cis-HALOVINYLTHIOACETAMIDO SIDE CHAIN, A NEW EFFECTIVE STRUCTURAL ELEMENT FOR 7β-SUBSTITUTION IN CEPHEM AND OXACEPHEM ANTIBIOTICS

II. 7β-cis-FLUOROVINYLTHIOACETAMINO-7α-METHOXY-1-OXACEPHEMS

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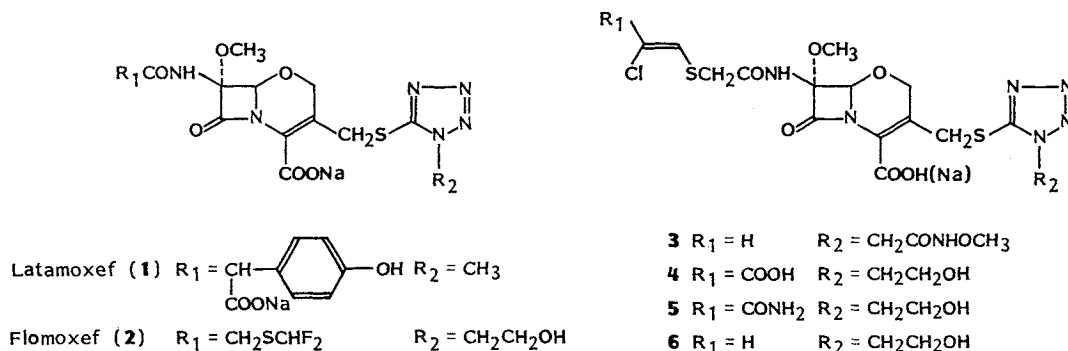Fukushima-ku, Osaka 553, Japan

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The synthesis and *in vitro* activity of 1-oxacephem derivatives having a substituted or a non-substituted *cis*-fluorovinylthioacetamido side chain at C-7 are described. Of these new 1-oxacephem antibiotics, 2355-S (**42a**) shows good antibacterial activity against Gram-positive and Gram-negative bacteria, and very favorable pharmacokinetic properties.

Latamoxef (moxalactam) (**1**), known as the first oxacephem antibiotic[1], is currently used clinically as one of the representative so-called third-generation cephalosporins. The common feature of cephalosporins of this generation is their weakness against Gram-positive bacteria and their strength against Gram-negative bacteria. Latamoxef is not exceptional and is weak in its activity against Gram-positive bacteria.

This drawback was alleviated in flomoxef (**2**)[2], which is equally active against Gram-positive and Gram-negative bacteria. It is now under clinical study as a candidate for a new generation of β-lactams. In parallel with this work, we synthesized a large number of 1-oxacephem derivatives bearing variously substituted vinylthioacetamido C-7 side chains and examined their biological properties. Part of this study was reported in the preceding paper[3], in which we discussed mainly oxacephem derivatives bearing substituted or non-substituted *cis*-chlorovinylthioacetamido side chains. Among

Fig. 1.

Latamoxef (**1**) $R_1 = CH\text{-}\!\!\!\!\!\!\text{-}OH$ $R_2 = CH_3$

Flomoxef (**2**) $R_1 = CH_2SCHF_2$ $R_2 = CH_2CH_2OH$

3 $R_1 = H$ $R_2 = CH_2CONHOCH_3$
4 $R_1 = COOH$ $R_2 = CH_2CH_2OH$
5 $R_1 = CONH_2$ $R_2 = CH_2CH_2OH$
6 $R_1 = H$ $R_2 = CH_2CH_2OH$

them, oxacephem 3 was found to be the most attractive in both antibacterial activity and pharmaco-
kinetics.   However, we were disappointed to realize that its MICs were not reflected well in its protective
effect on experimental infection in mice.   A similar trend was also observed with oxacephems 4, 5, 6,
each of which has a chlorine atom in the vinylthioacetamido C-7 side chain, as shown in Table 2.   We
thought that replacement of chlorine by fluorine would improve such unfavorable properties and inves-
tigation along this line confirmed our strategy.   We finally found a new oxacephem 2355-S (42a), which
exhibited more favorable pharmacokinetic properties than flomoxef (2).   The present paper describes
the synthesis and the biological properties of 2355-S and the related oxacephem derivatives.

<div align="center">Chemistry</div>

After several unsuccessful trials, we eventually could prepare cis-fluorovinylthioacetic acid (14)
starting from fluoroethyl p-toluenesulfonate (7)[4] (Fig. 2).   The tosylate 7 was treated with thiogly-
colate and triethylamine in N,N-dimethylformamide to give 8.   Chlorination of 8 with excess chlorine
at 0°C in methylene chloride afforded the dichloride 9, which was oxidized with m-chloroperbenzoic
acid (MCPBA) into the sulfoxide 10.   The sulfoxide 10 was less reactive and could be reduced to the
sulfide 9 when subjected to Pummerer reaction using $SOCl_2$, Ac_2O or $(CF_3CO)_2O$ with or without
base.   This reaction could also be done using a combination of trifluoromethanesulfonic anhydride
and 2,6-di-tert-butyl-4-methylpyridine even at a low temperature, providing 12 directly in ca. 90%
yield as a single product.   It is noteworthy that no trans isomer was detected on the NMR spectrum.
This high stereo-selectivity suggests that a conformer with fluorine and sulfonium cation oriented in
the Gauche situation may be most stable in the transition state 11.   Studies on this problem will be
published elsewhere.   Reduction of 12 with zinc in CH_2Cl_2 containing acetic acid, followed by sa-
ponification, gave 14 in a good yield.

Carbamoyl- and N-methylcarbamoyl-fluorovinylthioacetic acids (18 and 19) were conveniently
synthesized by two methods, A and B.   In method A (Fig. 3), Claisen condensation of ethyl mono-
fluoroacetate with ethyl formate was effected in ether by the procedure of ELKIK et al.[5] to give a rather
unstable sodium enolate 15, which was mesylated with mesyl chloride to afford 16 as a single geo-
metrical isomer.   The cis assignment of the fluorine atom to the mesyl in 16 was based on the observed
large coupling constant ($J_{HF} = 16$ Hz) in the NMR spectrum.   The mesylate 16 was reacted with thio-

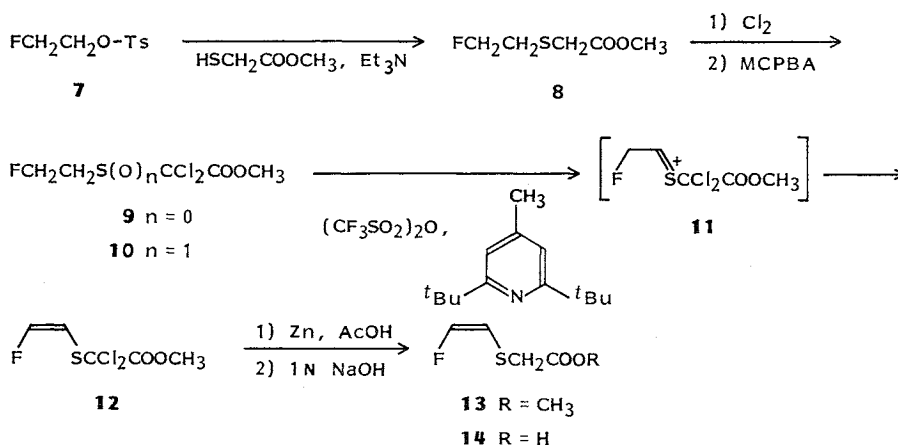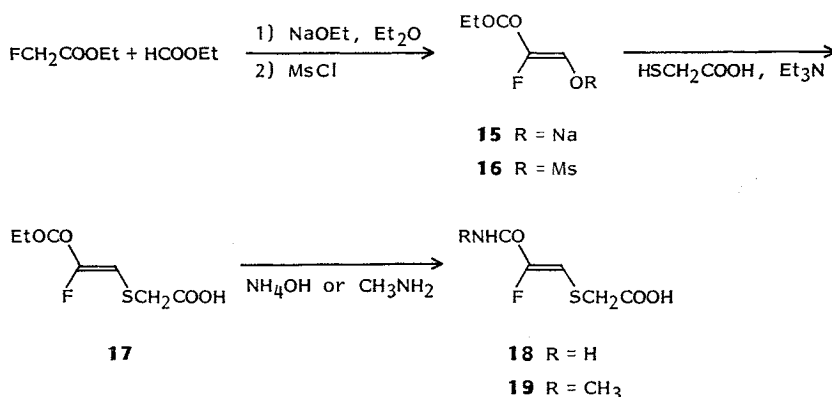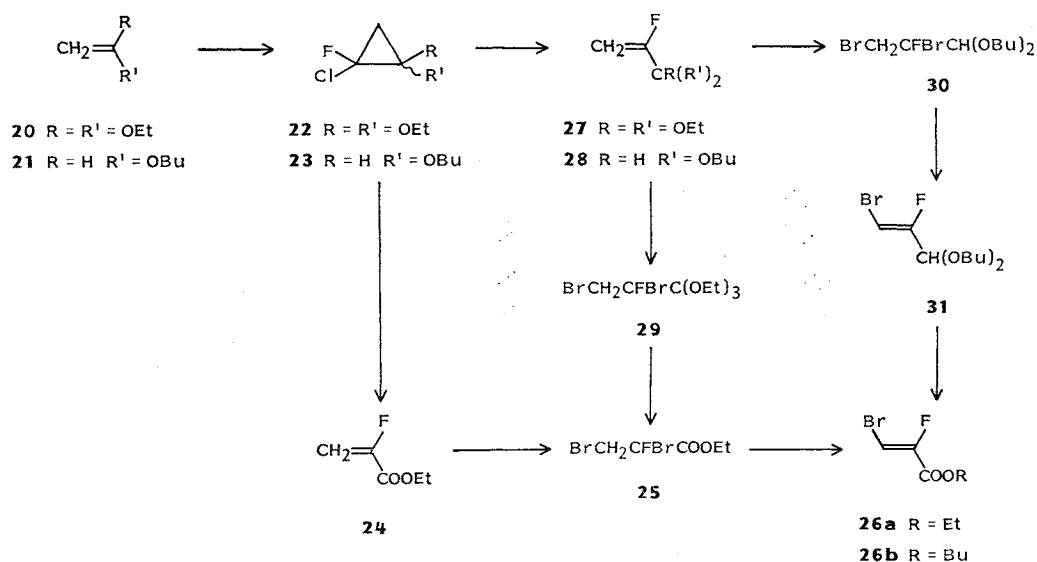<div align="center">Fig. 2.</div>

Fig. 3.

15 R = Na
16 R = Ms

17

18 R = H
19 R = CH3

Fig. 4.

20 R = R' = OEt
21 R = H R' = OBu

22 R = R' = OEt
23 R = H R' = OBu

27 R = R' = OEt
28 R = H R' = OBu

30

BrCH2CFBrC(OEt)3

29

31

BrCH2CFBrCOOEt

25

24

26a R = Et
26b R = Bu

glycolic acid in the presence of two equivalents of triethylamine in N,N-dimethylformamide at room temperature affording 17 with complete retention of the stereochemistry. From a practical point of view, it is worthy to note that these three steps could be conveniently carried out in one pot with 50% overall yield from ethyl fluoroacetate. Aminolysis of 17 with ammonium hydroxide or aqueous methylamine in ethanol followed by acidification gave 18 and 19, respectively.

To avoid the use of toxic ethyl monofluoroacetate, we searched for other useful methods and were able to establish method B (Fig. 4) which involves carbene insertion to vinyl acetal 20 or 21 and subsequent pyrolysis of the resultant cyclopropanes 22 or 23 as key reactions[6,7]. Thus, chlorofluorocarbene, generated *in situ* from Freon 21 (dichlorofluoromethane) with potassium *tert*-butoxide in hexane at $-20°C \sim -10°C$ was captured with ketene diethylacetal (20) giving 1,1-diethoxy-2-chloro-2-fluorocyclopropane (22) in 60% yield. To avoid possible polymerization of the expected pyrolysis product 24, the pyrolysis of 22 was carried out by heating it at 140°C in 1,2,4-trichlorobenzene in the presence of trace amounts of hydroquinone and the resulting α-fluoroacrylate was removed from the

Fig. 5.
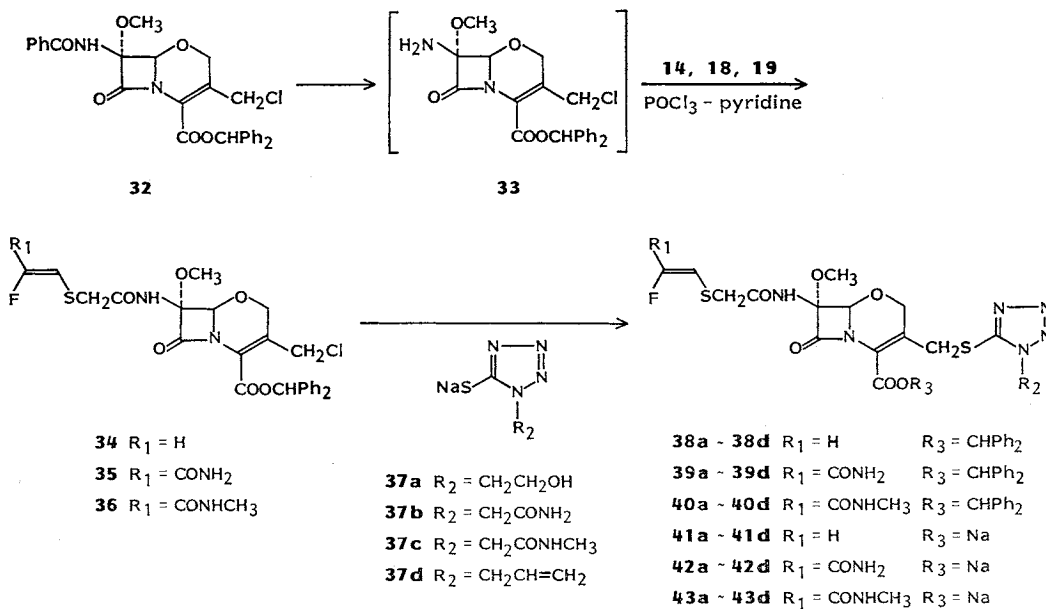
reaction mixture by concomitant distillation to give 24[†] in 76% yield.   Bromination of 24 with bromine in CCl$_4$ under reflux and subsequent base treatment provided α-fluoro-β-bromoacrylate 26a in a completely stereo-selective manner.   Although we thus obtained 26a in an acceptable yield, we still found that it was not suitable for large-scale preparation of 26a because the operation was complicated by the unstability of the key intermediate 24.   On the other hand, pyrolysis of the cyclopropane 22 could be more conveniently carried out by heating it with a slight excess of ethanol and pyridine in refluxing benzene.   Unlike the former case, the product obtained in 70% yield was 27 in this case, providing us with an excellent practical method.   Bromination of 27 in carbon tetrachloride at 5°C followed by hydrolysis with 2 N HCl in ethanol gave 25[†] in good yield.

In an alternative procedure, chlorofluorobutoxycyclopropane (23), prepared in good yield by addition of chlorofluorocarbene to butyl vinyl ether (21), was converted to 31 via the ring-opened acetal 28 and the brominated product 30.   The acetal 31 was then subjected to oxidative cleavage of the acetal moiety with persulfate to give 26b in 60% yield.   After our study was completed, NGUYEN et al.[9)] reported an analogous method for preparation of phenyl ester 26.   Compounds 26a and 26b were finally transformed into 18 or 19 by the same procedure as applied to the mesylate 16.

The carboxylic acids 14, 18 and 19 were coupled with the methoxyamine 33 using a combination of phosphorous oxychloride and pyridine to afford the corresponding acylamino derivatives 34, 35 and 36.   These 3-chloromethyl-1-oxacephems reacted with various N-substituted mercaptotetrazoles 37a~37d in N,N-dimethylformamide or in a two-phase system with a catalytic amount of Bu$_4$N$^+$Br$^-$ to give 38a~38d, 39a~39d and 40a~40d, respectively, in quantitative yields.   Removal of the benzhydryl group was performed by a well-established procedure using AlCl$_3$ and anisole to give the

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[†] An alternative synthetic method of 24 and 25 has been previously reported by M. HUDLICKY.   Literature bp 24, 110°C (728 mm); 25, 67~67.5°C (3.2 mm), see ref 8.

free oxacephems[10], which were neutralized with sodium bicarbonate and purified by chromatography (Diaion HP-20) to give the corresponding sodium salts **41a ~ 41d**, **42a ~ 42d** and **43a ~ 43d** in a pure state.

Biology

The MICs of those oxacephem antibiotics bearing *cis*-fluorovinylthioacetamido C-7 side chains are shown in Table 1. All of these compounds show excellent antibacterial activity against both Gram-positive and Gram-negative bacteria, and a good parallelism between their *in vitro* and *in vivo* activity in marked contrast with the corresponding chloro analogues (Table 2). C-7 non-substituted fluorovinyl-thioacetamido analogues **41a ~ 41d** proved to be the most active and showed antibacterial activity comparable to those of the chloro congeners. Compounds **42** and **43** having additional groups ($CONH_2$, $CONHCH_3$) show slightly decreased activity but more favorable pharmacokinetic properties compared with **41** (Table 3). In every series, modification of the C-3' position with variously substituted tetra-

Table 1. MIC (μg/ml) of 1-oxacephem antibiotics **41**, **42** and **43**.

Compound	S.a. JC-1	S.a. C-14	E.c. NIHJJC-2	E.c. 73	K. sp. 363	P.m. PR-4	P.v. CN-329
41a	0.2	0.2	0.05	0.1	0.05	0.1	0.2
41b	0.1	0.2	0.05	0.1	0.05	0.1	0.2
41c	0.2	0.4	0.1	0.2	0.05	0.1	0.2
41d	0.1	0.2	0.2	0.8	0.1	0.2	0.4
42a	0.4	0.4	0.05	0.1	0.05	0.2	0.4
42b	0.4	0.4	0.05	0.1	0.05	0.1	0.4
42c	0.4	0.8	0.05	0.1	0.05	0.2	0.4
42d	0.2	0.4	0.2	0.4	0.05	0.2	0.2
43a	0.4	0.8	0.05	0.2	0.1	0.2	0.4
43b	0.4	0.4	0.05	0.2	0.05	0.1	0.2
43c	0.8	0.8	0.2	0.4	0.1	0.2	0.4
43d	0.2	0.4	0.4	1.6	0.2	0.4	0.8

Abbreviations: S.a.; *Staphylococcus aureus*, E.c.; *Escherichia coli*, K.; *Klebsiella*, P.m.; *Proteus mirabilis*, P.v.; *Proteus vulgaris*.

Table 2. Activity of 1-oxacephem antibiotics in mouse protection tests[a].

Compound	*Streptococcus pyogenes* C-203			*Escherichia coli* EC-14		
	MIC (μg/ml)	ED_{50} (mg/kg)	(ED_{50}/MIC)	MIC (μg/ml)	ED_{50} (mg/kg)	(ED_{50}/MIC)
3	0.05	2.11	(42)	0.2	0.33	(1.7)
4	0.8	19.3	(24)	0.01	0.042	(4.2)
5	0.05	3.35	(67)	0.05	0.054	(1.1)
6	0.05	2.69	(54)	0.05	0.18	(3.6)
41a	0.2	3.27	(16)	0.05	0.12	(2.4)
42a	0.1	1.92	(19)	0.05	0.087	(1.7)
42b	0.1	1.43	(14)	0.05	0.12	(2.4)

[a] Mice dosed 1 and 5 hours post infection.

Table 3. Plasma levels of 1-oxacephem antibiotics **41**, **42** and **43** in monkeys.

Compound	**41a**	**41b**	**42a**	**42b**	**43a**	**43b**
AUC (μg·hours/ml)	20	30	42	52	51	50
Half life (minutes)	27	35	39	50	53	61

Dose: 20 mg/kg, iv.

zolylthio groups had only little influence on the activity.   Taking the overall biological properties into account, **42a**, designated as 2355-S, was selected for further biological evaluation[11].

Experimental

MP and BP were uncorrected. ^{1}H NMR spectra were recorded at 60 MHz on a Varian T-60 NMR Spectrometer and at 90 MHz on a Varian EM-390 NMR Spectrometer using TMS as an internal (in organic solvent) or external (in D_2O) standard. ^{19}F NMR spectra were determined on a Varian EM-360 with C_6F_6 as the internal reference.   IR spectra were recorded on Hitachi 260-10 and 215 Spectrometers.   Anhydrous solvents dried over Molecular Sieves type 4A were used for reactions under anhydrous conditions.

Methyl (2-Fluoroethylthio)acetate (8)

Methyl thioglycolate (2.2 ml, 24.6 mmol) was dissolved in DMF (20 ml), and 5.2 N NaOCH$_3$ - MeOH (4 ml, 20.8 mmol) and the tosylate **7** (4.36 g, 20 mmol) were added.   After being stirred for 1.5 hours at room temp, the reaction mixture was partitioned between ether and water, and the organic layer was dried and evaporated.   The residue was distilled to give 2.85 g of **8** (93.8%): BP 100~102°C/17 mmHg; IR (CHCl$_3$) 1730 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 2.95 (2H, dt, J=21 and 6 Hz), 3.30 (3H, s), 3.75 (3H, s), 4.60 (2H, dt, J=47 and 6 Hz).

Sulfoxide 10

A solution of chlorine (1 M solution in CCl$_4$, 10 ml, 10 mmol) was added to the sulfide **8** (0.75 g, 4.93 mmol) in CH$_2$Cl$_2$ (10 ml) under ice cooling.   After 5 minutes the reaction mixture was evaporated *in vacuo* to give the crude dichloride **9** (0.91 g): ^{1}H NMR (CDCl$_3$) δ 3.33 (2H, dt, J=22 and 7 Hz), 3.90 (3H, s), 4.67 (2H, dt, J=46 and 7 Hz).   The dichloride **9** was dissolved in CH$_2$Cl$_2$ (15 ml) and 80% MCPBA (1.1 g, 5.10 mmol) in CH$_2$Cl$_2$ (20 ml) was added (the reaction was monitored by TLC). The reaction mixture was washed with aq Na$_2$SO$_3$ solution, aq NaHCO$_3$ solution and brine, dried and evaporated to dryness.   Chromatography on silica gel gave 0.83 g of the sulfoxide **10** (70.4%); IR (CHCl$_3$) cm^{-1} 1760, 1750; ^{1}H NMR (CDCl$_3$) δ 2.57~3.67 (2H, m), 3.97 (3H, s), 4.43~5.47 (2H, m).

Methyl (cis-Fluorovinylthio)dichloroacetate (12)

Trifluoromethanesulfonic anhydride (7.5 ml, 44.6 mmol) was slowly added to a mixture of the sulfoxide **10** (9.7 g, 40.6 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (23.5 g, 114.4 mmol) in anhydrous CH$_2$Cl$_2$ (80 ml) at −30°C.   After being stirred for 30 minutes at the same temp, the resulting white precipitates were filtered off and the filtrate was washed with water, dried and evaporated *in vacuo*.   The residue was chromatographed on silica gel to afford **12** (8.0 g, 89.2%) as an oil: IR (CHCl$_3$) 1750 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 3.93 (3H, s), 5.87 (1H, dd, J=4 and 36 Hz), 6.93 (1H, dd, J=4 and 80 Hz).

Methyl (cis-Fluorovinylthio)acetate (13)

To a solution of the dichloride **12** (8 g, 36.5 mmol) in CH$_2$Cl$_2$ (80 ml) containing MeOH (5 ml) and AcOH (5 ml), zinc (8.0 g) was portion wise added over 10 minutes under ice-cooling.   After stirring for another 10 minutes at the same temp, the reaction mixture was filtered.   The filtrate was washed with dilute HCl (2 times) and brine, dried and evaporated to yield **13** (5.8 g, 106%) as an oil: IR (CHCl$_3$) 1730 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 3.38 (2H, s), 3.75 (3H, s), 5.53 (1H, dd, J=4 and 38 Hz), 6.68 (1H, dd, J=4 and 82 Hz).

(cis-Fluorovinylthio)acetic Acid (14)

To the ester **13** (5.8 g, 38.7 mmol) in MeOH (20 ml) at 0°C, 2 N NaOH (19.5 ml, 39 mmol) was added.   After 20 minutes at 0°C, the reaction mixture was partitioned between water and ether, and the aqueous layer was acidified with 2 N HCl and extracted twice with EtOAc.   The combined extract was washed with brine, dried and evaporated to dryness to give the acid **14** (5.4 g, 103%): IR (CHCl$_3$) cm^{-1} 3100, 1710; ^{1}H NMR (CDCl$_3$) δ 3.42 (2H, s), 5.50 (1H, dd, J=38 and 4 Hz), 6.72 (1H, dd, J=81 and 4 Hz).

Mesylate 16

To a suspension of NaH (60% in mineral oil, 8.65 g, 216.3 mmol) in anhydrous butyl ether (200 ml), anhydrous ethanol (12.7 ml, 216.4 mmol) was added dropwise. After being stirred for 1 hour at room temp, a mixture of ethyl fluoroacetate (20 g, 118.5 mmol) and ethyl formate (23 ml, 270 mmol) was slowly added over 10 minutes, and the mixture was stirred for 3 hours. Anhydrous DMF (100 ml) was added to dissolve the gummy precipitate and the resultant clear solution was cooled to −5°C and mesyl chloride (14.6 ml, 188.6 mmol) was added. After stirring for 30 minutes at 0°C and 30 minutes at room temp, the reaction mixture was poured into water and extracted with EtOAc. The extract was washed with brine, dried and evaporated to give the crude mesylate 16 in *ca.* 60% yield: IR (CHCl$_3$) cm^{-1} 1730, 1680; ^{1}H NMR (CDCl$_3$) δ 1.33 (3H, t, J=7 Hz), 3.23 (3H, s), 4.32 (2H, q, J=7 Hz), 7.40 (1H, d, J=16 Hz).

((Z)-2-Fluoro-2-ethoxycarbonylvinylthio)acetic Acid (17)

A mixture of thioglycolic acid (3.28 ml, 47.2 mmol) and triethylamine (14.5 ml, 104 mmol) in DMF (5 ml) was added to the mesylate 16 (10 g, 47.2 mmol) in DMF (30 ml) at 10~20°C. After 1.5 hours at room temp the reaction mixture was partitioned between ether and water. The aqueous layer was acidified with 3% HCl and extracted with EtOAc (2 to 3 times). The combined extract was washed with water, dried and evaporated to afford the acid 17 (8.07 g, 90.5%) as an oil: IR (CHCl$_3$) cm^{-1} 1715, 1615; ^{1}H NMR (CDCl$_3$) δ 1.33 (3H, t, J=7 Hz), 3.62 (2H, s), 4.30 (2H, q, J=7 Hz), 6.98 (1H, d, J=32 Hz), 10.45 (1H, br s).

(2-Fluoro-2-carbamoylvinylthio)acetic Acid (18)

The half ester 17 (0.54 g, 2.6 mmol) was dissolved in 28% ammonium hydroxide (2 ml) and the resulting solution was allowed to stand overnight at room temp. After condensation *in vacuo* to *ca.* 10 ml followed by acidification with conc HCl, the resulting crystals were filtered and washed with ice water to afford 0.43 g of 18 (92.4%): MP 204~206°C; IR (Nujol) cm^{-1} 3430, 3210, 1710, 1660, 1640, 1610, 1580; ^{1}H NMR (DMSO-d_6) δ 3.72 (2H, s), 6.90 (1H, d, J=36 Hz), 7.40~8.10 (2H, m).

(2-Fluoro-2-methylcarbamoylvinylthio)acetic Acid (19)

A mixture of the half-ester 17 (6.0 g, 28.9 mmol) and 40% methylamine solution in water (0.97 ml) was stirred for 2 hours at room temp. After removal of the excess methylamine *in vacuo*, the reaction mixture was diluted with water (10 ml) and then acidified with conc HCl. The resulting crystals were filtered and washed with a minimum amount of ice water to afford 19 (2.73 g). IR (Nujol) cm^{-1} 3280, 3090, 1720, 1660, 1615, 1600, 1550; ^{1}H NMR (DMSO-d_6) δ 2.67 (3H, d, J=5 Hz), 3.72 (2H, s), 6.83 (1H, d, J=35 Hz).

1,1-Diethoxy-2-chloro-2-fluorocyclopropane (22)

To a suspension of potassium *tert*-butoxide (14.5 g, 129.2 mmol) in anhydrous hexane (95 ml) containing ketene diethylacetal (10 g, 86.2 mmol), dichlorofluoromethane (25 g, 242.7 mmol) in anhydrous hexane (50 ml) was added at −20~−10°C over 35 minutes. After stirring at the same temp for 1 hour, the reaction mixture was poured into water and extracted with hexane. The extract was washed with aq NaHCO$_3$ solution and water, dried and distilled to give 22 (9.31 g, 59.2%): BP 54~57°C/20 mmHg; ^{1}H NMR (CDCl$_3$) δ 1.24 (6H, t, J=7.5 Hz), 1.17~1.88 (2H, m), 3.78 (4H, q, J=7.5 Hz); ^{19}F NMR (CDCl$_3$) δ +15.92 (dd, J=9.4 and 18.8 Hz).

Ethyl α-Fluoroacrylate (24)

The cyclopropane 22 (6.1 g, 33.4 mmol) in 1,2,4-trichlorobenzene (TCB) (6.1 g) was added dropwise to TCB (6.1 g) containing a trace amount of *p*-hydroquinone at 145°C under reduced (360 mmHg) nitrogen atmosphere. The distillate collected bp 40~45°C (360 mm), was 24 (3.0 g, 76%): IR (CHCl$_3$) cm^{-1} 1730, 1660, 1325, 1175, 1100; ^{1}H NMR (CDCl$_3$) δ 1.32 (3H, t, J=7.5 Hz), 4.29 (2H, q, J=7.5 Hz), 5.29 (1H, dd, J=3 and 13.5 Hz), 5.65 (1H, dd, J=3 and 44 Hz); ^{19}F NMR (CDCl$_3$) δ 44.1 (1H, dd, J=13.16 and 43.24 Hz).

Ethyl α-Fluoro-β-bromoacrylate (26a)

Bromine (2.7 g, 16.9 mmol) was added to a solution of 24 (2.0 g, 16.9 mmol) in CCl$_4$ (50 ml).

After heating under reflux, the reaction mixture was washed with aq $Na_2S_2O_3$ solution and water, dried and evaporated *in vacuo*. The residue was dissolved in benzene (47 ml) and heated under reflux with DBU (2.35 ml, 15.7 mmol). After cooling and filtration of the resultant precipitate, the filtrate was washed with water and evaporated to give an oily residue (2.69 g), which when purified by distillation gave **26a** (2.15 g, 64.6%): BP 80°C/40 mmHg; ^1H NMR (CDCl$_3$) δ 1.33 (3H, t, J=7.5 Hz), 4.31 (2H, q, J=7.5 Hz), 6.93 (1H, d, J=24 Hz).

Triethyl Orthofluoroacrolate (27)

The cyclopropane **22** (5 g, 27.4 mmol) was heated under reflux in anhydrous benzene (25 ml) with anhydrous ethanol (2.38 ml, 40.6 mmol) and pyridine (2.65 ml, 33.1 mmol) for 1 hour. The reaction mixture was washed with water, dried and distilled under reduced pressure to yield 3.7 g of **27** (91.2%): BP 73~77°C/40 mmHg; IR (CHCl$_3$) cm^{-1} 1678, 1097; ^1H NMR (CDCl$_3$) δ 1.20 (9H, t, J=7.5 Hz), 3.54 (6H, q, J=7.5 Hz), 4.94 (1H, dd, J=16.5 and 2.3 Hz), 4.99 (1H, dd, J=48 and 2.3 Hz); ^{19}F NMR (CDCl$_3$) δ +45.5 (dd, J=16.9 and 48.9 Hz).

Ethyl α,β-Dibromo-α-fluoropropionate (25) from 27

To a solution of the orthoacrylate **27** (4.58 g, 30.95 mmol) in anhydrous CCl$_4$ (46 ml), bromine (1.22 ml, 24 mmol) in CCl$_4$ (10 ml) was added dropwise at 5°C over 20 minutes. After 5 minutes, the reaction mixture was washed with aq 5% Na$_2$S$_2$O$_3$ solution and water, dried and evaporated to give an oily residue (7.4 g). It was stirred in EtOH (130 ml) containing 2 N HCl (41 ml) at room temp. After 1 hour, the mixture was poured into water and extracted with hexane (3 times). The combined extract was washed, dried and distilled to yield **25** (5.18 g, 60.2%): BP 79~85°C/15 mmHg; IR (CHCl$_3$) cm^{-1} 1765, 1310, 1043; ^1H NMR (CDCl$_3$) δ 1.37 (3H, t, J=7.5 Hz), 3.90~4.52 (2H, m), 4.40 (2H, q, J=7.5 Hz).

1-Chloro-1-fluoro-2-butoxycyclopropane (23)

To an ice-cooled mixture of *n*-butyl vinyl ether (60 g, 0.6 mol), Adogen 464 (10 g) and dichlorofluoromethane (120 g, 1.165 mol) in a three-necked flask equipped with a dry-ice condenser, KOH (66 g, 1.176 mol) in H$_2$O (45 ml) was slowly added over 30 minutes under vigorous stirring. After being stirred at room temp for 4 hours, additional dichlorofluoromethane (120 g, 1.165 mol) and KOH (66 g, 1.176 mol) in H$_2$O (45 ml) were added, and the mixture was stirred for 2 hours. The reaction mixture was partitioned between ether and water. Distillation of the organic layer *in vacuo* gave **23** (65.05 g, 65.1%): BP 43~45°C/7 mmHg; IR (film) cm^{-1} 1170, 1125, 1080; ^1H NMR (CDCl$_3$) δ 0.91 (3H, t, J=7 Hz), 1.15~1.85 (6H, m), 3.3~3.8 (3H, m).

α-Fluoroacrolein Dibutylacetal (28)

A mixture of **23** (42 g, 252.3 mmol), butanol (150 ml) and pyridine (24 ml, 300 mmol) was heated under reflux for 17 hours. The reaction mixture was partitioned between ether and aq K$_2$CO$_3$ solution. The organic layer was separated and its distillation gave **28** (36.9 g, 76.6%): BP 83~85°C/10~12 mmHg; IR (film) cm^{-1} 1680, 1115, 1070; ^1H NMR (CDCl$_3$) δ 0.93 (6H, t, J=7 Hz), 1.2~1.8 (8H, m), 3.35~3.75 (4H, m), 4.80 (1H, dd, J=50 and 3 Hz), 4.80 (1H, dd, J=17 and 3 Hz), 4.92 (1H, d, J=3 Hz).

α-Fluoro-β-bromoacrolein Dibutylacetal (31)

Bromine (14.4 g, 90.1 mmol) was added to a solution of **28** (18.1 g, 94.8 mmol) in CCl$_4$ (150 ml), under ice cooling. After stirring for 1.5 hours at room temp, the reaction mixture was condensed *in vacuo* to give the dibromide **30**. It was dissolved in CH$_2$Cl$_2$ (150 ml) and heated under reflux with DBU (16.2 g, 106.2 mmol) for 4 hours. The reaction mixture was diluted with CH$_2$Cl$_2$, washed successively with dilute HCl, aq K$_2$CO$_3$ solution and water, dried and evaporated. Purification of the residue by distillation gave 17.85 g of **31** (69.7%): BP 96~98°C/4 mmHg; IR (film) cm^{-1} 1670, 1100, 1070; ^1H NMR (CDCl$_3$) δ 0.91 (6H, t, J=7 Hz), 1.15~1.75 (8H, m), 3.35~3.75 (4H, m), 4.97 (1H, s), 5.94 (1H, d, J=28 Hz).

Butyl α-Fluoro-β-bromoacrylate (26b)

Caro's acid (7.8 g) was added to a solution of the acetal **31** (4.29 g, 15.9 mmol) in butanol (15 ml),

and the mixture was stirred for 2 hours at room temp. Additional Caro's acid (3.91 g) was added and stirring was continued for 1 hour at room temp and 1 hour at 50~60°C. The reaction mixture was partitioned between CH_2Cl_2 and water. The organic layer was distilled to give 2.98 g of **26b** (61%): BP 73~75°C/5 mmHg; IR (film) cm^{-1} 1735, 1643; ^{1}H NMR (CDCl$_3$) δ 0.8~2.0 (7H, m), 4.23 (2H, t, J=6 Hz), 6.87 (1H, d, J=24 Hz).

7α-Methoxy-7β-(cis-fluorovinylthio)acetamido-3-chloromethyl-1-oxacephem (34)

To a solution of the methoxy-amine **33** prepared from **32** (19.14 g, 36.77 mmol) in CH_2Cl_2 (200 ml), pyridine (12.1 ml), the carboxylic acid **14** (5.4 g, 39.7 mmol) and phosphorous oxychloride (3.53 ml, 37.9 mmol) were successively added at −30°C. After being warmed to 0°C over 20 minutes, the reaction mixture was washed with dilute HCl and water, dried and evaporated to dryness. Recrystallization of the solid residue from CH_2Cl_2 - ether afforded **34** (11.0 g, 56% from **32**): MP 197~199°C; IR (Nujol) cm^{-1} 3250, 1776, 1720, 1680, 1654; ^{1}H NMR (DMSO-d_6) δ 3.42 (2H, s), 3.47 (3H, s), 4.53 (4H, br s), 5.20 (2H, s), 5.75 (1H, dd, J=42 and 4 Hz), 6.88 (1H, s), 6.2~7.66 (12H, m).

7α-Methoxy-7β-(2-fluoro-2-carbamoylvinylthio)acetamido-3-chloromethyl-1-oxacephem (35)

To a solution of the methoxy-amine **33** prepared from **32** (4.1 g, 7.88 mmol) in CH_2Cl_2 (30 ml) were added pyridine (1.6 ml) and a mixture of the carboxylic acid **18** (1.32 g, 7.37 mmol) and pyridine (0.5 ml, 6.25 mmol) in anhydrous DMF (4 ml). After being cooled to −30°C, phosphorous oxychloride (0.56 ml, 6 mmol) was added dropwise and the mixture was stirred for 30 minutes at the same temp. Usual work-up gave a solid residue which was purified by chromatography and recrystallized from CH_2Cl_2 - ether to afford **35** (2.37 g, 52.1% from **32**): MP 160°C; IR (CHCl$_3$) cm^{-1} 3390, 1780, 1715, 1690, 1630; ^{1}H NMR (DMSO-d_6) δ 3.45 (3H, s), 3.63 (2H, s), 4.55 (4H, br s), 5.23 (1H, s), 6.93 (1H, s), 6.97 (1H, d, J=32 Hz), 7.20~7.77 (13H, m).

7α-Methoxy-7β-(2-fluoro-2-N-methylcarbamoylvinylthio)acetamido-3-chloromethyl-1-oxacephem (36)

From the carboxylic acid **19** (17.9 g, 92.7 mmol) and **32** (59.6 g, 114.5 mmol) the same procedure as **35** afforded **36** (49.5 g, 73.1% from **25**): MP 178~180°C; IR (CHCl$_3$) cm^{-1} 3440, 3360, 1785, 1720, 1690, 1635; ^{1}H NMR (DMSO-d_6) δ 2.68 (3H, d, J=5 Hz), 3.47 (3H, s), 3.65 (2H, s), 4.55 (4H, br s), 5.23 (1H, s), 6.93 (1H, s), 6.67~8.50 (12H, m), 9.30 (1H, br s).

General Procedure of 38~40

Sodium heterocyclic thiolate **37** (2.2 mmol) in DMF (2 ml) was added to a solution of the 3-chloromethyl-1-oxacephem **34~36** (2 mmol) in DMF (5 ml) under ice cooling. After 30 minutes, the reaction mixture was partitioned between water and EtOAc, and the organic layer was washed twice with water, dried and evaporated *in vacuo*. The residue was chromatographed to give the product **38~40** in more than 90% yield.

38a: IR (CHCl$_3$) cm^{-1} 3350, 1782, 1700, 1623; ^{1}H NMR (CDCl$_3$) δ 3.38 (2H, br s), 3.55 (3H, s), 3.77~4.10 (2H, m), 4.10~4.40 (4H, m), 4.57 (2H, br s), 5.03 (1H, s), 5.43 (1H, dd, J=40 and 4 Hz), 6.87 (1H, s), 6.23~7.73 (12H, m).

38b: IR (CHCl$_3$) cm^{-1} 3330, 1780, 1708, 1623; ^{1}H NMR (CDCl$_3$) δ 3.35 (2H, br s), 3.50 (3H, s), 3.92~5.13 (7H, m), 5.43 (1H, dd, J=40 and 4 Hz), 6.83 (1H, s), 5.92~7.77 (14H, m).

38c: IR (CHCl$_3$) cm^{-1} 3340, 1785, 1672, 1630; ^{1}H NMR (CDCl$_3$) δ 2.70 (3H, d, J=5 Hz), 3.40 (2H, s), 3.56 (3H, s), 4.17 (2H, br s), 4.57 (2H, br s), 4.81 (2H, br s), 5.03 (1H, s), 5.47 (1H, dd, J=38 and 4 Hz), 6.72 (1H, s), 5.97~7.67 (13H, m).

38d: IR (Nujol) cm^{-1} 3200, 3160, 1780, 1726, 1650; ^{1}H NMR (CDCl$_3$) δ 3.38 (2H, s), 3.55 (3H, s), 4.60~6.10 (8H, m), 6.66 (1H, dd, J=81 and 4 Hz), 6.90 (1H, s), 7.20~7.60 (11H, m).

39a: IR (CHCl$_3$) cm^{-1} 3500, 3380, 1783, 1700, 1630; ^{1}H NMR (CDCl$_3$) δ 3.50 (2H, br s), 3.57 (3H, s), 3.70~4.80 (8H, m), 5.03 (1H, s), 5.90~6.47 (2H, m), 6.78 (1H, d, J=34 Hz), 6.90 (1H, s), 7.2~7.8 (12H, m).

39b: IR (KBr) cm^{-1} 3375, 1785, 1680, 1660; ^{1}H NMR (Me$_2$CO-d_6) δ 3.52 (3H, s), 3.70 (2H, s), 4.2~4.4 (2H, m), 4.63 (2H, br s), 5.12 (3H, s), 6.70~7.77 (16H, m).

39c: IR (KBr) cm^{-1} 3380, 1786, 1720, 1680, 1630; ^{1}H NMR (Me$_2$CO-d_6) δ 2.77 (3H, d, J=9 Hz),

3.55 (3H, s), 3.72 (2H, s), 4.22 (2H, br s), 4.63 (2H, br s), 5.07 (2H, s), 5.13 (1H, s), 6.90 (1H, s), 6.77∼7.77 (15H, m).

39d: IR (CHCl$_3$) cm^{-1} 3500, 3400, 1785, 1700, 1630; ^{1}H NMR (CDCl$_3$) δ 3.53 (5H, s), 4.26 (2H, s), 4.5∼6.2 (9H, m), 6.70 (1H, s), 6.89 (1H, d, $J=36$ Hz), 7.2∼7.9 (1H, m).

40a: IR (CHCl$_3$) cm^{-1} 3450, 3360, 1783, 1700, 1672, 1640; ^{1}H NMR (CDCl$_3$) δ 2.73 (3H, d, $J=5$ Hz), 3.52 (5H, s), 3.73∼4.80 (8H, m), 5.02 (1H, s), 6.25∼6.70 (1H, m), 6.75 (1H, d, $J=34$ Hz), 6.87 (1H, s), 7.1∼7.77 (11H, m).

40b: IR (KBr) cm^{-1} 3430, 3340, 1780, 1715, 1685, 1620; ^{1}H NMR (DMSO-d_6) δ 2.67 (3H, d, $J=5$ Hz), 3.42 (3H, s), 3.65 (2H, s), 4.10∼4.43 (2H, m), 4.47∼4.78 (2H, m), 5.03 (2H, br s), 5.17 (1H, s), 6.88 (1H, s), 6.68∼8.33 (14H, m).

40c: IR (CHCl$_3$) cm^{-1} 3430, 3320, 1780, 1710, 1680, 1630; ^{1}H NMR (CDCl$_3$) δ 2.7∼2.9 (6H, m), 3.57 (5H, s), 4.20 (2H, br s), 4.57 (2H, br s), 4.90 (2H, s), 5.07 (1H, s), 6.82 (1H, d, $J=34$ Hz), 6.88 (1H, s), 7.30∼7.77 (13H, m).

40d: IR (CHCl$_3$) cm^{-1} 3450, 3360, 1785, 1700, 1675; ^{1}H NMR (CDCl$_3$) δ 2.90 (3H, d, $J=4$ Hz), 3.58 (5H, s), 3.70 (2H, s), 4.70 (2H, s), 4.83 (1H, s), 5.0∼6.2 (5H, m), 6.95 (1H, s), 6.5∼7.8 (13H, m).

General Procedure for Removal of the Protecting Group of 41∼43

A solution of aluminum chloride (5∼10 mmol) in anisole (5∼10 ml)/nitromethane (5∼10 ml) was added to the ester **38∼40** (1 mmol) in anhydrous CH$_2$Cl$_2$ (5∼10 ml) at −10°C. After 30 minutes at the same temp, the reaction mixture was poured into ice water and extracted with 2-butanone (3 times). The combined extract was washed with brine and re-extracted with aq NaHCO$_3$ solution. After being washed with EtOAc, the aqueous extract was brought to pH 2 with 1 N HCl and extracted several times with a mixture of 2-butanone - ethyl acetate (1 : 1). The combined extract was washed with brine, dried and evaporated *in vacuo*. The residue was dissolved in Me$_2$CO (10 ml) and water (5 ml), and the pH of the solution was brought to 6 by adding aq NaHCO$_3$ solution. The solution was condensed to 5 ml, re-adjusted at pH 6 and freeze-dried to obtain the sodium salt **41∼43**.

41a: IR (KBr) cm^{-1} 3420, 1770, 1685, 1630, 1610; ^{1}H NMR (D$_2$O) δ 3.95 (5H, s), 4.22∼5.07 (8H, m), 5.60 (1H, s), 6.08 (1H, dd, $J=40$ and 4 Hz), 7.28 (1H, dd, $J=82$ and 4 Hz).

41b: IR (KBr) cm^{-1} 3400, 1766, 1688, 1630, 1606; ^{1}H NMR (D$_2$O) δ 3.63 (5H, s), 4.57∼4.70 (2H, m), 4.95 (2H, br s), 5.25 (1H, s), 5.38 (2H, s), 6.03 (1H, dd, $J=40$ and 4 Hz), 7.28 (1H, dd, $J=81$ and 4 Hz).

41c: IR (KBr) cm^{-1} 3340, 1767, 1678, 1610; ^{1}H NMR (D$_2$O) δ 3.28 (3H, s), 4.00 (5H, s), 4.68 (2H, s), 5.00 (2H, br s), 5.65 (1H, s), 5.70 (2H, s), 6.08 (1H, dd, $J=40$ and 4 Hz), 7.36 (1H, dd, $J=82$ and 4 Hz).

41d: IR (KBr) cm^{-1} 3330, 1760, 1680, 1610; ^{1}H NMR (D$_2$O) δ 3.98 (3H, s), 4.65 (2H, s), 4.98 (2H, s), 5.4∼6.7 (7H, m), 7.39 (1H, dd, $J=83$ and 5 Hz).

42a: IR (KBr) cm^{-1} 3400, 1770, 1680, 1605; ^{1}H NMR (D$_2$O) δ 3.97 (3H, s), 4.17 (2H, s), 4.33∼5.10 (8H, m), 5.58 (1H, s), 7.30 (1H, d, $J=34$ Hz).

42b: IR (KBr) cm^{-1} 3375, 1765, 1685, 1607; ^{1}H NMR (D$_2$O) δ 3.97 (3H, s), 4.15 (2H, s), 4.50, 4.77 (2H, ABq, $J=13$ Hz), 4.92 (2H, br s), 5.57 (1H, s), 5.70 (2H, s), 7.27 (1H, d, $J=34$ Hz).

42c: IR (KBr) cm^{-1} 3400, 1770, 1680, 1610; ^{1}H NMR (D$_2$O) δ 3.25 (3H, s), 3.97 (3H, s), 4.15 (2H, s), 4.57∼4.73 (2H, m), 4.75 (2H, br s), 5.60 (1H, s), 5.67 (2H, s), 7.37 (1H, d, $J=34$ Hz).

42d: IR (KBr) cm^{-1} 3380, 1760, 1678, 1600; ^{1}H NMR (D$_2$O) δ 4.00 (3H, s), 4.17 (2H, s), 4.55, 4.74 (2H, ABq, $J=12$ Hz), 4.88, 5.02 (2H, ABq, $J=10$ Hz), 5.4∼6.8 (6H, m), 7.37 (1H, d, $J=33$ Hz).

43a: IR (KBr) cm^{-1} 3400, 1768, 1665, 1610; ^{1}H NMR (D$_2$O) δ 3.25 (3H, s), 3.97 (3H, s), 4.13 (2H, s), 4.33∼4.73 (4H, m), 4.87∼5.03 (4H, m), 5.58 (1H, s), 7.25 (1H, d, $J=34$ Hz).

43b: IR (Nujol) cm^{-1} 3300, 1760, 1675, 1605; ^{1}H NMR (D$_2$O) 3.27 (3H, s), 3.95 (3H, s), 4.12 (2H, s), 4.5∼4.7 (2H, m), 4.90 (2H, br s), 5.57 (1H, s), 5.70 (2H, s), 7.21 (1H, d, $J=34$ Hz).

43c: IR (Nujol) cm^{-1} 3250, 1765, 1670, 1610; ^{1}H NMR (CDCl$_3$) 3.23 (6H, s), 3.95 (3H, s), 4.13 (2H, s), 4.53∼4.72 (2H, m), 4.90 (2H, br s), 5.55 (1H, s), 5.62 (2H, s), 7.20 (1H, d, $J=35$ Hz).

43d: IR (KBr) cm^{-1} 3400, 1782, 1668, 1608; ^{1}H NMR (D$_2$O) δ 3.26 (3H, s), 4.00 (3H, s), 4.54, 4.73 (2H, ABq, $J=12$ Hz), 4.8∼6.8 (8H, m), 7.28 (1H, d, $J=34$ Hz).

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