl ethyl ketone (MEK, 2.0 L) was added at a rate such that the temperature did not exceed 10 °C. Crystallization of the product started during the addition of MEK. After stirring for 2 h the product was filtered and washed with MEK (4 × 100 mL). (Caution! If the cake was not washed thoroughly, it darkened during the drying process). The product was dried under vacuum at 25 °C to a constant weight to give 146.7 g (84.4%) of salt **18**, AP 96.9. The compound was stored at 5 °C.

*Method B: By Selective Silylation of the Diacid **9**.* 2-Amino-α-[(1-carboxy1-methylethoxy)imino]-4-thiazoleacetic acid (**9**)[1e] (109.2 g, 0.4 mol) and DMF (500 mL) were charged into a 1-L flask, and DMF (300 mL) was distilled on a rotary evaporator (50 °C bath temperature) to remove water. Trimethylchlorosilane (TMSCl, 70.0 mL, 0.55 mol) was added in one portion, and the mixture was stirred for 15 min. Excess TMSCl along with DMF (∼50 mL) was evaporated at 65 °C bath temperature, and the solution was transferred to a three-necked flask. The residual material was transferred with DMF (2 × 20 mL). The reaction flask was cooled in a ice/NaCl bath to −5 °C. *N*-Hydroxysuccinimide (50.0 g, 0.43 mol) was added, and the mixture was stirred for 3 min. A solution of DCC (95.0 g, 0.46 mol) in EtOAc (400 mL) was added dropwise at such a rate that the temperature did not exceed 5 °C. The addition took ∼1 h, and external cooling was necessary during this process. After the mixture stirred for 2 h, Et_3N (30.0 g) was added through the addition funnel over 1 min. The temperature of the mixture rose to 10 °C. After stirring for 1 min, the precipitated mixture of DCU and Et_3NHCl was filtered, and the filter cake was washed with a mixture (4:1) of EtOAc and DMF (200 mL) and EtOAc (100 mL). The filtrate was cooled to 5 °C, and MeOH (28 mL) was added with agitation. Methanesulfonic acid (36.0 mL) was added within 5 min. The reaction was exothermic, and its temperature was kept below 10 °C. The MSA salt of the OSu-ester (**18**) crystallized out. After 10 min EtOAc (300 mL) was added, and the mixture was stirred at 5 °C for 20 min. The product was filtered, washed with EtOAc (200 mL), and dried under vacuum to a constant weight to yield 185.0 g (78.3%), HPLC[14] AP 100, mp ∼140 °C, dec. The compound was stored at 5 °C. ^{1}H NMR (DMSO-d_6, 270 MHz) δ 1.51 (s, 6H), 2.49 (s, 3H), 2.89 (s, 4H), 7.13 (s, 1H), 9.0 (broad band for $(NH_3)^+$ and acidic H. Anal. Calcd for $C_{14}H_{18}N_4O_{10}S_2$·1.0DMF: C, 37.84; H, 4.67; N, 12.98; S, 11.88. Found: C, 37.63; H, 4.64; N, 13.0; S, 11.9.

[2*S*-[2α,3*β*-(*Z*)]]-3[[(2-Amino-4-thiazolyl)[(1-carboxy-1-methylethoxy)-imino]acetyl]amino]-2-methyl-4-oxo-1-azetidinesulfonic Acid (Aztreonam 1). *Method A: By Acylation of Zwitterion **22** with Active Amide **15**.* Triethylamine (3.0 mL, 21.5 mmol) was added to a stirring suspension of azetidinone **22**[1e] (0.901 g, 5.0 mmol) in 30% aqueous EtOH (9.8 mL) precooled to −6 °C. A clear, colorless solution was obtained. Active amide **15** (2.44 g, 5.02 mmol) was added portionwise over 1 h. EtOH (0.7 mL) was used to transfer the residual active amide to the reaction mixture. The mixture was stirred further at −6 to −3 °C for 2 h. Concentrated HCl (1.75 mL) was added dropwise, and product started precipitating within 2 min. The mixture was allowed to stand at −3 to 0 °C for 2.5 h. The product was filtered, washed with a mixture (1:1) of 95% EtOH and H_2O (2 × 2 mL) and EtOH (2 × 2 mL), and dried under vacuum to give 2.38 g (yield ∼81%) of aztreonam **1**. ^{1}H NMR (DMSO-d_6, 270 MHz) δ 1.42 (d, 3H, J = 5.9 Hz), 1.49 (s, 6H), 3.72 (ddd, 1H, J = 2.3, 5.9 and 8.2 Hz), 4.49 (dd, 1H, J = 2.35 and 7.6 Hz), 4.4−6.1 (broad band for NH_3 and OH), 6.96 (s, 1H), 9.32 (d, 1H, J = 8.2 Hz). Typical AP of the aztreonam made by this method was ∼98. The spectral data of this product was consistent with the reported[15] data.

*Method B: Telescoped Process from Azetidinone **21**[1e] and Active OSu-ester **18**).* A mixture (1:1) of MeOH and H_2O (1.4 L) was charged into a 2-L, three-necked flask equipped with a mechanical stirrer, gas inlet tube, and a pH electrode. Azetidinone **21** (150.0 g, 0.445 mol) was added, and the

(14) HPLC method: Column: identical to that in ref 13. Solvent: 0.01 M TBA−HSO_4/CH_3CN = 68:32; flow rate 2.0 mL/min; run time 8 min; sample 0.25 mg/mL anhydrous CH_3CN; UV detection at 236 nm; R_t diacid **9** = 1.94 min, **17** = 3.53 min.

(15) (a) Florey, K., Ed. Aztreonam. In *Analytical Profiles of Drug Substances*; Academic Press: New York, 1988; Vol 17, pp 1−40 and references therein. (b) Kleeman, A.; Engel, J.; Kutscher, B.; Reichert, D. *Pharmaceutical Substances*, 3rd ed.; Theime Stuttgart: New York, 1999; pp 154−156.

suspension was flushed with nitrogen gas. Pd−C (with 50% H_2O, 30.0 g) was introduced, and a stream of H_2 gas was passed through the reaction mixture. The pH was kept in the range of 6.8−7 with the addition of 2 N HCl as required. After 2 h TLC (silica gel: EtOAc−MeOH = 4:1, visualized by UV light and Rydon's spray, R_f of **21** = 0.7) indicated completion of the reduction. The mixture was filtered with suction over Diacel, and the filter cake was washed with mixture (1:1) of MeOH and H_2O (100 mL). (Note: If Hyflo is used instead of Diacel, the filtrate turns brown). The filtrate was transferred to a 4-L open vessel equipped with a mechanical stirrer, pH electrode, thermometer, and a dropping funnel. The solution was cooled to 0 °C, and Et_3N (∼5.0 mL) was added to adjust the pH to 8.0. OSu-ester MSA salt **18** (225.5 g, 0.477 mol) was added portionwise, and the pH was maintained in the range of 8.0−8.5 with the addition of Et_3N (∼175.0 mL). After the pH became constant, the reaction was checked for completeness by TLC (silica gel: EtOAc−AcOH−H_2O = 2:1:1, visualized by UV light and Rydon's spray; R_f of **22** = 0.47 and **1** = 0.69). The pH of the mixture was adjusted to 4.3 with concentrated HCl and then stirred with Diacel (10.0 g) for 10 min. The Diacel was removed by filtration, and the cake was washed with 1:1 MeOH−H_2O (100 mL). The filtrate was rapidly acidified to pH 1.3, keeping the temperature below 10 °C. In the case of premature precipitation before pH 1.3, the HCl addition was interrupted until the precipitate dissolved. Seeds of aztreonam **1** were added, and stirring was stopped to allow growth. After 10 min the mixture was cooled to 0 °C and stirred for 0.5 h. The precipitate was filtered, and the filter cake was washed with a cold mixture (1:1) of MeOH and H_2O (100 mL). The product was dried under vacuum to furnish 174.2 g (yield 86%) of aztreonam **1**, HPLC AP 97.8.[16] The product was identical (^{1}H NMR) to aztreonam prepared by method A.[15]

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(16) HPLC for quantitative assay of aztreonam **1**. Column: identical to that in ref 13. Solvents A = 0.05 phosphate buffer (pH 3.0), B = MeOH, UV light 262 nm; flow rate = 1.5 mL/min. Gradient: 74% A (4 min), 45% A (4 min), and 74% A; R_t aztreonam **1** = 4.4 min and diacid **9** = 2.8 min.