SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS IN THE CEFPIROME SERIES

III. 7α-METHOXY AND 7α-FORMAMIDO ANALOGUES OF CEFPIROME

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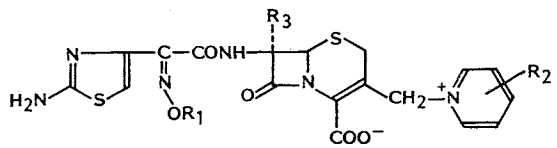
(Received for publication February 1, 1988)

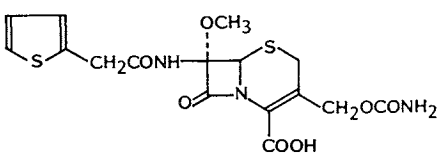
7α-Methoxy and 7α-formamido derivatives of cefpirome (HR 810) have been synthesized and tested in comparison with cefpirome and some analogues **1** against aerobic and anaerobic bacteria. Cefpirome and analogues **1** have good activity against Gram-positive and only limited activity against Gram-negative anaerobic bacteria. 7α-Methoxy derivatives **2** show only a slight improvement of activity against Gram-negative anaerobes and are less active against all aerobes. Introduction of the 7α-formamido group (compounds **3**) results in an overall loss of activity towards both aerobic and anaerobic bacteria.

In the preceding papers[1] the synthesis and biological evaluation of 7-[2-(2-aminothiazol-4-yl)-2-(*Z*)-oxyiminoacetamido]-3′-pyridinium cephalosporins have been described. Our main task of obtaining cephalosporins with both high anti-staphylococcal and high anti-pseudomonal activity was highly successful. Cefpirome (**1a**) and related compounds of the general formula **1** having pyridinium groups with fused rings, cycloalkyl and alkoxy substituents have been found to be very promising

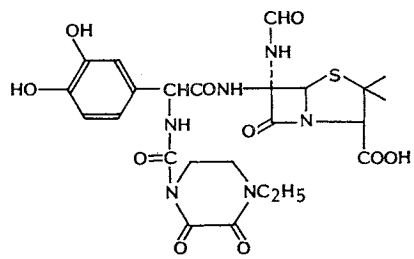


1a ~ 1d R_3 = H
(**1a**: Cefpirome, HR 810)
2a ~ 2d R_3 = OCH_3
3a ~ 3c R_3 = NHCHO

a R_1 = CH_3 R_2 = 2,3-Cyclopenteno
b R_1 = CH_3 R_2 = 4- 
c R_1 = CH_3 R_2 = 4-OCH_3
d R_1 = $C(CH_3)_2COOH$ R_2 = 2,3-Cyclopenteno

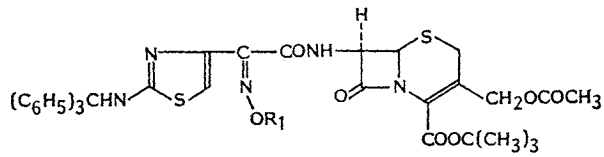


Cefoxitin



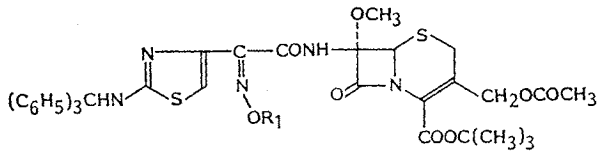
BRL 36650

Scheme 1. Synthesis of 7α-methoxy compounds **2** and **6**.



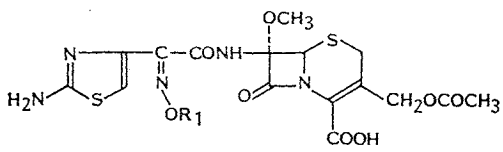
4a $R_1 = CH_3$
4b $R_1 = C(CH_3)_2COOC(CH_3)_3$

$CH_3OH, (CH_3)_3COCl, CH_3COOH$ — Method D

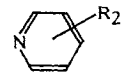


5a $R_1 = CH_3$
5b $R_1 = C(CH_3)_2COOC(CH_3)_3$

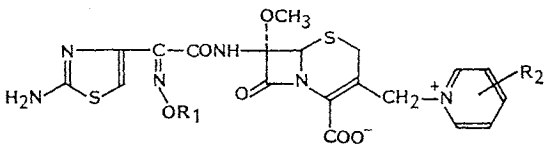
90% CF_3COOH



6a $R_1 = CH_3$
6b $R_1 = C(CH_3)_2COOH$



H_2O – KI — Method A



2a ~ 2d

with regard to their antibacterial activity and other biological properties.

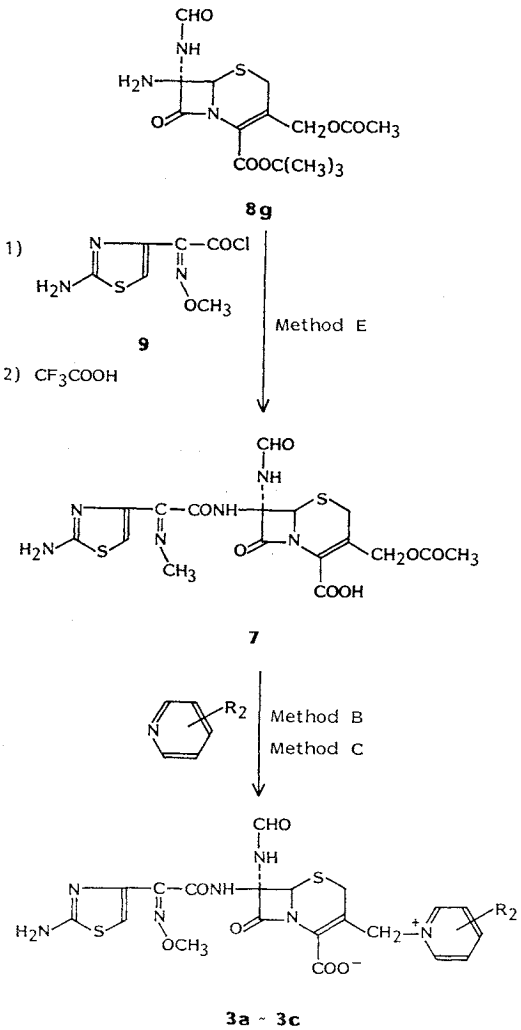
It is known that incorporation of a 7α-methoxy group in both penicillins and cephalosporins has led to a considerable increase in β-lactamase stability. 7α-Methoxy cephalosporins, *e.g.* cefoxitin, have excellent activity against β-lactamase forming anaerobes, *e.g. Bacteroides*. Recently 7α-formamido cephalosporins were isolated as fermentation products of various Gram-negative bacteria[2~4] and potent 6α-formamido penicillins, *e.g.* BRL 36650, have been synthesized[5,6].

These findings prompted us to prepare 7α-methoxy and 7α-formamido derivatives **2** and **3** in analogy to the cefpirome series from pyridinium cephalosporins of type **1**. The synthesis and antibacterial properties of some representative compounds are described in this paper.

Chemistry

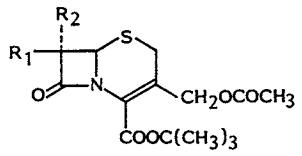
The synthesis of the parent compounds **1a**~**1d** has been described in the preceding papers[1]. 7α-Methoxy compounds **2a**~**2d** were prepared as outlined in Scheme 1. The protected cefotaxime derivatives **4a** and **4b** were converted to the 7α-methoxy analogues **5a** and **5b** with lithium methoxide - *tert*-butyl hypochlorite in THF at −70°C[7]. Separation from starting material was achieved by chromatography on silica gel with Et_2O as eluent. Deprotection with 90% trifluoroacetic acid (TFA) gave the 7α-methoxy compounds **6a** and **6b**. Displacement of the 3′-acetoxy group with pyridines was achieved in aqueous solution in the presence of potassium iodide at 65°C (Method A)[1]. The target compounds **2a**~**2d** were obtained in a yield of approximately 10% after chromatography on silica gel.

Scheme 2. Synthesis of 7α-formamido compounds **3** and **7**.



Starting material for 7α-formamido cefotaxime (**7**) was *tert*-butyl 7-amino-7α-formamido cephalosporanate (**8g**) (Scheme 2). This product was obtained by a 6-step procedure starting from 7-ACA *tert*-butyl ester (**8a**) (Scheme 3) *via* the *p*-nitrobenzaldehyde Schiff base **8b** and 7α-methylthio compound **8c**[8]. In contrast to reports in the literature[6], **8c** could be easily cleaved to the amine **8d** with Girard's reagent T in the presence of *p*-toluenesulfonic acid. Mercury (II) acetate mediated displacement of the methylthio group by the formamido group using *N*,*N*-bis(trimethylsilyl)formamide afforded **8f**[5]. Crystalline **8g** was obtained in an overall yield of 41%. Acylation of **8g** with the acid chloride **9** (phosgene Method E) gave the *tert*-butyl ester of **7** in excellent yield (92%), that upon treat-

Scheme 3. Synthesis of compound **8g** from 7-ACA *tert*-butyl ester (**8a**).



8a $R_1=NH_2$ $R_2=H$

8b $R_1=O_2N-C_6H_4-CH=N-$ $R_2=H$ (mp 147~151°C)

8c $R_1=O_2N-C_6H_4-CH=N-$ $R_2=SCH_3$ (crude oil)

8d $R_1=NH_2$ $R_2=SCH_3$ (crude oil)

8e $R_1=CCl_3CH_2OCONH-$ $R_2=SCH_3$ (mp 123~124°C (Et_2O))

8f $R_1=CCl_3CH_2OCONH-$ $R_2=NHCHO$ (crude oil)

8g $R_1=NH_2$ $R_2=NHCHO$ (mp 168~171°C)

8a → 8b: $O_2N-C_6H_4-CHO$ (C_2H_5OH, room temp, 91%)

8b → 8c: 0.65 equiv LDA, 1.4 equiv $CH_3SSO_2CH_3$, DMF, 1 hour −75 to −5°C, 100%

8c → 8d: Girard T, 0.2 equiv *p*-toluenesulfonic acid, aq DMF, 1 hour room temp, 78%

8d → 8e: CCl_3CH_2OCOCl, pyridine, CH_2Cl_2, 72%

8e → 8f: $HCON(Si(CH_3)_3)_2$, $Hg(OAc)_2$, DMF, 99%

8f → 8g: Zn, THF, 1 M phosphate buffer, pH 4.4, 81%

ment with TFA afforded 7α-formamido cefotaxime (**7**) (Scheme 2). Pyridinium derivatives **3a~3c** were prepared from **7** and the corresponding pyridine bases according to the iodotrimethylsilane procedures B and C[1], and were obtained in approximately 20% yield.

Antibacterial Activity

Cefpirome (**1a**) and the analogues **1b** and **1c** with a neutral methoxyimino group have an exceptionally broad antibacterial spectrum against aerobic bacteria. MICs are in the range of 0.001~3.13 μg/ml against most Gram-negative and Gram-positive strains. Compounds with an acidic oxyimino function, *e.g.* **1d**, possess excellent activity against Gram-negative but reduced activity against Gram-positive bacteria[1]. Introduction of the 7α-methoxy group results in an overall reduction of antibacterial activity. Older 7α-methoxy cephalosporins, *e.g.* cefoxitin, show increased β-lactamase stability. In contrast, all 7α-methoxy derivatives **2** of Table 1 are less active against β-lactamase producing Gram-negative strains (*Escherichia coli* TEM, *Klebsiella aerogenes* 1082 E, *Enterobacter cloacae* P 99) compared to their non-methoxylated analogues **1**. Similarly, 7α-methoxy cefotaxime (**6a**) is less potent than cefotaxime itself. 7α-Formamido compounds **3a~3c** exhibit an extremely decreased antibacterial activity except against *Streptococcus pyogenes* 77 A. 7α-Formamido cefotaxime **7** is less potent than 7α-methoxy cefotaxime **6a** (Table 1).

The antibacterial activity of cefpirome and analogues with neutral oxime substituents (**1a~1c**) against anaerobes *in vitro* is comparable to that of other new cephalosporins, *e.g.* cefotaxime[9]. Table 2 shows that Gram-positive anaerobes (*Peptostreptococcus*, *Propionibacterium*, *Clostridium*) are susceptible with MICs $\leq$3.13 μg/ml. Compound **1d** with an acidic oxime substituent is less active against these strains. The activities against Gram-negative species (*Bacteroides*, *Fusobacterium*) is modest. Cefotaxime (CTX) susceptible isolates (*Bacteroides fragilis* 17 390) are inhibited at 6~12 μg/ml; against

Table 1. Antibacterial activity[a] of compounds **1**, **2** and **3** against aerobic bacteria *in vitro*.

	Compound	*S.a.* SG 511	*S.p.* 77 A	*S.f.* D	*P.a.* 1771	*P.a.* 1771 M	*E.c.* TEM	*K.a.* 1082 E	*K.a.* 1522 E	*E.cl.* P 99
1a	(cefpirome sulfate)	0.19	<0.002	1.56	1.56	0.39	0.013	1.56	0.013	0.78
1b		0.39	<0.002	50	1.56	1.56	0.007	0.78	0.004	12.5
1c		0.39	<0.002	100	1.56	0.39	0.025	1.56	0.013	25
1d		6.25	0.098	>100	1.56	0.39	0.39	0.78	0.19	12.5
2a	(7α-CH_3O-cefpirome)	3.13	0.025	>100	12.5	6.25	0.39	6.25	0.19	25
2b		3.13	0.004	50	6.25	3.13	0.098	3.13	0.19	25
2c		3.13	0.004	>100	6.25	3.13	0.098	3.13	0.19	25
2d		6.25	0.19	>100	12.5	1.56	0.78	6.25	0.78	50
3a	(7α-NHCHO-cefpirome)	12.5	0.19	>100	>100	100	12.5	50	12.5	>100
3b		12.5	0.049	>100	>100	100	3.13	3.13	3.13	25
3c		12.5	0.098	>100	>100	100	12.5	50	12.5	100
Cefotaxime (CTX)		1.56	<0.002	25	6.25	0.098	0.025	1.56	0.004	100
6a	(7α-CH_3O-CTX)	6.25	0.12	>100	12.5	0.62	1.25	15.6	1.25	125
7	(7α-NHCHO-CTX)	25	3.13	>100	>100	12.5	50	50	50	>100
Cefoxitin		3.12	0.39	25	>100	1.56	1.56	0.78	3.12	100

[a] MIC (μg/ml): Agar dilution test, Mueller-Hinton Agar (Difco); inoculum 5×10^4 cfu/spot.

S.a.: *Staphylococcus aureus*, *S.p.*: *Streptococcus pyogenes*, *S.f.*: *Streptococcus faecium*, *P.a.*: *Pseudomonas aeruginosa*, *E.c.*: *Escherichia coli*, *K.a.*: *Klebsiella aerogenes*, *E.cl.*: *Enterobacter cloacae*.

Table 2. Antibacterial activity[a] of compounds **1**, **2** and **3** against anaerobic bacteria *in vitro*.

	Compound	*Pe.an.* 932	*Pr.ac.* 6919	*C.p.* 194	*B.f.* 312	*B.f.* 960	*B.f.* 17 390	*B.o.* 103	*B.d.* 1366	*F.v.* 5262
1a	(Cefpirome sulfate)	0.19	0.39	0.78	>100	>100	12.5	>100	3.13	>100
1b		<0.1	0.19	1.56	>100	>100	6.25	>100	3.13	>100
1c		0.19	1.56	3.13	>100	>100	12.5	>100	12.5	>100
1d		12.5	12.5	3.13	>100	>100	100	>100	12.5	>100
2a	(7α-CH_3O-cefpirome)	1.56	1.56	1.56	25	12.5	12.5	50	6.25	50
2b		1.56	0.19	0.19	25	25	6.25	25	6.25	50
2c		3.13	6.25	0.78	50	50	12.5	50	12.5	50
2d		6.25	12.5	1.56	>100	>100	50	>100	50	>100
3a	(7α-NHCHO-cefpirome)	100	0.39	100	6.25	25	50	100	100	100
3b		100	6.25	50	12.5	50	50	100	100	50
3c		50	3.13	50	25	50	50	100	100	50
Cefotaxime (CTX)		0.19	0.19	0.39	100	>100	3.13	100	>0.1	>100
6a	(7α-CH_3O-CTX)	1.56	1.56	0.39	25	25	12.5	25	ND	50
7	(7α-NHCHO-CTX)	100	0.78	>100	6.25	25	50	12.5	6.25	>100
Cefoxitin		0.78	0.19	0.78	1.56	3.12	3.12	6.25	1.56	6.25

[a] MIC (μg/ml): Agar dilution test, Schaedler Agar (Oxoid); inoculum 5×10^5 cfu/spot.

Pe.an.: *Peptostreptococcus anaerobius*, *Pr.ac.*: *Propionibacterium acnes*, *C.p.*: *Clostridium perfringens*, *B.f.*: *Bacteroides fragilis*, *B.o.*: *Bacteroides ovatus*, *B.d.*: *Bacteroides distasonis*, *F.v.*: *Fusobacterium varium*.

ND: not determined.

cefotaxime-resistant strains (*B. fragilis* 312, 960, *Bacteroides ovatus*, *Fusobacterium varium* 5262) no activity is found.

Some 7α-methoxy cephalosporins, *e.g.* cefoxitin, have improved activity against Gram-negative *B. fragilis* (cefoxitin; range 1.56~6.25 μg/ml). Introduction of the 7α-methoxy group in **1a~1c** to **2a~2c** also results in an improved activity against these bacteria in the range of 6.25~50 μg/ml. Compound **2d** is almost inactive. Compared to the non-methoxylated analogues **1**, the activity of **2a~2d** against Gram-positive anaerobes is slightly diminished (range 0.19~12.5 μg/ml). The 7α-formamido derivatives **3a~3c** exhibit negligible activity against all anaerobes except *Propionibacterium acnes* 6919 and *B. fragilis* 312. Similarly 7α-formamido-CTX (**7**) exhibits the lowest overall activity compared to CTX and 7α-methoxy CTX (**6a**).

Experimental

^{1}H NMR spectra were recorded on a Bruker WP-60 and AM 270 spectrometers using TMS as internal standard. Medium pressure (1 bar) chromatography was conducted on Lobar silica gel columns obtained from Merck AG, Darmstadt, FRG. The MICs were determined as already described[9].

7-[2-(2-Aminothiazol-4-yl)-2-(*Z*)-methoxyiminoacetamido]-7α-methoxy-3-[(4-methoxy-1-pyridinio)-methyl]ceph-3-em-4-carboxylate (**2c**)

Method A: A mixture of **6a** trifluoroacetate (1.2 g, 2 mmol), potassium iodide (6.64 g, 40 mmol), 4-methoxypyridine (2.18 g, 20 mmol) and water (10 ml) was heated at 65°C for 3 hours while stirring. After cooling the solution was diluted with Me_2CO (80 ml) and the mixture was chromatographed over a column of silica gel (4×60 cm). KI was eluted with Me_2CO - H_2O (8:1) and the reaction product with Me_2CO - H_2O (4:1) to give 105 mg (10%) of **2c** as an amorphous solid after lyophilization.

^{1}H NMR (60 MHz, DMSO-d_6) δ 3.25 (2H, br s, SCH_2), 3.45 (3H, s, 7α-OCH_3), 3.80 (3H, s, $NOCH_3$), 4.06 (3H, s, OCH_3), 5.03 (1H, s, 6-H), 5.2~5.7 (2H, AB, CH_2N), 6.80 (1H, s, thiazole), 7.22 (2H, br s, NH_2), 7.62 and 9.25 (4H, AA'XX', J=7 Hz, pyridine), 9.88 (1H, s, NH).

Analogously, **2a** (12%) and **2b** (11%) were prepared by treating **6a** with 2,3-cyclopentenopyridine and 4-cyclopropylpyridine, respectively, and **2d** (9%) was prepared by treating **6b** with 2,3-cyclopentenopyridine.

^{1}H NMR (60 MHz, DMSO-d_6):

2a: δ 1.9~2.6 (2H, m, cyclopentene), 2.5~3.7 (6H, m, 4 cyclopentene-H, SCH_2), 3.46 (3H, s, 7α-OCH_3), 3.82 (3H, s, $NOCH_3$), 5.01 (1H, s, 6-H), 5.26 (2H, br s, CH_2N), 6.81 (1H, s, thiazole), 7.15 (2H, br s, NH_2), 7.86 (1H, dd, J=7 Hz, pyridine), 8.35 (1H, d, J=7 Hz, pyridine), 9.26 (1H, d, J=7 Hz, pyridine), 9.90 (1H, s, NH).

2b: δ 1.1~1.5 (4H, m, cyclopropyl), 1.9~2.1 (1H, m, cyclopropyl), 3.3~3.5 (2H, m, SCH_2), 3.47 (3H, s, 7α-OCH_3), 3.82 (3H, s, $NOCH_3$), 5.02 (1H, s, 6-H), 5.2~5.4 (2H, AB, CH_2N), 6.80 (1H, s, thiazole), 7.12 (2H, br s, NH_2), 7.80 and 9.15 (4H, AA'XX', J=7 Hz, pyridine), 9.90 (1H, s, NH).

2d: δ 1.40 (6H, s, 2×CH_3), 1.9~2.4 (2H, m, cyclopentene), 2.5~3.8 (6H, m, 4 cyclopentene-H, SCH_2), 3.48 (3H, s, 7α-OCH_3), 5.01 (1H, s, 6-H), 5.28 (2H, br s, CH_2N), 6.86 (1H, s, thiazole), 7.18 (2H, br s, NH_2), 7.87 (1H, dd, J=7 Hz, pyridine), 8.33 (1H, d, J=7 Hz, pyridine), 9.22 (1H, d, J=7 Hz, pyridine), 9.82 (1H, s, NH).

7-[2-(2-Aminothiazol-4-yl)-2-(*Z*)-methoxyiminoacetamido]-7α-formamido-3-[(4-cyclopropyl-1-pyridinio)methyl]ceph-3-em-4-carboxylate (**3b**)

Method B: A mixture of **7** trifluoroacetate (270 mg, 0.44 mmol), *N*-methyl-*N*-(trimethylsilyl)-trifluoroacetamide (0.34 ml, 1.83 mmol) and CH_2Cl_2 (2 ml) was stirred for 1.5 hours at room temperature. Iodotrimethylsilane (0.22 ml, 1.54 mmol) was added and stirring was continued for 15 minutes. CH_2Cl_2 was evaporated, the oily residue was dissolved in CH_3CN (2 ml), and 4-cyclopropylpyridine

(0.2 ml, 1.7 mmol) was added. After 2 hours at room temperature, 10% aq $NaHCO_3$ (2 ml) was added, and the mixture was chromatographed over a Lobar-B column of silica gel, eluting with Me_2CO - H_2O (3 : 1). **3b** was obtained from fractions 20~30 (160 ml) as an amorphous solid after freeze drying. Yield 40 mg (16%).

^1H NMR (270 MHz, CF_3COOD) δ 1.2~1.3 (2H, m, cyclopropyl), 1.6~1.8 (2H, m, cyclopropyl), 2.2~2.35 (1H, m, cyclopropyl), 3.42 and 3.58 (2H, AB, J=18 Hz, SCH_2), 4.28 (3H, s, OCH_3), 5.52 and 6.11 (2H, AB, J=15 Hz, CH_2N), 5.57 (1H, s, 6-H), 7.51 (1H, s, thiazole), 7.68 and 8.72 (4H, AA'XX', J=7 Hz, pyridine), 8.50 (1H, s, CHO).

7-[2-(2-Aminothiazol-4-yl)-2-(*Z*)-methoxyiminoacetamido]-7α-formamido-3-[(2,3-cyclopenteno-1-pyridinio)methyl]ceph-3-em-4-carboxylate (**3a**)

Method C: To a solution of **7** trifluoroacetate (184 mg, 0.3 mmol) and 2,3-cyclopentenopyridine (406 mg, 3.4 mmol) in CH_2Cl_2 (5 ml) was added iodotrimethylsilane (0.33 ml, 2.3 mmol). The mixture was heated under reflux for 1.5 hours. The solvent was evaporated, the residue dissolved in 5% $NaHCO_3$ (2 ml). The dark red solution was chromatographed over a Lobar-B column of silica gel, eluting with Me_2CO - H_2O (3 : 1). Freeze drying of the product fractions gave 37 mg (20%) of **3a** as an amorphous solid.

^1H NMR (270 MHz, DMSO-d_6) δ 2.15~2.35 (2H, m, cyclopentene), 3.05~3.25 (2H, m, cyclopentene), 3.3~3.45 (4H, m, 2 cyclopentene-H, SCH_2), 3.55 (3H, s, OCH_3), 5.21 (2H, br s, CH_2N), 5.36 (1H, s, 6-H), 6.62 (1H, s, thiazole), 7.12 (2H, br s, NH_2), 7.65~8.05 (2H, m, 1 pyridine-H and NH), 8.15~8.52 (2H, m, 1 pyridine-H and CHO), 9.25 (1H, d, J=7 Hz, pyridine), 9.95 (1H, s, 7α-NH).

3c was similarly obtained from **7** and 4-methoxypyridine as an amorphous solid after chromatography on silica gel (yield 18%).

^1H NMR (270 MHz, CF_3COOD) δ 3.46 and 3.60 (2H, AB, J=18 Hz, SCH_2), 4.08 (3H, s, OCH_3), 4.28 (3H, s, OCH_3), 5.88 (1H, s, 6-H), 5.68 and 6.22 (2H, AB, J=15 Hz, CH_2N), 7.48 (1H, s, thiazole), 7.84 and 9.32 (4H, AA'XX', J=7 Hz, pyridine), 8.48 (1H, s, CHO).

7-[2-(2-Aminothiazol-4-yl)-2-(*Z*)-methoxyiminoacetamido]-7α-methoxycephalosporanic Acid (**6a**) Trifluoroacetate

Method D: To a stirred solution of lithium (0.73 g, 105 mmol) in anhydrous MeOH (120 ml) at −70°C under N_2 was added anhydrous THF (750 ml) followed by a solution of **4a** (22.6 g, 30 mmol) in anhydrous THF (450 ml), cooled to −70°C. *tert*-Butyl hypochlorite (4.32 g, 40 mmol) was added during 1 minute, whereupon the temperature rose from −70 to −65°C. After stirring for 15 minutes at −65°C, AcOH (30 ml) was added and the solution poured into a mixture of CH_2Cl_2 (5 liters) and water (2.5 liters). The organic phase was separated, washed 3 times with water (3 liters) and dried (Na_2SO_4). The solvent was evaporated, and the residue chromatographed over a column of silica gel (600 g), eluting with Et_2O. The fractions containing the product were evaporated to give **5a** (12.5 g, 53%) as an amorphous solid. This product was dissolved in 90% trifluoroacetic acid. After 1 hour at room temperature, the mixture was evaporated, and the residue triturated with Et_2O (5×100 ml) to give the TFA salt of **6a** (9.1 g, 94%).

^1H NMR (60 MHz, DMSO-d_6) δ 2.01 (3H, s, OAc), 3.3~3.6 (5H, m, SCH_2 and 7α-OCH_3), 3.89 (3H, s, OCH_3), 4.66 and 4.90 (2H, AB, J=15 Hz, 3-CH_2), 5.17 (1H, s, 6-H), 6.90 (1H, s, thiazole), 7.32 (2H, br s, NH_2), 10.00 (1H, s, NH).

5b was similarly prepared from **4b** (yield 58%). Deprotection with 90% CF_3COOH gave the TFA salt of **6b** (90%).

^1H NMR (60 MHz, DMSO-d_6) δ 1.46 (6H, s, 2×CH_3), 2.03 (3H, s, OAc), 3.53 (5H, br s, SCH_2 and 7α-OCH_3), 4.53~5.20 (2H, AB, 3-CH_2), 5.16 (1H, s, 6-H), 6.96 (1H, s, thiazole), 7.23 (2H, br s, NH_2), 9.93 (1H, s, NH).

7-[2-(2-Aminothiazol-4-yl)-2-(*Z*)-methoxyiminoacetamido]-7α-formamidocephalosporanic Acid Trifluoroacetate (**7**)

Method E: To a stirred mixture of 2-(2-aminothiazol-4-yl)-2-(*Z*)-methoxyiminoacetic acid (5.02 g, 25 mmol), water (0.21 g, 11.7 mmol), *N*,*N*-dimethylacetamide (3.72 ml, 40 mmol) and CH_2Cl_2

(60 ml), cooled to −5°C, was added a solution of phosgene in toluene (41 ml, 4.1 mmol). After 2 hours at 0°C, a solution of *tert*-butyl 7-amino-7α-formamido cephalosporanate (**8g**, 4.1 g, 11 mmol) and pyridine (2.4 ml, 30 mmol) in CH_2Cl_2 (40 ml) was added, and stirring was continued for 3 hours at 10°C. The solution was then washed 3 times with 5% $NaHCO_3$ and water, and dried ($MgSO_4$). Evaporation of the solvent and trituration with Et_2O gave 5.6 g (92%) of the *tert*-butyl ester of **7** as a light yellow crystalline solid.

^{1}H NMR (270 MHz, DMSO-d_6) δ 1.48 (9H, s, $(CH_3)_3C$), 2.02 (3H, s, OAc), 3.41 and 3.63 (2H, AB, J=18 Hz, SCH_2), 3.82 (3H, s, OCH_3), 4.60 and 4.88 (2H, AB, J=15 Hz, 3-CH_2), 5.22 (1H, s, 6-H), 6.91 (1H, s, thiazole), 7.21 (2H, br s, NH_2), 8.08 (1H, s, CHO), 9.24 (1H, s, NH), 9.89 (1H, s, 7α-NH).

This product was dissolved in TFA (80 ml). After 20 minutes at 20°C, TFA was evaporated and the residue triturated with Et_2O (3×50 ml) to give the TFA salt of **7** in quantitative yield.

^{1}H NMR (270 MHz, DMSO-d_6) δ 2.03 (3H, s, OAc), 3.40 and 3.62 (2H, AB, J=18 Hz, SCH_2), 3.84 (3H, s, OCH_3), 4.68 and 4.95 (2H, AB, J=15 Hz, 3-CH_2), 5.22 (1H, s, 6-H), 6.98 (1H, s, thiazole), 8.06 (1H, s, CHO), 9.42 (1H, s, NH), 9.92 (1H, s, 7α-NH).

Acknowledgment

The authors thank Mr. GEISS and LEUBE for their competent technical assistance and Dr. H.-W. FEHLHABER for measuring and discussing the NMR spectra.

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