C(3)-CYCLOPROPYL CEPHEMS AND CARBACEPHEMS

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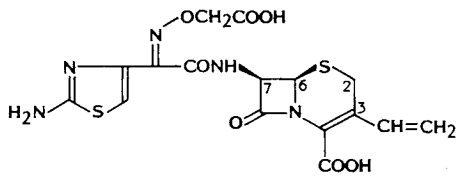
A series of C(3)-cyclopropyl cephems and carbacephems has been prepared by palladium catalyzed addition of diazomethane to the corresponding C(3)-vinyl derivatives. The phenylglycyl cyclopropyl cephem derivatives exhibit better Gram-positive activity than cephalexin or cefaclor, while the aminothiazole oxime cyclopropyl cephem derivatives were not as active as the corresponding C(3)-vinyl cephems.

Cefixime (**1**) is an orally active cephalosporin type β-lactam antibiotic consisting of an aminothiazole acetic acid oxime side chain and a C(3)-vinyl group. As an oral cephalosporin it possesses an expanded antimicrobial spectrum with high stability to β-lactamases[1]. Since it is known that the cyclopropyl group can, in many ways, mimic a double bond[2~4] we turned our attention to the synthesis of the C(3)-cyclopropyl cephem and carbacephem derivatives **2**.

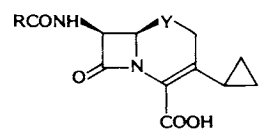
Chemistry

Various approaches to the syntheses of the C(3)-cyclopropyl derivatives were attempted, starting with the 7-β-phenoxyacetamido-3-vinyl-3-cephem carboxylate **3A** and the carbon analog (Y=CH_2) **3B**[5]. Thus we tried the Simmons Smith reaction[6] using methylene iodide and zinc-copper couple, carbene chemistry using either (a) SEYFERTH's phenyl(trihalomethyl)mercury[7] or (b) the Buchner reaction using ethyl diazoacetate with copper or rhodium catalysts[8], and oxosulfonium ylide chemistry using JOHNSON's (dimethylamino)phenyloxosulfonium methylide[9,10]. In most cases we recovered starting material, and in no case did we isolate the C(3)-cyclopropyl derivative.

A recent publication by BERES and CROUCH, Jr.[11] on the cyclopropanation of cinnamic esters using diazomethane and palladium(II) acetate prompted us to review this reaction. Thus we find that **3A** and **3B** readily undergo palladium catalyzed cyclopropanation with diazomethane at 5°C to give good yields of the corresponding C(3)-cyclopropyl derivatives **4A** and **4B**.



Cefixime (**1**)



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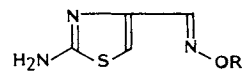
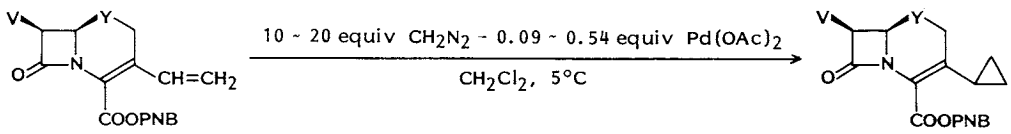
Y=S, CH_2
R=PhCH(NH_2) (D configuration),



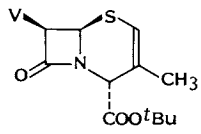
R'=CH_3, CH_2COOH, $C(CH_3)_2COOH$



3A Y=S
3B Y=CH_2

4A Y=S (57~65% yield)
4B Y=CH_2 (85~95% yield)

V=$PhOCH_2CONH$



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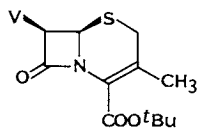

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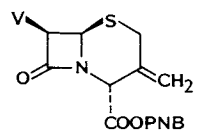

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The reaction is virtually quantitative by TLC. There is no evidence for any sulfur ylide products resulting from **3A** or **4A**, even though a large excess of diazomethane was used. The reaction consists of distilling diazomethane, generated by the base treatment of *p*-toluenesulfonylmethylnitrosamide[†,12], into a cooled (5°C), stirred methylene chloride solution of the olefin and palladium(II) acetate. In this manner only small amounts of diazomethane are present at one time since the reaction with the catalyst is quite rapid.

Other palladium catalysts, $PdCl_2$ and $Pd(Ph_3P)_4$, were less effective, and $RhCl_3 \cdot 3H_2O$ or $Rh_2(OAc)_4$ were totally ineffective.

Under the diazomethane-palladium(II) acetate conditions **5**, **6** and **7** failed to cyclopropanate, while substituted C(3)-vinyls, for example the 2',2'-dibromo[13], 2'-methyl (*cis* propenyl) or 2'-ethoxycarbonyl, also failed to cyclopropanate.

The mechanism of such diazomethane-palladium catalyzed cyclopropanation is believed to be initial coordination of the olefin with palladium to form a coordination complex which reacts with diazomethane to form a second coordination complex. This then loses nitrogen, giving an intermediate which breaks down to give the cyclopropyl product and the metal. Rhodium(II) carboxylate complexes, on the other hand, have only one coordination site per molecule and cyclopropanate by a carbenoid mechanism[14].

Palladium catalyzed cyclopropanations are known to be very sensitive to steric effects[14,15], which explains our problems with the substituted vinyls and the lack of reactivity of the cephem and carbacephem-Δ^3-double bond. The fact that the palladium catalyzed reaction does not involve a carbenoid also explains why we see no sulfur ylide products.

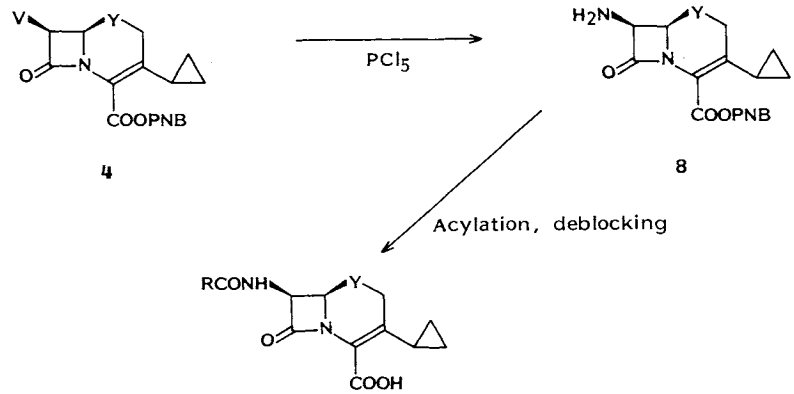
Compounds required for microbiological testing were then prepared by cleavage of the phenoxyacetyl side chain using PCl_5, followed by acylation and deblocking (Scheme 1).

Biological Results and Discussion

MIC values of the cyclopropyl derivatives **9** against several Gram-positive and Gram-negative bacteria are shown in Table 1 compared with cephalexin, cefaclor, loracarbef, cefixime and cefetamet[16]. **9a** and its carbon analog **9d** show better Gram-positive antibacterial activity than cephalexin or cefaclor. Compound **9a** has better *Haemophilus influenzae* activity than cephalexin, but not as good as that of cefaclor. The aminothiazole oxime derivative **9h** is not nearly as active as cefixime, but it is more active than the

† Sold by Aldrich under the name DIAZALD.

Scheme 1.



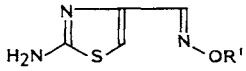
9a	R=PhCH(NH_2)	Y=S
9b	R=PhCH(NH_2)	Y=S(O)-α-sulfoxide
9c	R=*m*-(CH_3SO_2NH)PhCH(NH_2)	Y=S
9d	R=PhCH(NH_2)	Y=CH_2
9e	R=PhCH(OCHO)	Y=S
	R= 	
9f	R'=CH_3	Y=S
9g	R'=CH_3	Y=CH_2
9h	R'=CH_2COOH	Y=S
9i	R'=$C(CH_3)_2COOH$	Y=S

Table 1. MIC values (μg/ml).

	S.a.	*S.py.*	*S.pn.*	*E.f.*	*H.i.*		*E.c.*		*K.p.*	*E.cl.*	*Salmonella* sp.	*S.m.*	*M.m.*
	X1.1	C203	PK	2041	(−)	(+)	EC14	TEM	X26	EB5	X514	SE3	PR15
Cephalexin	4	1	1	128	16	8	4	8	4	64	2	128	128
9a	0.25	0.06	0.5	32	4	4	4	4	2	64	8	32	128
9b	0.25	0.06	0.5	32	4	4	4	4	2	128	4	128	128
9c	0.25	0.125	5	32	8	128	4	16	1	128	8	128	128
9d	0.5	0.125	2	128	8	8	4	4	4	128	8	128	128
9e	0.25	0.25	0.5	64	8	4	8	8	4	64	8	128	128
Cefaclor	1	0.125	1	32	2	1	0.5	2	0.5	4	0.25	32	128
Loracarbef	0.5	0.25	1	32	1	1	0.25	1	0.5	2	0.25	32	128
Cefixime	16	0.125	0.125	8	0.03	0.03	0.06	0.5	0.03	1	0.06	0.5	0.25
9f	8	0.008	0.06	4	0.125	0.06	0.5	0.125	0.03	2	0.5	4	1
9g	32	0.25	0.25	4	0.5	0.5	0.5	0.5	0.125	4	1	16	0.5
9h	32	0.5	0.5	16	0.125	0.125	0.25	0.25	0.06	2	0.25	4	0.5
9i	32	0.25	1	128	0.03	0.015	0.25	1	0.25	1	0.5	2	2
Cefetamet	64	0.06	0.06	32	0.25	0.125	8	128	32	128	2	128	128

Abbreviations: *S.a.*, *Staphylococcus aureus*; *S.py.*, *Streptococcus pyogenes*; *S.pn.*, *S. pneumoniae*; *E.f.*, *Enterococcus faecalis*; *H.i.*, *Haemophilus influenzae*; *E.c.*, *Escherichia coli*; *K.p.*, *Klebsiella pneumoniae*; *E.cl.*, *Enterobacter cloacae*; *S.m.*, *Serratia marcescens*; *M.m.*, *Morganella morganii*.
(−): β-Lactamase non-producing, (+): β-lactamase producing.

corresponding C(3)-methyl (cefetamet). The carba derivatives (**9d** and **9g**) were somewhat less active than the corresponding sulfur analogs (**9a** and **9f**).

The pharmacokinetic profiles of compounds **9a**, **9c** and **9d** were evaluated in male Sprague-Dawley rats. The results (Table 2 and Fig. 1) indicate that **9a** and **9d** are similar to both cephalexin and loracarbef.

Table 2. Pharmacokinetic parameters of cephalexin, loracarbef and compounds **9a**, **9c** and **9d** in rats following intravenous administration of a 20-mg/kg dose.

Compound	AUC (μg·hour/ml)	C 0.5 hour (mg/ml)	Half-life (hours)
Cephalexin	3.8	7.0	0.45
Loracarbef	2.6	7.0	0.49
9a	9.1	21.1	0.52
9c	34.4	28.7	2.2
9d	16.6	34.1	0.38

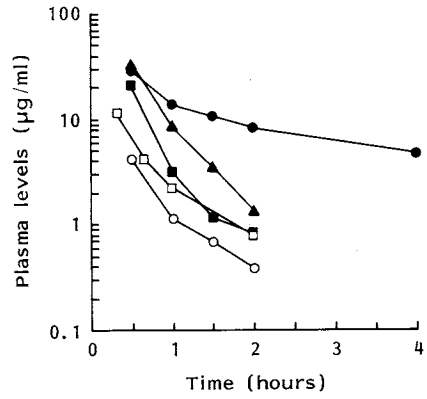
Table 3. Urinary recovery of antimicrobial activity in CD-1 mice.

Compound	Urinary recovery (% dose)		Oral bioavailability (%)[a]
	iv	po	
Cephalexin	79.6	73.3	92.1
Loracarbef	68.0	66.6	98.0
Cefaclor	57.3	56.4	98.4
9a	67.7	54.4	80.2
9c	57.5	45.2	78.6
9d	60.6	43.8	72.2
Cefixime	69.6	22.5	32.3
9h	65.4	15.8	24.1

[a] Oral bioavailability = urinary recovery(po)/urinary recovery (iv).

Fig. 1. Plasma levels of antibiotic activity following iv administration of compounds at 20 mg/kg.

□ Cephalexin, ○ loracarbef, ■ **9a**, ● **9c**, ▲ **9d**.



The half-lives of the phenylglycyl derivatives ranged from 0.38 to 0.52 hour, while the area under the curve (AUC) ranged from 2.6 to 16.6 μg·hour/ml. These results suggest that there are no significant pharmacokinetic differences between the 1-S (**9a**) and 1-C (**9d**) compounds. Compound **9c** exhibited a markedly longer half-life than its analog **9a**. We have observed this *m*-methylsulfonamido substitution effect previously, in the case of the loracarbef analog LY228238[17]. The importance of the *m*-methylsulfonamido moiety to the pharmacokinetic disposition of **9c** in humans is not known.

The oral absorption of this series of compounds was tested experimentally in CD-1 mice. Oral bioavailability was calculated as the po/iv ratio of antibacterial activity recovered in the urine following a 20-mg/kg dose. The results (Table 3) demonstrate that the 3-cyclopropyl compounds (**9a**, **9c**, **9d** and **9h**) were bioequivalent to the 3-alkyl and halo analogs tested. The oral bioavailability of the phenylglycyl cyclopropyl cephems (72.2~80.2%) are significantly greater than those of the aminothiazole acetic acid cephems; **9h**, (3-cyclopropyl, 24.1%) and cefixime (3-vinyl, 32.3%), which were equivalent.

The pharmacokinetic profiles of cephalexin, cefaclor, loracarbef and cefixime in laboratory animals and human volunteers have been reported[18~23]. In this report, compounds **9a**, **9c**, **9d** and **9h** were demonstrated to be pharmacokinetically equivalent to their respective 3-alkyl or halo analogs in mice.

After preparation of this manuscript we observed a report on the synthesis of the C-3-diphenylcyclopropyl cephem *via* the pyrazoline; no yield or microbiological data was given[24].

Experimental

Biological

MICs were determined by the known agar-dilution method[25] using Mueller-Hinton agar (BBL Microbiology System, Cockeysville, Md). The medium was supplemented with 1% supplement C (Difco Labs., Detroit, MI) to enhance the growth of non-enterococcal Streptococci and *H. influenzae*. The antibiotics

used in this agar dilution test were incorporated directly into the melted agar prior to pouring the plates. For most bacterial strains inocula of approximately 10^4 cfu were prepared by appropriate dilution of overnight broth cultures of organisms in fresh Brain-Heart infusion broth (Difco) and were applied to plates using a 36-prong, Cathra, inoculating device. The plates were examined after 18~20 hours of incubation at 37°C.

Male Sprague-Dawley rats, 225~265 g, were dosed intravenously with test compounds at 20 mg/kg in 0.9% saline. Dosing and blood sampling were carried out through an indwelling jugular vein cannula, thus permitting serial sampling from individual rats. Each compound was administered to 3 animals. Plasma levels were determined from samples collected at 0.5, 1.0, 1.5, 2.0 and 4.0 hours post-dose. Samples were stored at −70°C prior to analysis. Plasma half-life was calculated as 0.693/beta, where beta is the slope of the terminal portion of the plasma vs. time curve. AUC was calculated using SIMPSON's rule.

Male CD-1 mice, 20~24 g, were dosed both orally and intravenously with test compounds at 20 mg/kg in 0.9% saline. Compounds were tested in 4 animals per route of administration. The 0~4-hour urinary recovery was collected in 0.1 M sodium citrate buffer, pH 6.5, on ice and stored at −70°C prior to analysis. The ratio of antibiotic activity following oral and intravenous administration was used to calculate oral bioavailability.

Antibiotic concentrations were determined in plasma or urine with an agar well diffusion assay employing *Escherichia coli* (ATCC 4157) or *Micrococcus luteus* (ATCC 9341) as the bacterial test strain. Standard curves from rat plasma spiked with the compound under study were employed for analysis of plasma samples. Urine samples were analyzed by comparison to a standard prepared in 0.1 M sodium citrate buffer, pH 6.5. Urine samples were diluted with citrate buffer so that the drug concentration would fall into the range of the standard curve.

Chemical

The following instruments were used for obtaining spectral data: ^{1}H NMR, G. E. QE-300; IR spectra, Perkin Elmer 281; MS data, Varian-m.a.t.-731, V. G. ZAB-3. All chromatographic separations were done using Merck Silica gel (Kieselgel 60). HPLC separations were done using a Waters Prep 3000 solvent delivery system, a model 481 variable wavelength detector equipped with a semi-preparative flow cell and a Rainin Dynamax C18 column, 41.4×250 mm with a 41.4×50 mm guard module.

p-Nitrobenzyl (PNB) (7β)-Phenoxyacetamido-3-cyclopropyl-3-cephem-4-carboxylate (**4A**)

Approximately 6 g diazomethane, generated[11] by the dropwise (1 hour) addition of 43 g DIAZALD in 250 ml Et_2O to a heated (65°C) solution of 12 g KOH in 20 ml H_2O, 70 ml of 2-(2-ethoxyethoxy)ethanol and 20 ml Et_2O, was codistilled with ether into a cooled (5°C), stirred solution of PNB (7β)-phenoxyacetamido-3-vinyl-3-cephem-4-carboxylate (**3A**) (3.535 g, 7.13 mmol) in 200 ml CH_2Cl_2 containing 0.865 g (3.85 mmol, 0.54 equiv) $Pd(OAc)_2$. When the distillation of diazomethane was complete the reaction mixture was filtered through Celite, evaporated to dryness and chromatographed on silica gel using a 100% toluene vs. 70% ethyl acetate-toluene gradient to give (fraction 34~45) 2.069 g (57%) product as a yellow froth: MS *m/z* 510; IR ν_{max} ($CHCl_3$) cm^{-1} 1775; ^{1}H NMR ($CDCl_3$) δ 0.6~1.0 (4H, m, cyclopropyl methylene), 2.6 (1H, m, cyclopropyl methine), 2.84 and 2.98 (2H, AB, J=17 Hz, C-2 methylene), 4.56 (2H, s, phenoxyacetyl), 5.03 (1H, d, J=5 Hz, 6-H), 5.75 (1H, dd, J=5 Hz, 7-H).

PNB (7β)-Phenoxyacetamido-3-cyclopropyl-3-carbacephem-4-carboxylate (**4B**)

Approximately 3 g of diazomethane was slowly codistilled with ether into a cooled (5°C), stirred solution of PNB (7β)-phenoxyacetamido-3-vinyl-3-carbacephem-4-carboxylate (**3B**) (3.641 g, 7.62 mmol) in 150 ml CH_2Cl_2 containing 152 mg (0.78 mmol, 0.089 equiv) $Pd(OAc)_2$. Following distillation the solution was filtered through Celite, evaporated to dryness and chromatographed on silica gel using a toluene vs. ethyl acetate gradient to give (fraction 21~32) 3.198 g (85%) product as a froth: MS *m/z* 491; IR ν_{max} ($CHCl_3$) cm^{-1} 1755; ^{1}H NMR ($CDCl_3$) δ 0.5~0.9 (4H, m, cyclopropyl methylene), 1.3~1.9 (4H, m, C-1 and C-2 methylene), 2.52 (1H, m, cyclopropyl methine), 3.77 (1H, m, 6-H), 4.48 (2H, s, phenoxyacetamido), 5.2~5.4 (3H, m, 7-H + PNB).

PNB (7β)-Amino-3-cyclopropyl-3-cephem-4-carboxylate (**8A**, Y=S)

4A (2.372 g, 4.66 mmol) in 8 ml CH_2Cl_2 was cooled to 0°C and 0.46 ml (5.73 mmol, 1.23 equiv) pyridine was added followed by 1.115 g (5.35 mmol, 1.15 equiv) PCl_5. After stirring at room temperature for 2 hours the reaction mixture was cooled to 0°C, and 2.30 ml (24.9 mmol, 5.35 equiv) 2-butanol was added. After stirring at room temperature for 1 hour the slurry containing the amine hydrochloride was cooled to −78°C and excess (100 ml) *n*-heptane was added. After decanting the supernate, the hydrochloride was dissolved in an EtOAc-aq $NaHCO_3$ solution, converting it to the free amine, and the EtOAc layer was washed with H_2O, brine, dried over Na_2SO_4 and evaporated to give 1.81 g (103%) crude amino ester (**8A**, Y=S). This was acylated directly without further purification.

PNB (7β)-Amino-3-cyclopropyl-3-carbacephem-4-carboxylate (**8B**, Y=CH_2)

8B (Y=CH_2) was prepared using the same procedure described in **8A** (Y=S). Thus 3.198 g (6.51 mmol) of **4B** were treated with 0.65 ml (8.01 mmol, 1.23 equiv) pyridine, 1.558 g (7.48 mmol, 1.15 equiv) PCl_5 and 3.22 ml (34.8 mmol, 5.35 equiv) 2-butanol to give, after workup, 1.966 g (84%) crude amino ester which was acylated directly without further purification.

7β-D-α-Aminophenylacetamido-3-cyclopropyl-3-cephem-4-carboxylic Acid (**9a**)

To the crude amino ester (**8A**, Y=S) (1.748 g, 4.66 mmol) in 15 ml THF was added 1.463 g (5.82 mmol, 1.25 equiv) D-*N*-*tert*-butoxycarbonyl (BOC)-α-aminophenylacetic acid and 1.439 g (5.82 mmol, 1.25 equiv) 2-ethoxyl-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) in 15 ml THF. After stirring at room temperature for 16 hours the reaction mixture was combined with cold EtOAc and washed once with cold saturated aqueous $NaHCO_3$, once with brine, dried (Na_2SO_4), evaporated to dryness and chromatographed on silica gel using a toluene vs. ethyl acetate gradient to give (fraction 27~33) 1.705 g (60%) product as a froth. The PNB ester group was then removed by hydrogenolysis (67%) (5% Pd-C in MeOH at 3.54 kg/cm^2 H_2 for 1 hour) followed by removal of the BOC group using 98% formic acid (10 ml) and 3 ml Et_3SiH at room temperature for 1 hour. The crude amino acid (99%) was further purified by HPLC to give **9a** as a white solid: MS *m/z* 374: IR ν_{max} (KBr) cm^{-1} 1762; UV $\lambda_{max}^{H_2O}$ nm (ε) 268 (8,390); ^{1}H NMR (D_2O-DCl) δ 0.5~0.82 (4H, m, cyclopropyl methylene), 2.34~2.39 (1H, m, cyclopropyl methine), 2.61 and 2.72 (2H, AB, J=17 Hz, C-2 methylene), 4.95 (1H, d, J=4 Hz, 6-H), 5.11 (1H, s, PhC*H*), 5.38 (1H, d, J=4 Hz, 7-H), 7.38 (5H, s, Ph).

7β-D-α-Aminophenylacetamido-3-cyclopropyl-3-carbacephem-4-carboxylic Acid (**9d**)

The procedure for the synthesis of **9d** was the same as that described for **9a**. The acylation yield was 70%, hydrogenolysis (95%), removal of the *N*-BOC protecting group and HPLC purification went in 45% to give **9d**: MS *m/z* 356; IR ν_{max} (KBr) cm^{-1} 1754; ^{1}H NMR (D_2O-DCl) δ 0.5~1.0 (4H, m, cyclopropyl methylene), 1.5~1.9 (4H, m, C-1 and C-2 methylene), 2.21 (1H, m, cyclopropyl methine), 3.78 (1H, m, 6-H), 5.14 (1H, s, PhC*H*), 5.30 (1H, d, J=5 Hz, 7-H), 7.43 (5H, s, Ph).

7β-D-α-Aminophenylacetamido-3-cyclopropyl-3-cephem-4-carboxylic Acid-1-α-oxide (**9b**)

1.885 g (3.10 mmol) of the PNB (7β)-D-*N*-BOC-α-aminophenylacetamido-3-cyclopropyl-3-cephem-4-carboxylate in 120 ml CH_2Cl_2 plus 13 ml saturated aq $NaHCO_3$ was treated with 1.2 equiv Cl_2 (7.90 ml of a 0.47 M chlorine solution in CH_2Cl_2) at room temperature for 20 minutes. The reaction mixture was washed once with brine, dried (Na_2SO_4), filtered, evaporated and chromatographed on silica gel using a toluene vs. 10% ethyl acetate-toluene gradient to give 620 mg (32%) α-sulfoxide and 17% β-sulfoxide. The PNB and BOC were removed as in **9a** to give **9b**: MS *m/z* 490; IR ν_{max} (KBr) cm^{-1} 1784; UV $\lambda_{max}^{H_2O}$ nm (ε) 264 (7,200); ^{1}H NMR (D_2O-DCl) δ 0.6~0.95 (4H, m, cyclopropyl methylene), 2.65 (1H, m, cyclopropyl methine), 3.2 and 3.4 (2H, AB, J=17 Hz, C-2 methylene), 4.6 (1H, d, J=4 Hz, 6-H), 5.1 (1H, s, PhC*H*), 5.4 (1H, d, J=4 Hz, 7-H), 7.3 (5H, s, Ph).

7β-α-Amino-*m*-methylsulfonylaminophenylacetamido-3-cyclopropyl-3-cephem-4-carboxylic Acid (**9c**)

MS *m/z* 467; IR ν_{max} (KBr) cm^{-1} 1762; UV $\lambda_{max}^{H_2O}$ nm (ε) 269 (7,790); ^{1}H NMR (D_2O-DCl) δ 0.5~0.85 (4H, m, cyclopropyl methylene), 2.36~2.41 (1H, m, cyclopropyl methine), 2.61 and 2.73 (2H, AB, J=17 Hz, C-2 methylene), 3.00 (3H, s, SO_2CH_3), 5.0 (1H, d, J=4 Hz, 6-H), 5.13 (1H, s, PhC*H*), 5.41 (1H, d, J=4 Hz,

7-H), 7.29~7.4 (4H, m, Ar).

7β-α-*O*-Formylphenylacetamido-3-cyclopropyl-3-cephem-4-carboxylic Acid (**9e**)

MS *m/z* 403: IR ν_{max} (KBr) cm^{-1} 1764; UV $\lambda_{max}^{H_2O}$ nm (ε) 268 (9,690); ^1H NMR ($CDCl_3$) δ 0.6~1.0 (4H, m, cyclopropyl methylene), 2.7 (1H, m, cyclopropyl methine), 2.80 and 2.88 (2H, AB, *J*=17 Hz, C-2 methylene), 5.00 (1H, d, *J*=4 Hz, 6-H), 6.27 (1H, s, PhC*H*), 7.16 (1H, d, *J*=8 Hz, NH), 7.4~7.5 (5H, m, Ph), 8.2 (1H, s, CHO).

7β-[(2-Amino-4-thiazoyl)(methoxyimino)acetylamino]-3-cyclopropyl-3-cephem-4-carboxylic Acid (**9f**)

8A (Y=S) (1.510 g, 4.02 mmol) in 25 ml CH_2Cl_2 was treated with 1.784 g (1.0 equiv) of 2-*N*-trityl-amino-4-thiazoylmethoxyiminoacetic acid and 0.830 g (1.0 equiv) 1,3-dicyclohexylcarbodiimide (DCC). After stirring 18 hours at room temperature the resulting slurry was filtered through Celite, evaporated to dryness and chromatographed on silica gel using a toluene vs. ethyl acetate gradient to give (fraction 28~76) 3.35 g (104%) product plus dicyclohexyl urea. The PNB group was then removed by hydrogenolysis (5% Pd-C in MeOH at 3.54 kg/cm^2 for 1 hour) followed by deblocking of the *N*-trityl group (HCOOH, room temperature, 1 hour). HPLC purification gave pure **9f** (21% overall): MS *m/z* 424; IR ν_{max} (KBr) cm^{-1} 1766; ^1H NMR (D_2O-DCl) δ 0.57~0.86 (4H, m, cyclopropyl methylene), 2.45~2.50 (1H, m, cyclopropyl methine), 2.85 (2H, s, C-2 methylene), 3.89 (3H, s, OCH_3), 5.07 (1H, d, *J*=4 Hz, 6-H), 5.40 (1H, d, *J*=4 Hz, 7-H), 7.06 (1H, s, thiazole proton). **9g**, **9h** and **9i** were prepared in the same manner, except deblocking the *N*-trityl group on **9h** required TFA at room temperature for 6 hours and **9i** required TFA for 2 hours at room temperature.

7β-[(2-Amino-4-thiazoyl)(methoxyimino)acetylamino]-3-cyclopropyl-3-carbacephem-4-carboxylic Acid (**9g**)

9g: MS *m/z* 406; IR ν_{max} (KBr) cm^{-1} 1752; ^1H NMR (D_2O-DCl) δ 0.5~0.8 (4H, m, cyclopropyl methylene), 1.4~2.0 (4H, m, C-1 and C-2 methylene), 2.3 (1H, m, cyclopropyl methine), 3.9 (1H, m, 6-H), 3.94 (3H, s, OCH_3), 5.35 (1H, d, *J*=5 Hz, 7-H), 6.99 (1H, s, thiazole proton).

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References

1) YAMANAKA, H.; T. CHIBA, K. KAWABATA, H. TAKASUGI, T. MASUGI & T. TAKAYA: Studies on β-lactam antibiotics. IX. Synthesis and biological activity of a new orally active cephalosporin, cefixime (FK027). J. Antibiotics 38: 1738~1751, 1985
2) DE MEIJERE, D.: Bonding properties of cyclopropane and their chemical consequences. Angew. Chem. Int. Ed. Engl. 18: 809~826, 1979
3) RAPPOPORT, Z. (*Ed.*): The Chemistry of The Cyclopropyl Group. Vol. 1. Wiley, 1987
4) RAPPOPORT, Z. (*Ed.*): The Chemistry of The Cyclopropyl Group. Vol. 2. Wiley, 1987
5) COOK, G. K.; W. J. HORNBACK, C. L. JORDAN, J. H. MCDONALD III & J. E. MUNROE: Palladium-catalyzed chemistry of β-lactam vinyl triflates: Coupling with organostannanes and alkoxycarbonylation. J. Org. Chem., in press
6) SIMMONS, H. E. & R. D. SMITH: A new synthesis of cyclopropanes. J. Am. Chem. Soc. 81: 4256~4264, 1959
7) SEYFERTH, D.: Phenyl(trihalomethyl)mercury compounds: Exceptionally versatile dihalocarbene precursors. Acc. Chemical Research 5: 65~74, 1972
8) DOYLE, M. P.; D. VAN LEUSEN & W. H. TAMBLYN: Efficient alternative catalysts and methods for the synthesis of cyclopropanes from olefins and diazo compounds. Synthesis 1981: 787~789, 1981
9) JOHNSON, C. R.; M. HAAKA & C. W. SCHROECK: Preparation and synthetic applications of (dimethylamino)phenyloxosulfonium methylide. J. Am. Chem. Soc. 92: 6594~6598, 1970
10) SPRY, D. O.: C_2-Spirocyclopropyl cephalosporins. Tetrahedron Lett. 1973: 2413~2416, 1973
11) BERES, J. A. & R. D. CROUCH, Jr.: Synthesis of methyl *trans*-2-phenylcyclopropane carboxylate. Org. Prep. and Procedures Int. 20: 187~191, 1988

12) *In* Reagents For Organic Synthesis. Vol. I. *Eds.*, L. F. FIESER & M. FIESER, pp. 191～192, Wiley, 1967
13) KAWABATA, K.; T. MASUGI & T. TAKAYA: Studies on β-lactam antibiotics. XI. Synthesis and structure-activity relationships of new 3-(2,2-dihalovinyl)cephalosporins. J. Antibiotics 39: 384～393, 1986
14) ANCIAUX, A. J.; A. J. HUBERT, A. F. NOELS, N. PETINIOT & P. TEYSSIÉ: Transition-metal-catalyzed reactions of diazo compounds. I. Cyclopropanation of double bonds. J. Org. Chem. 45: 695～702, 1980
15) MENDE, U.; B. RADÜCHEL, W. SKUBALLA & H. VORBRÜGGEN: A new simple conversion of α-β-unsaturated carbonyl compounds into their corresponding cyclopropyl ketones and esters. Tetrahedron Lett. 1975: 629～632, 1975
16) KOUP, J. R.; U. C. DUBACH, R. BRANDT, R. WYSS & K. STOECKEL: Pharmacokinetics of cefetamet (Ro 15-8074) and cefetamet pivoxil (Ro 15-8075) after intravenous and oral doses in humans. Antimicrob. Agents Chemother. 32: 573～579, 1988
17) KASHER, J. S.; J. A. EUDALY, R. JOHNSON & J. SHOUFLER: Pharmacokinetics of orally absorbed beta-lactam antibiotics LY228238 and LY257128 in laboratory animals. Program and Abstracts of the 28th Intersci. Conf. on Antimicrob. Agents Chemother., No. 535, p. 202, Los Angeles, Oct. 23～26, 1988
18) KORZENIOWSKI, O. M.; W. M. SCHELD & M. A. SANDE: Comparative pharmacology of cefaclor and cephalexin. Antimicrob. Agents Chemother. 12: 157～162, 1977
19) SULLIVAN, H. R.; S. L. DUE, D. L. K. KAU, J. F. QUAY & W. M. MILLER: Metabolism of [^{14}C]cefaclor, a cephalosporin antibiotic, in three species of laboratory animals. Antimicrob. Agents Chemother. 10: 630～638, 1976
20) TURNER, J. C.; H. R. SULLIVAN, J. F. QUAY, L. S. FINCH & J. F. STUCKY: Absorption, distribution, metabolism and elimination of LY163892 (KT3777), an orally absorbed β-lactam, in laboratory animals. Program and Abstracts of the 27th Intersci. Conf. on Antimicrob. Agents Chemother., No. 1204, p. 307, New York, Oct. 4～7, 1987
21) BLACK, H. R.; K. A. DESANTE, J. D. WOLNY & G. L. BRIER: Pharmacology and pharmacokinetics of single oral doses of LY163892. Program and Abstracts of the 28th Intersci. Conf. on Antimicrob. Agents Chemother., No. 123, p. 132, Los Angeles, Oct. 23～26, 1988
22) STONE, J. W.; G. LINONG, J. M. ANDREWS & R. WISE: Cefixime, *in-vitro* activity, pharmacokinetics and tissue penetration. J. Antimicrob. Chemother. 23: 221～228, 1989
23) SAKAMOTO, H.; T. HIROSE & Y. MINE: Pharmacokinetics of FK027 in rats and dogs. J. Antibiotics 38: 496～504, 1985
24) PITLIK, J.; I. MISKOLCZI, K. E. KÖVÉR, C. H. JÁSZBERÉNYI & F. SZTARICSKAI: Cycloaddition reactions of vinylcephalosporins with diazomethane. Tetrahedron Lett. 30: 2005～2008, 1989
25) WASHINGTON, J. A. & V. L. SUTTER: Dilution susceptibility test: Agar and macro-broth dilution procedure. *In* Manual of Clinical Microbiology. 3rd Ed. *Ed.*, E. H. LENNETTE *et al.*, pp. 453～458, American Society for Microbiology, 1980