# SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF NOVEL AMINOTHIAZOLYL β-LACTAM DERIVATIVES

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The synthesis and *in vitro* antibacterial profile of a series of (*Z*)-(2-amino-4-thiazolyl)-[(2,3-dialkoxypropoxy)imino]acetyl derivatives of 7-aminocephalosporanic acid and 3-amino-monobactamic acid are reported.

A popular approach to the identification of important β-lactam antimicrobial agents has been the incorporation of novel acyl groups on the amino functionality at C-7 in the cephalosporin molecule and more recently at C-3 in the monobactam nucleus. A successful application of this strategy has been the use of suitably functionalized α-oxime aminothiazole acyl side chains to afford such agents as cefotaxime, ceftizoxime, ceftazidime, aztreonam, *inter alia*.[1~8] As an extension of this concept, we sought to introduce novel bifunctional three carbon substituents onto the oxime segment of the aminothiazole moiety in an effort to further define the structural parameters of antibacterial action. Herein are described the synthesis and antibacterial profile of the simplest members of this series.

The syntheses of the title compounds are illustrated in Scheme 1. Alkylation of aminothiazole **1** with 1-bromo-3-methoxy-2-propanone[9] in dimethylformamide containing potassium carbonate afforded **2** in 64% yield. Reduction of **2** using sodium borohydride gave racemic alcohol **3** in 90% yield. Treatment of **3** with sodium hydride followed by methyl iodide gave a many component product; high performance liquid chromatographic purification furnished *dl*-**4** as a homogeneous oil, albeit in low yield (43%). By contrast, **3** was converted under standard conditions, to the analytically pure *tert*-butyldimethylsilyl ether (TBDMS) *dl*-**5** in 96% yield.

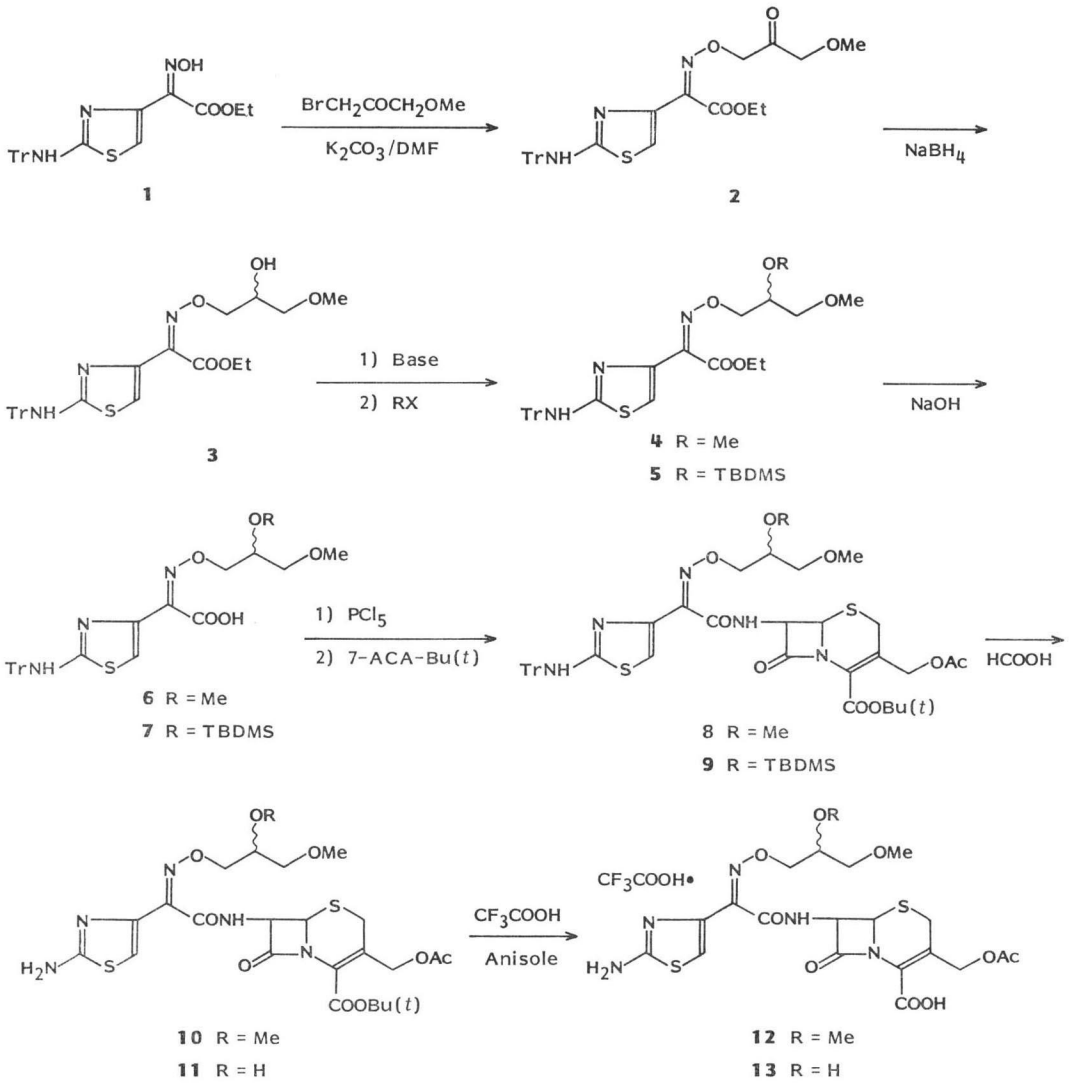
Saponification of **4** and **5** gave acids **6** (94%) and **7** (66%), respectively. Coupling of *dl*-**6** (*via* the acid chloride) with 7-aminocephalosporanic acid *tert*-butyl ester (7-ACA-Bu(*t*)) afforded **8** (83%) as a mixture of epimers. Detritylation of **8** using aqueous formic acid provided **10** in moderate yield (57%). Treatment of **10** with trifluoroacetic acid in the presence of anisole at 0°C furnished **12** (69%). Cephalosporin derivatives **13** were prepared in similar fashion from **7**.

The synthesis of the analogous monobactam derivatives is depicted in Scheme 2. Thus, coupling of aminothiazoles **7** and **14** with (3*S*-*trans*)-3-amino-4-methyl-2-oxoazetidine-1-sulfonic acid (**15**)[10] by the standard methodology (*vide infra*) yielded epimeric monobactams **16** and **17**, respectively.

The results of *in vitro* antibacterial evaluation are summarized in Table 1. Cephalosporin derivatives **12** and **13** show high activity against a variety of Gram-positive and Gram-negative organisms with modest activity against *Pseudomonas aeruginosa*. In contrast, monobactam congeners **16** and **17** display good activity against some Gram-negative bacteria, but are ineffective *versus* Gram-positive organisms and *P. aeruginosa* at the concentrations tested. The most potent compounds in the series, cephalosporin **13** and monobactam **16**, contain a hydrophilic group on the oxime side chain;† none-

† For similar observations with related oximino substituents, see ref 6 and 7.

Scheme 1.




**1**

**2**

**3**

**4** R = Me

**5** R = TBDMS

**6** R = Me

**7** R = TBDMS

**8** R = Me

**9** R = TBDMS

**10** R = Me

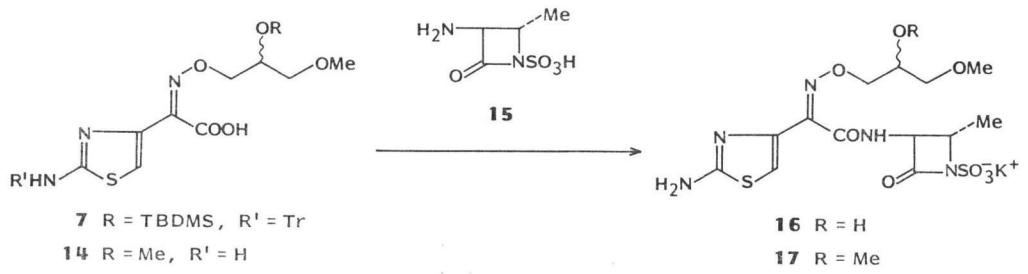
**11** R = H

**12** R = Me

**13** R = H

Tr = Triphenylmethyl

Scheme 2.




**15**

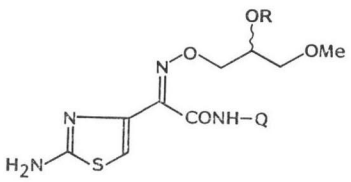
**7** R = TBDMS, R' = Tr

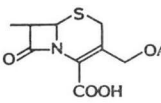
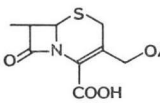
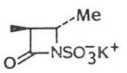
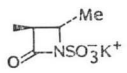
**14** R = Me, R' = H

**16** R = H

**17** R = Me

Table 1. *In vitro* antibacterial screening results (MIC $\mu$g/ml).



| Compound | Q | R | *Sa** | *Ef* | *Ecl* | *Ec* | *Kp* | *Pv* | *Pa* | *Sm* |
|---|---|---|---|---|---|---|---|---|---|---|
| **12** |  | Me | 8 | 256 | 32 | 4 | 4 | 2 | 64 | 32 |
| **13** |  | H | 4 | 4 | 16 | 0.5 | 0.25 | 0.25 | 32 | 4 |
| **16** |  | H | >256 | >256 | 1 | 1 | 0.5 | 1 | 256 | 2 |
| **17** |  | Me | 256 | >256 | 8 | 8 | 4 | 4 | 256 | 8 |
| Cefotaxime | | | 1 | 128 | 0.125 | 0.015 | 0.03 | 0.06 | 8 | 0.25 |
| Aztreonam | | | 128 | 256 | 1 | 0.125 | 0.06 | 0.015 | 2 | 0.125 |

* *Sa*; *Staphylococcus aureus* ATCC 29213, *Ef*; *Enterococcus faecalis* ATCC 29212, *Ecl*; *Enterobacter cloacae* ATCC 13047, *Ec*; *Escherichia coli* ATCC 25922, *Kp*; *Klebsiella pneumoniae* KL-1, *Pv*; *Proteus vulgaris* A84354 1, *Pa*; *Pseudomonas aeruginosa* ATCC 27853, *Sm*; *Serratia marcescens* ATCC 13880.

theless, these compounds are significantly less active than cefotaxime and aztreonam, respectively.

## Experimental

Elemental analyses were performed with a Perkin-Elmer Model 240 elemental analyzer by the Analytical Section of these laboratories. IR spectra were recorded on a Perkin-Elmer 299 infrared spectrophotometer. NMR spectra were obtained on either a Varian FT-80A or Varian XL-300 spectrometer in the indicated solvents with $Me_4Si$ as the internal standard. HPLC purifications were performed using a Waters Prep-500 unit.

(*Z*)-$\alpha$-[(3-Methoxy-2-oxopropoxy)imino]-2-[(triphenylmethyl)amino]-4-thiazoleacetic Acid Ethyl Ester (**2**)

A mixture of 34.0 g (0.204 mol) of 1-bromo-3-methoxy-2-propanone,[9] 25.0 g (0.0547 mol) of (*Z*)-$\alpha$-(hydroxyimino)-2-[(triphenylmethyl)amino]-4-thiazoleacetic acid ethyl ester (**1**), 25.0 g (0.181 mol) of $K_2CO_3$, and 300 ml of DMF was stirred at 0~5°C for 6 hours, then at ambient temperature overnight. The reaction mixture was diluted with $H_2O$ and extracted with EtOAc. The combined organic extracts were washed copiously with $H_2O$, then brine, dried over $Na_2SO_4$, and concentrated *in vacuo* to give a brown oily solid. Trituration with $Et_2O$ afforded 19.0 g (64%) of **2**: IR (KBr) 3340, 1740, 1530, 1030 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 7.33 (s, 15H), 6.94 (br s, 1H, exchangeable), 6.55 (s, 1H), 4.86 (s, 2H), 4.4 (q, 2H, $J$=7 Hz), 4.27 (s, 2H), 3.43 (s, 3H), and 1.36 (t, 3H, $J$=7 Hz).

*Anal* Calcd for $C_{30}H_{29}N_3O_5S$: C 66.28, H 5.38, N 7.73.
Found: C 65.95, H 5.24, N 8.00.

(*Z*)-α-[(2*RS*-Hydroxy-3-methoxypropoxy)imino]-2-[(triphenylmethyl)amino]-4-thiazoleacetic Acid Ethyl Ester (**3**)

To a mixture of 10.0 g (0.0184 mol) of aminothiazole **2** and 100 ml of MeOH at 0°C was added portionwise 720 mg (0.0190 mol) of $NaBH_4$. The reaction mixture was stirred at this temperature for 1 hour, then carefully poured into 1 N HCl at 0°C, and extracted with EtOAc. The combined extracts were washed with brine, dried over $Na_2SO_4$, and concentrated *in vacuo* to give 9.0 g (90%) of **3** as an amber glass. Crystallization of the glass from MeOH - $H_2O$ afforded 4.9 g (49%) of the analytical sample: IR (KBr) 3405, 3300, 1725, 1525, 1280, 1180 $cm^{-1}$; NMR ($CDCl_3$ - $D_2O$) $\delta$ 7.3 (s, 15H), 6.53 (s, 1H), 4.65~4.0 (m, 5H), 3.5~3.25 (m, 2H), 3.35 (s, 3H), and 1.33 (t, 3H, $J$=7 Hz).

*Anal* Calcd for $C_{30}H_{31}N_3O_5S$: C 66.03, H 5.73, N 7.70.
Found: C 66.55, H 5.59, N 7.58.

(*Z*)-α-[(2*RS*,3-Dimethoxypropoxy)imino]-2-[(triphenylmethyl)amino]-4-thiazoleacetic Acid Ethyl Ester (**4**)

To a mixture of 300 mg (7.5 mmol) of NaH (60% oil dispersion) and 10 ml of anhydrous THF, cooled to 0°C under a nitrogen atmosphere was added dropwise a solution of 4.0 g (7.3 mmol) of aminothiazole **3** and 30 ml of THF. After 5 minutes, 1.6 ml (3.65 g, 25.7 mmol) of methyl iodide was added. The reaction mixture was stirred at ambient temperature for 24 hours, carefully treated with satd $NH_4Cl$ solution, and extracted with EtOAc. The combined extracts were dried over $Na_2SO_4$ and concentrated *in vacuo*. The residue was purified by high performance liquid chromatography (silica gel; elution with EtOAc - $CH_2Cl_2$, 2: 98) to afford 1.78 g (43%) of **4** as a pale yellow oil: IR (neat) 3300, 1730, 1525, 1270, 1180, 1020 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 7.3 (s, 15H), 6.9 (br s, 1H, exchangeable), 6.5 (s, 1H), 4.45~4.15 (m, 4H), 3.75~3.55 (m, 1H), 3.5~3.25 (m, 2H), 3.45 (s, 3H), 3.35 (s, 3H), and 1.33 (t, 3H, $J$=7 Hz).

*Anal* Calcd for $C_{31}H_{33}N_3O_5S$: C 66.53, H 5.94, N 7.51.
Found: C 66.33, H 5.99, N 7.37.

(*Z*)-α-[[2*RS*-(*tert*-Butyldimethylsilyloxy)-3-methoxypropoxy]imino]-2-[(triphenylmethyl)amino]-4-thiazoleacetic Acid Ethyl Ester (**5**)

A mixture of 29.15 g (53.4 mmol) of aminothiazole **3**, 10.91 g (160.3 mmol) of imidazole, and 50 ml of DMF was stirred at 0°C. A solution of 12.08 g (80.0 mmol) of *tert*-butyldimethylsilyl chloride and 50 ml of DMF was added dropwise to the mixture which was stirred at 0°C for 1 hour, then at ambient temperature overnight. The reaction mixture was diluted with $H_2O$, cooled to 0°C, and then acidified with a 1 N HCl solution. The acidified solution was extracted with EtOAc. The combined extracts were washed with $H_2O$ and brine, dried over $Na_2SO_4$, and concentrated under reduced pressure to give 33.78 g (96%) of **5** as a gold oil: IR (neat) 1740, 1530, 1030 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 7.29 (s, 15H), 6.87 (s, 1H), 6.48 (s, 1H), 4.50~3.90 (m, 5H), 3.45~3.20 (m, 2H), 3.32 (s, 3H), 1.32 (t, 3H, $J$=7 Hz), 0.85 (s, 9H), and 0.05 (s, 6H).

*Anal* Calcd for $C_{36}H_{45}N_3O_5SSi$: C 65.52, H 6.87, N 6.37.
Found: C 65.26, H 6.60, N 6.12.

(*Z*)-α-[(2*RS*,3-Dimethoxypropoxy)imino]-2-[(triphenylmethyl)amino]-4-thiazoleacetic Acid (**6**)

A mixture of 400 mg (0.7 mmol) of aminothiazole **4**, 2 ml of EtOH, and 2 ml of 1 N NaOH solution was stirred at ambient temperature overnight. The reaction mixture was carefully acidified using a 1 N HCl solution (0°C) and immediately extracted with EtOAc. The combined extracts were dried over $Na_2SO_4$ and concentrated under reduced pressure to furnish 350 mg (94%) of **6** as a tan waxy solid. The analytical sample was prepared by trituration with $Et_2O$ to give a tan waxy solid: IR (KBr) 3410 (br), 1720 (br), 1445, 1030 $cm^{-1}$; NMR ($CDCl_3$ - $D_2O$) $\delta$ 7.4 (s, 15H), 6.68 (s, 1H), 4.4~4.3 (m, 2H), 3.76~3.66 (m, 1H), 3.60~3.4 (m, 2H), 3.45 (s, 3H), and 3.35 (s, 3H).

*Anal* Calcd for $C_{29}H_{29}N_3O_5S \cdot \frac{1}{2}H_2O$: C 64.43, H 5.59, N 7.77.
Found: C 64.21, H 5.53, N 7.50.

(*Z*)-α-[[2*RS*-(*tert*-Butyldimethylsilyloxy)-3-methoxypropoxy]imino]-2-[(triphenylmethyl)amino]-4-thiazoleacetic Acid (**7**)

A mixture of 41.91 g (63.5 mmol) of aminothiazole **5**, 190 ml of a 2 N NaOH solution, and 200 ml

of absolute EtOH was stirred under reflux for 3 hours. Upon cooling, the solution was acidified with a 1 N HCl solution and extracted with EtOAc. The combined extracts were washed with brine, dried over $Na_2SO_4$, and concentrated under reduced pressure. The residue was triturated with $Et_2O$ to yield 26.28 g (66%) of **7** as an off-white waxy solid: IR (KBr) 1710 (br), 1635 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 7.34 (s, 15H), 6.78 (s, 1H), 4.46~4.04 (m, 3H), 3.56~3.40 (m, 2H), 3.34 (s, 3H), 0.85 (s, 9H), and 0.06 (s, 6H).

*Anal* Calcd for $C_{34}H_{41}N_3O_5SSi \cdot \frac{1}{2}H_2O$: C 63.70, H 6.61, N 6.56.
Found: C 63.85, H 6.32, N 6.30.

7-[[(*Z*)-[(2*RS*,3-Dimethoxypropoxy)imino]-[2-[(triphenylmethyl)amino]-4-thiazolyl]acetyl]amino]-cephalosporanic Acid *tert*-Butyl Ester (**8**)

To a solution of 2.0 g (3.8 mmol) of aminothiazole **6**, 0.60 ml (0.44 g, 4.3 mmol) of $Et_3N$, and 40 ml of $CH_2Cl_2$ at 0°C under a nitrogen atmosphere was added portionwise 815 mg (3.9 mmol) of $PCl_5$. After 30 minutes, the solution was concentrated *in vacuo*. The residue was dissolved in $CH_2Cl_2$ and again concentrated *in vacuo*. The resulting solid was dissolved in 20 ml of $CH_2Cl_2$ and added dropwise to a solution of 1.25 g (3.8 mmol) of 7-aminocephalosporanic acid *tert*-butyl ester, 10 ml of $CH_2Cl_2$, and 0.60 ml (0.59 g, 7.4 mmol) of pyridine at 0°C under a nitrogen atmosphere. After 2 hours, the reaction mixture was carefully acidified using a 1 N HCl solution and diluted with $H_2O$. The aqueous phase was separated and extracted with $CH_2Cl_2$. The extracts were combined with the initial organic phase, washed with satd $NaHCO_3$ solution and brine, dried over $Na_2SO_4$, and concentrated under reduced pressure to give 2.66 g (83%) of **8**. The analytical sample was prepared by column chromatography (silica gel; elution with EtOAc - $CH_2Cl_2$, 1: 4): IR (KBr) 3380, 3270, 1790, 1735, 1710, 1685, 1525, 1240, 700 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 7.32 (s, 15H), 7.0 (s, 1H), 6.78 (s, 1H), 5.98~5.88 (m, 1H), 5.14~5.02 (m, 2H), 4.82 (d, 1H, $J$=13 Hz), 4.48~4.32 (m, 2H), 3.78~3.68 (m, 1H), 3.62~3.3 (m, 4H), 3.46 (s, 3H), 3.36 (s, 3H), 2.1 (s, 3H), and 1.54 (s, 9H).

*Anal* Calcd for $C_{43}H_{47}N_5O_9S$: C 61.34, H 5.63, N 8.32.
Found: C 61.25, H 5.77, N 8.08.

7-[[(*Z*)-[[2*RS*-(*tert*-Butyldimethylsilyloxy)-3-methoxypropoxy]imino]-[2-[(triphenylmethyl)amino]-4-thiazolyl]acetyl]amino]cephalosporanic Acid *tert*-Butyl Ester (**9**)

To a solution of 9.54 g (15.1 mmol) of aminothiazole **7**, 2.5 ml (17.9 mmol) of $Et_3N$, and 100 ml of $CH_2Cl_2$ at 0°C under a nitrogen atmosphere was added portionwise 3.38 g (30.8 mmol) of $PCl_5$. After stirring for 30 minutes at 0°C, the solution was concentrated under reduced pressure. The residue was dissolved in $CH_2Cl_2$ and again concentrated under reduced pressure. The resulting solid was dissolved in 50 ml of $CH_2Cl_2$ and added dropwise to a solution of 4.96 g (15.1 mmol) of 7-aminocephalosporanic acid *tert*-butyl ester, 25 ml of $CH_2Cl_2$, and 2.5 ml (30.8 mmol) of pyridine at 0°C under a nitrogen atmosphere. After 3 hours, the reaction mixture was acidified using a 1 N HCl solution and diluted with $H_2O$. The aqueous phase was separated and extracted with $CH_2Cl_2$. The extracts were combined with the initial organic phase, washed with a satd $NaHCO_3$ solution and brine, dried over $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by HPLC ($CH_2Cl_2$ - EtOAc, 95: 5) to yield 2.14 g (15%) of **9**: IR (KBr) 1788, 1722, 1680, 1540 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 7.34 (s, 15H), 6.97 (s, 1H), 6.76 (s, 1H), 6.00~5.90 (m, 1H), 5.10 (d, 1H, $J$=13 Hz), 5.08~5.02 (m, 1H), 4.83 (d, 1H, $J$=13 Hz), 4.42~4.10 (m, 3H), 3.60~3.26 (m, 4H), 3.30 (s, 3H), 2.10 (s, 3H), 1.54 (s, 9H), 0.86 (s, 9H), and 0.06 (s, 6H).

7-[[(*Z*)-(2-Amino-4-thiazolyl)-[(2*RS*,3-dimethoxypropoxy)imino]acetyl]amino]cephalosporanic Acid *tert*-Butyl Ester (**10**)

A solution of **8** and 10 ml of HCOOH (88%) was stirred at 0°C for 15 minutes, then at ambient temperature for 2.5 hours. The reaction mixture was filtered. The filtrate was cooled to 0°C, diluted with $H_2O$, treated with satd $NaHCO_3$ solution, and extracted with $CH_2Cl_2$. The combined extracts were washed with a 1 N HCl solution, brine, and dried over $Na_2SO_4$. The solvent was removed *in vacuo*. The residue was applied to a silica gel column. After initial elution with EtOAc - $CH_2Cl_2$ (1: 9), the product was obtained by elution with EtOAc (120 mg). An additional 285 mg was obtained by elution with MeOH - $CH_2Cl_2$ (1: 9); total yield 405 mg (57%): IR (KBr) 3400 (br), 3260 (br), 1780,

1720 (br), 1670, 1530, 1025 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 7.54~7.44 (m, 1H), 6.94 (s, 1H), 6.02~5.92 (m, 3H), 5.14~5.06 (m, 2H), 4.84 (d, 1H, $J$=13 Hz), 4.42~4.34 (m, 2H), 3.8~3.7 (m, 1H), 3.64~3.36 (m, 4H), 3.46 (s, 3H), 3.4 (s, 3H), 2.1 (s, 3H), and 1.54 (s, 9H).

*Anal* Calcd for $C_{24}H_{33}N_5O_9S_2 \cdot 2EtOAc$: C 49.53, H 6.36, N 9.02.
Found: C 49.60, H 5.86, N 9.37.

7-[[(*Z*)-(2-Amino-4-thiazolyl)-[(2*RS*-hydroxy-3-methoxypropoxy)imino]acetyl]amino]cephalosporanic Acid *tert*-Butyl Ester (**11**)

A solution of 1.0 g (1.07 mmol) of **9** and 15 ml of HCOOH (88%) was stirred at ambient temperature for 3.5 hours. The reaction mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel; $CH_2Cl_2$ - EtOAc, 1:9; MeOH - $CH_2Cl_2$, 1:9). Concentration of the MeOH fractions under reduced pressure gave 190 mg (31%) of **11** as an amber glass: IR (KBr) 3300, 1788, 1725, 1678, 1540, 1380 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 8.17 (m, 1H, exchangeable), 6.79 (s, 1H), 6.05~5.7 (m, 1H), 5.35~3.85 (complex m, 9H (3H, exchangeable)), 3.60~3.10 (m, 4H), 3.35 (s, 3H), 2.05 (s, 3H), and 1.51 (s, 9H).

7-[[(*Z*)-(2-Amino-4-thiazolyl)-[(2*RS*,3-dimethoxypropoxy)imino]acetyl]amino]cephalosporanic Acid, Trifluoroacetate Salt (**12**)

To a mixture of 105 mg (0.18 mmol) of **10** and 0.5 ml of anisole at 0°C under a nitrogen atmosphere was added 5 ml of cold $CF_3COOH$. After 3 hours, the reaction mixture was diluted with toluene. The solvent and $CF_3COOH$ were removed under high vacuum. The residue was triturated with $Et_2O$ to afford 66 mg (69%) of **12**: IR (KBr) 3380~3200 (br), 2600~2320 (br), 1785, 1720 (br), 1670 (br), 1190, 1030 $cm^{-1}$; NMR (DMSO-$d_6$) $\delta$ 9.72~9.62 (m, 1H, exchangeable), 7.6~7.0 (br m, 3H, exchangeable), 5.88~5.78 (m, 1H), 5.28~5.16 (m, 1H), 5.02 (d, 1H, $J$=13 Hz), 4.7 (d, 1H, $J$=13 Hz), 4.14~4.06 (m, 2H), 3.68~3.20 (m, 3H), 3.34 (s, 3H), 3.26 (s, 3H), and 2.04 (s, 3H).

7-[[(*Z*)-(2-Amino-4-thiazolyl)-[(2*RS*-hydroxy-3-methoxypropoxy)imino]acetyl]amino]cephalosporanic Acid, Trifluoroacetate Salt (**13**)

To a mixture of 141 mg (0.24 mmol) of **11** and 0.54 ml of anisole at 0°C was added 5.5 ml of $CF_3COOH$. After stirring for 3 hours at 0°C, the $CF_3COOH$ was removed under high vacuum. The residue was triturated with $Et_2O$ to yield 102 mg (80%) of **13**: IR (KBr) 3320, 1780, 1720, 1660, 1190 $cm^{-1}$; NMR (DMSO-$d_6$) $\delta$ 9.65 (d, 1H, exchangeable), 6.84 (s, 1H), 5.94~5.80 (m, 1H), 5.21 (d, 1H, $J$=5 Hz), 5.03 (d, 1H, $J$=13 Hz), 4.72 (d, 1H, $J$=13 Hz), 4.12~3.86 (m, 3H), 3.67 (d, 1H, $J$=18 Hz), 3.49 (d, 1H, $J$=18 Hz), 3.44~3.20 (m, 2H), 3.27 (s, 3H), and 2.04 (s, 3H).

2-Amino-(*Z*)-$\alpha$-[(2*RS*,3-dimethoxypropoxy)imino]-4-thiazoleacetic Acid (**14**)

A solution of 1.0 g (1.9 mmol) of **6** and 10 ml of HCOOH (88%) was stirred at ambient temperature for 3 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give an oily solid. Recrystallization from EtOH - $H_2O$ furnished 308 mg (56%) of **14**: NMR (DMSO-$d_6$) $\delta$ 7.2 (br s, 2H, exchangeable), 6.85 (s, 1H), 4.2~4.0 (m, 2H), 3.7~3.0 (m, 3H), 3.31 (s, 3H), and 3.25 (s, 3H).

*Anal* Calcd for $C_{10}H_{15}N_3O_5$: C 41.51, H 5.23, N 14.52.
Found: C 41.80, H 5.06, N 13.68.

(3*S-trans*)-3-[[(*Z*)-(2-Amino-4-thiazolyl)-[(2*RS*-hydroxy-3-methoxypropoxy)imino]acetyl]amino]-4-methyl-2-oxo-1-azetidinesulfonic Acid, Potassium Salt (**16**)

To a solution of 2.0 g (3.2 mmol) of aminothiazole **7** and 25 ml of DMF at ambient temperature was added sequentially 0.5 ml (403 mg, 3.2 mmol) of diisopropylcarbodiimide and 435 mg (3.2 mmol) of 1-hydroxybenzotriazole. After 15 minutes, a solution of 575 mg (3.2 mmol) of (3*S-trans*)-3-amino-4-methyl-2-oxoazetidine-1-sulfonic acid,[10] 0.9 ml (653 mg, 6.5 mmol) of $Et_3N$, and 25 ml of DMF was added to the reaction mixture which then was stirred overnight at ambient temperature. The reaction mixture was diluted with 40% $Bu_4NOH$ solution and extracted with $CH_2Cl_2$. The combined extracts were washed with brine, dried over $Na_2SO_4$ and concentrated under reduced pressure. The residue was treated with 10 ml of HCOOH (88%) at ambient temperature for 3 hours, then filtered. The

filtrate was concentrated under high vacuum to give a brown oil. The oil was dissolved in 15 ml of acetone and filtered twice. To the resulting solution was added in one portion, a solution of 1.1 g (3.3 mmol) of potassium nonafluorobutane sulfonate and 25 ml of acetone. The resulting precipitate was collected to give a pasty solid which was triturated with $Et_2O$ to afford a white solid. The product was further purified by reverse phase high performance liquid chromatography ($CH_3CN$ - AcOH - $H_2O$, 2.5: 2.5: 95) to give, after lyophilization, 38 mg (3%) of **16** as a white solid: IR (KBr) 3300 (br), 1765, 1665, 1640, 1270, 1210 (br), 1040 $cm^{-1}$; NMR (DMSO-$d_6$) $\delta$ 9.44~9.34 (m, 1H, exchangeable), 9.04~8.98 (m, 1H, exchangeable), 6.89 (s, 1H), 4.86~4.78 (m, 1H), 4.52~4.44 (m, 1H), 4.14~4.02 (m, 2H), 3.96~3.84 (m, 1H), 3.38~3.22 (m, 2H), 3.28 (s, 3H), and 1.40 (d, 3H, $J$=7 Hz).

(3*S-trans*)-3-[[(*Z*)-(2-Amino-4-thiazolyl)-[2*RS*,3-dimethoxypropoxy)imino]acetyl]amino]-4-methyl-2-oxoazetidine-1-sulfonic Acid, Potassium Salt (**17**)

To a solution of 200 mg (6.9 mmol) of **14** and 5 ml of anhydrous DMF at ambient temperature under a nitrogen atmosphere was added sequentially 0.11 ml (89 mg, 0.7 mmol) of diisopropylcarbodiimide and 95 mg (0.7 mmol) of 1-hydroxybenzotriazole. After 30 minutes, a solution of 125 mg (0.69 mmol) of (3*S-trans*)-3-amino-4-methyl-2-oxoazetidine-1-sulfonic acid,[10] 0.19 ml (138 mg, 1.36 mmol) of $Et_3N$, and 5 ml of DMF was added to the reaction mixture which then was stirred overnight at ambient temperature. Removal of the volatiles under high vacuum gave a brown oil which was dissolved in 10 ml of acetone and filtered. The filtrate was treated with a solution of 300 mg (0.89 mmol) of potassium nonafluorobutane sulfonate and 5 ml of acetone. The resulting precipitate was collected and triturated with $Et_2O$ to give 123 mg (36%) of **17** as a light tan powder. A second crop was obtained when the acetone filtrate was treated with a small amount of $Et_2O$ (80 mg, 24%): IR (KBr) 3400, 3310, 3200, 1765, 1670, 1620, 1270, 1240, 1050 $cm^{-1}$; NMR (DMSO-$d_6$) $\delta$ 9.31 (m, 1H, exchangeable), 7.26 (s, 2H, exchangeable), 6.76 (s, 1H), 4.48~4.42 (m, 1H), 4.16~4.04 (m, 2H), 3.76~3.68 (m, 1H), 3.6~3.5 (m, 1H), 3.48~3.26 (m, 3H), 3.34 (s, 3H), 3.27 (s, 3H), and 1.4 (d, 3H, $J$=7 Hz).

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