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

I. 7β-*cis*-CHLOROVINYLTHIOACETAMINO-7α-METHOXY-1-OXACEPHEMS

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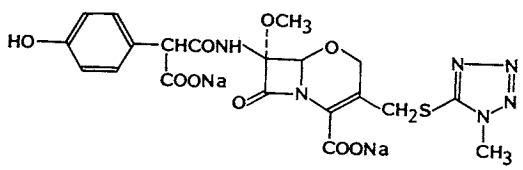
The synthesis and *in vitro* activity of 7β-(substituted vinylthioacetamido)-1-oxacephem antibiotics are described. The compounds having a *cis*-chlorovinylthioacetamido group at C-7 showed high activity against Gram-positive as well as Gram-negative bacteria. The most interesting compound of the series was **51 l** because of its high activity and high plasma level in mice.

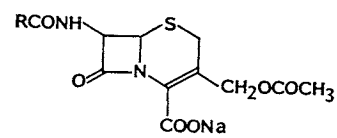
Extensive studies in β-lactam chemistry at our laboratories have led us to the discovery and practical use of latamoxef (**1**)[1], which belongs structurally to 1-oxacephem antibiotics and biologically to the so-called third-generation cephalosporins. In general, cephalosporins of this generation tend to be highly active against Gram-negative bacteria but weak against Gram-positive bacteria. We have continuously been working in quest of new derivatives to overcome this drawback, that is, drugs exhibiting antibacterial activity against Gram-positive as well as Gram-negative bacteria.

At the start of our study, the following was known about structure-activity relationships[1,2]: 1) 1-Oxacephem antibiotics with a few exceptions, exhibit 4- to 8-fold higher antibacterial activity than the corresponding 1-thia congeners; 2) the *N*-methyl-tetrazolylthio group is one of the most potent C-3′-

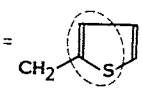
Fig. 1.



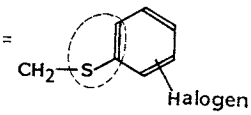
Latamoxef (**1**)

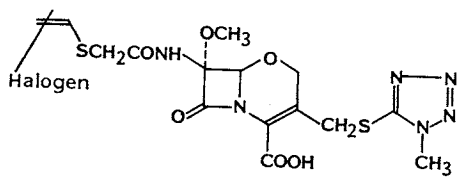


2a R =



2b R =





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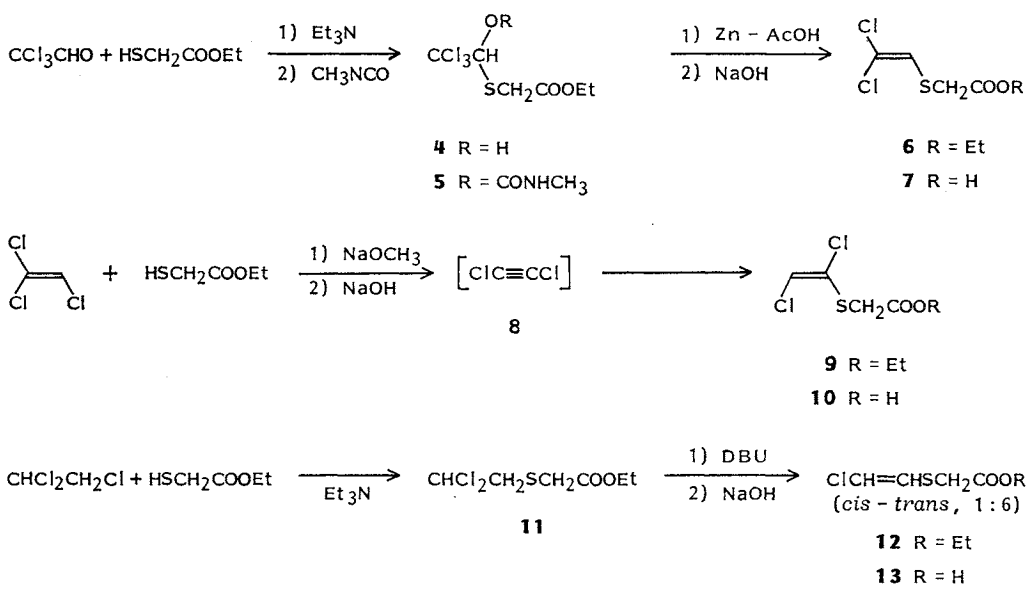
side chains imparting high activity particularly against Gram-negative bacteria; 3) C-7 side chains involving an aromatic ring and a sulfur atom impart high Gram-positive activity, as exemplified by **2a** and **2b**. We directed our attention particularly to the third point and assumed that the vinylthio or the halovinylthio unit structure in these side chains might enhance Gram-positive activity. Taking these relationships into consideration, we designed 1-oxacephems **3** as our target molecules. In this and the following papers, we report the synthesis and structure-activity relationships of a series of 1-oxacephem antibiotics bearing variously substituted vinylthioacetamido C-7β side chains.

Chemistry

We first prepared the chlorine-substituted vinylthioacetic acids, **7**†, **10**†† and **13** necessary for construction of the C-7 acylamino side chains in **3** according to the schemes in Fig. 2. Addition of thioglycolate to chloral in the presence of a catalytic amount of triethylamine to give **4** and subsequent acylation with methyl isocyanate afforded **5**. Reduction of **5** with zinc in methylene chloride containing acetic acid gave **6** which was then hydrolyzed to give the free acid **7**. 1,2-Dichlorovinylthioacetic acid (**10**) was formed as the sole isolable product by treatment of a mixture of trichloroethylene and thioglycolate with sodium methoxide followed by hydrolysis. The stereochemistry of **10** was deduced from the mode of the reaction mechanism, in which *trans* addition of thioglycolate to the initially formed dichloroacetylene (**8**) may be involved. Alkylation of thioglycolate with 1,1,2-trichloroethane was effected using triethylamine to give **11** and subsequent dehydrochlorination with DBU provided a mixture of *cis*- and *trans*-isomers **12** in a ratio of 1 to 6, which was hydrolyzed with sodium hydroxide in aqueous methanol to give a *cis* and *trans* mixture of **13** in the same ratio.

The coupling reaction of these carboxylic acids **7**, **10** and **13** with the methoxyamine **14**[5], a key intermediate in latamoxef synthesis, was carried out by the well-established procedure using phosphorous oxychloridepyridine to give the esters **15a**~**15d** after chromatographic purification. Removal

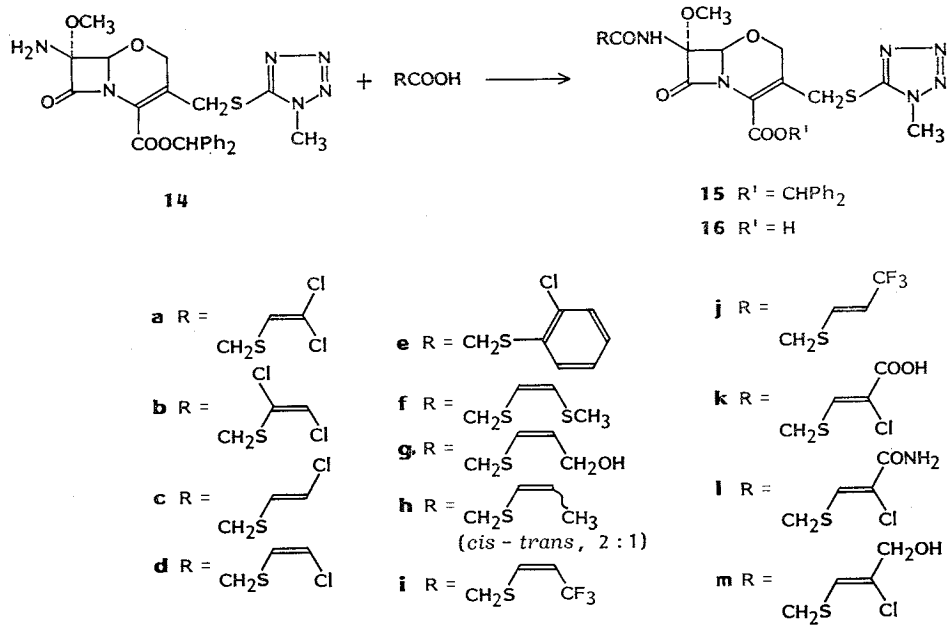
Fig. 2.



† The acid **7** has been synthesized by an alternative method see ref 3.

†† For one-step synthesis of **10** (no spectra data), see ref 4.

Fig. 3.

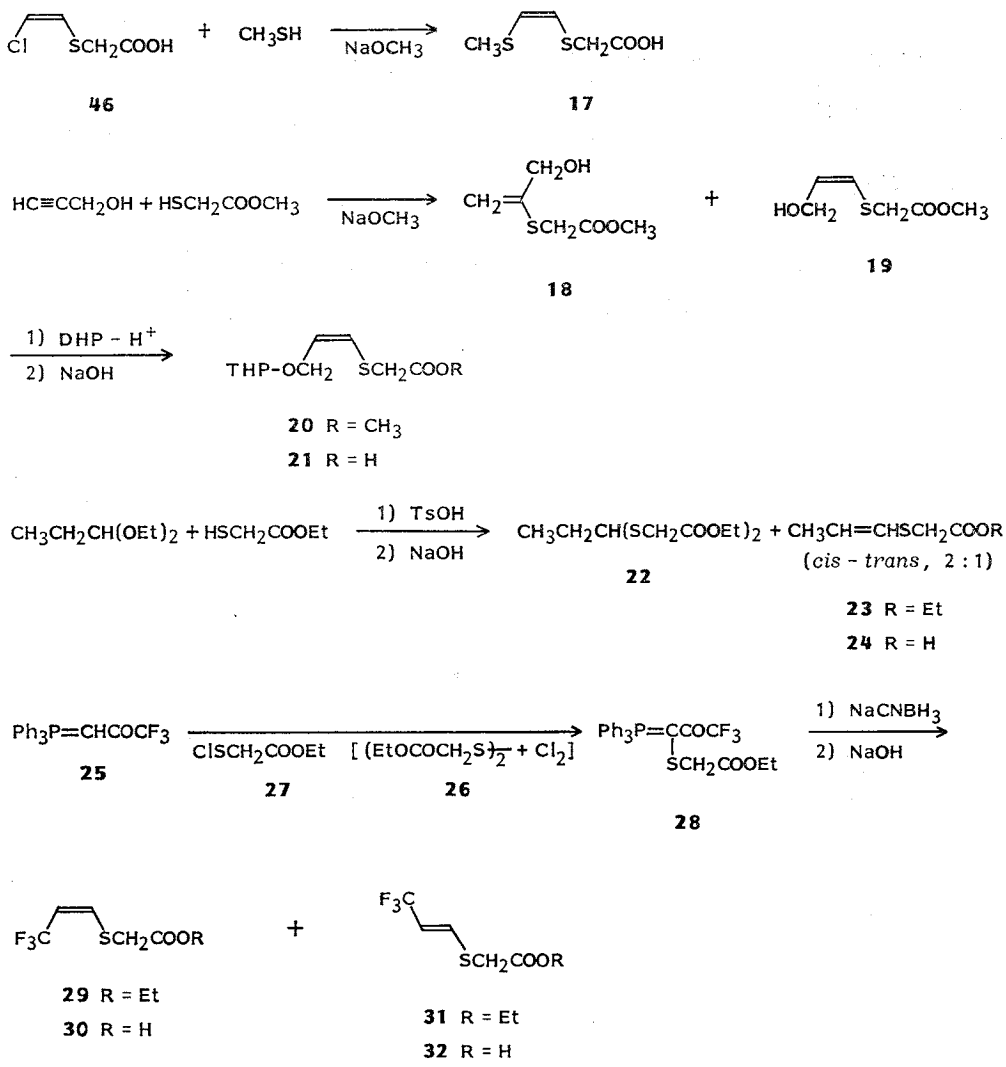


of the ester protecting group was effected with $AlCl_3$ - anisole[6] to give the free acids **16a**~**16d**. Oxacephem **16e** involving the *o*-chlorophenylthioacetamido side chain was also prepared as a reference compound. These oxacephems were then subjected to *in vitro* antibacterial assay. It turned out that all of these oxacephems **16a**~**16d**, especially *cis*-chlorovinylthio derivative **16d**, exhibited high and well-balanced antibacterial activity as discussed in the biology section below. The results were better than we had expected and prompted us to search for a possibly more effective vinylthioacetamido side chain having another *cis*-substituent such as SCH_3, CH_2OH, CH_3 or CF_3.

Preparation of the corresponding carboxylic acids **17**, **21**, **24**, **30** and **32** was thus carried out according to the schemes shown in Fig. 4. Treatment of *cis*-chlorovinylthioacetic acid (**46**) with methyl mercaptan and sodium methoxide gave **17** in a quantitative yield with complete retention of the stereochemistry. The stereochemical assignment is based upon the NMR data. Addition of methyl thioglycolate to propargyl alcohol under base-catalyzed condition was found to proceed not regioselectively but stereoselectively to provide an easily separable mixture of **18** and **19**. Protection of the hydroxy group of **19** with dihydropyran (DHP) and subsequent hydrolysis afforded **21**. 1,1-Diethoxypropane reacted with thioglycolate in the presence of TsOH (cat.) giving an unseparable mixture of *cis*- and *trans*-methylvinylthioacetates **23** in a ratio of 2 to 1 accompanied by dithioacetal **22**, which could be easily removed from **23** by distillation. This mixture underwent alkaline hydrolysis to give a mixture of the corresponding acids **24**. Trifluoromethyl derivatives **30** and **32** were synthesized starting from the phosphorane **25**[7]. Treatment of **25** with sulfenyl chloride **27**, which was generated *in situ* from the disulfide **26** and chlorine, gave **28**. This compound was reduced with sodium cyanoborohydride in acetic acid, providing a 1:2 mixture of *cis*- and *trans*-trifluorovinyl thioacetates **29** and **31**. After separation by chromatography, these esters were hydrolyzed to give **30** and **32** in good yields.

The new oxacephems **16f**~**16j** were synthesized by coupling of **14** with these acids **17**, **21**, **24**, **30**

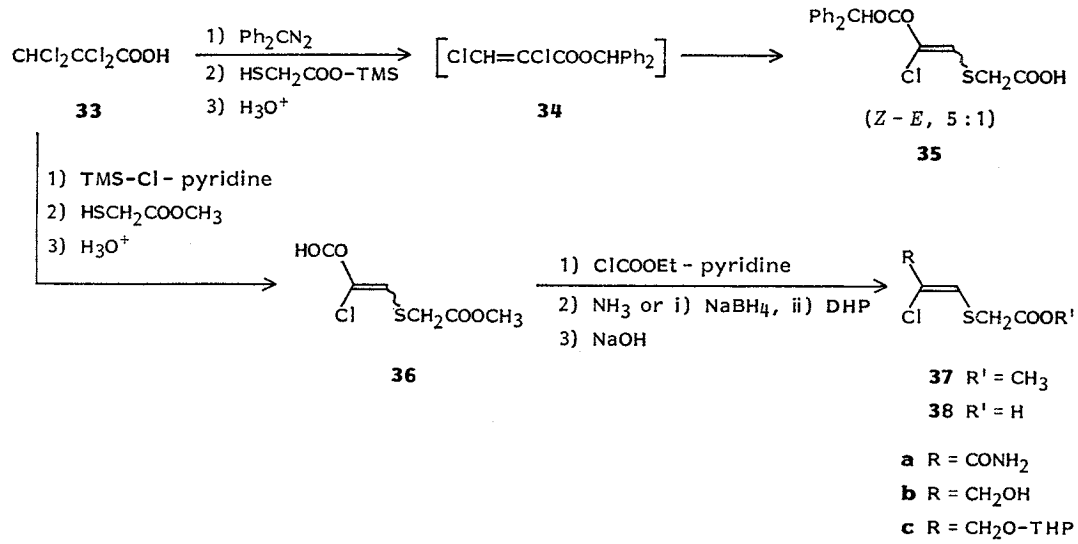
Fig. 4.



and **32** and found to be less active than the reference compound **16d** (Fig. 3). Consequently, the latter (**16d**) was selected as a candidate for further evaluation. As this compound showed a considerably low plasma level after intravenous injection in monkeys as described later, we then tried to improve the pharmacokinetic properties by either introduction of an additional group onto the double bond of the C-7 acyl group or modification at the C-3′ position.

We first tried to introduce a hydrophilic group, such as COOH, CH_2OH, $CONH_2$, onto the chlorovinyl bond in the C-7 acyl side chain, and the corresponding acids **35**, **38a** and **38c** were prepared according to the schemes shown in Fig. 5. Esterification of tetrachloropropionic acid (**33**) with diphenyldiazomethane and subsequent treatment with trimethylsilyl thioglycolate afforded, after acid work up, the half ester **35** as a mixture of *Z*- and *E*-isomers in a ratio of 5 to 1, the ratio being estimated by NMR spectrum. We assume that this reaction proceeds *via* the intermediate **34**, which is formed by reductive elimination of α- and β-chlorine in **33** with thioglycolate. This view was sup-

Fig. 5.



ported by the fact that more than three equivalents of thioglycolate were consumed to complete the reaction. In an analogous manner, **33** was first trimethylsilylated and subsequently treated with methyl thioglycolate to give, after acid work up, a 5 : 1 *Z*- and *E*-mixture of **36**. This mixture was converted with ethyl chloroformate into a mixed anhydride which subsequently underwent aminolysis with ammonia or sodium borohydride reduction, followed by treatment with DHP, to give **37a** or **37c**, respectively. Hydrolysis of esters **37a** and **37c** with sodium hydroxide in aqueous methanol gave the acids **38a** and **38c**. Coupling reaction of these acids **35**, **38a** and **38c** with oxacephem nucleus **14** followed by deprotection gave oxacephems **16k**~**16m** (Fig. 3).

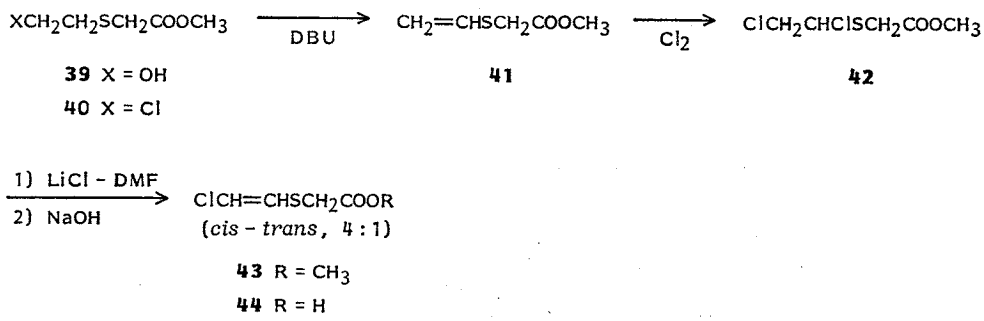
Our efforts were finally directed toward modification at C-3′, which involved replacement of the *N*-methyltetrazolylthio group with other heterocyclylthio groups including differently *N*-substituted tetrazolylthiols. For this objective, it was desirable to develop an efficient and practical method for large-quantity production of the side chain acid **46** and then to a common intermediate **49**. Two stereoselective synthetic methods, A and B, were established for this purpose as shown in Fig. 6. In method A, methyl hydroxyethylthioacetate (**39**) prepared by the procedure of SCHRADER[8], was converted to the vinyl thioglycolate **41**[9,10] by way of **40**. Compound **41** was further converted to the dichloride **42** by addition of chlorine. While dehydrochlorination of **42** with DBU resulted in the formation of a complex mixture, the reaction with lithium chloride in *N*,*N*-dimethylformamide at 60~70°C proceeded smoothly providing chlorovinylthioacetate **43** as a 4 : 1 mixture in favor of the *cis* isomer†. Hydrolysis of this mixture gave **44**, and from this mixture, *cis*-carboxylic acid **46** could be cleanly crystallized in a pure state. In method B, methyl *cis*-chlorovinylthioacetate (**45**) was formed in a completely stereo-controlled manner by reaction of *cis*-dichloroethylene and thioglycolate with DBU, but the yield was moderate.

The methoxy-amine **48** prepared *in situ* from **47**[11] by the conventional method using PCl_5-pyridine and methanol, was acylated with the *cis*-acid **46** to furnish the common intermediate **49** in a

† Regio- and stereochemical outcomes observed in the dehydrochlorination reaction of 1,2-dichloroethylbutylsulfide will be argued elsewhere.

Fig. 6.

Method A



Method B

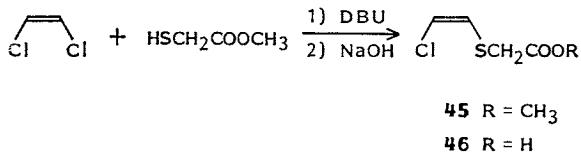
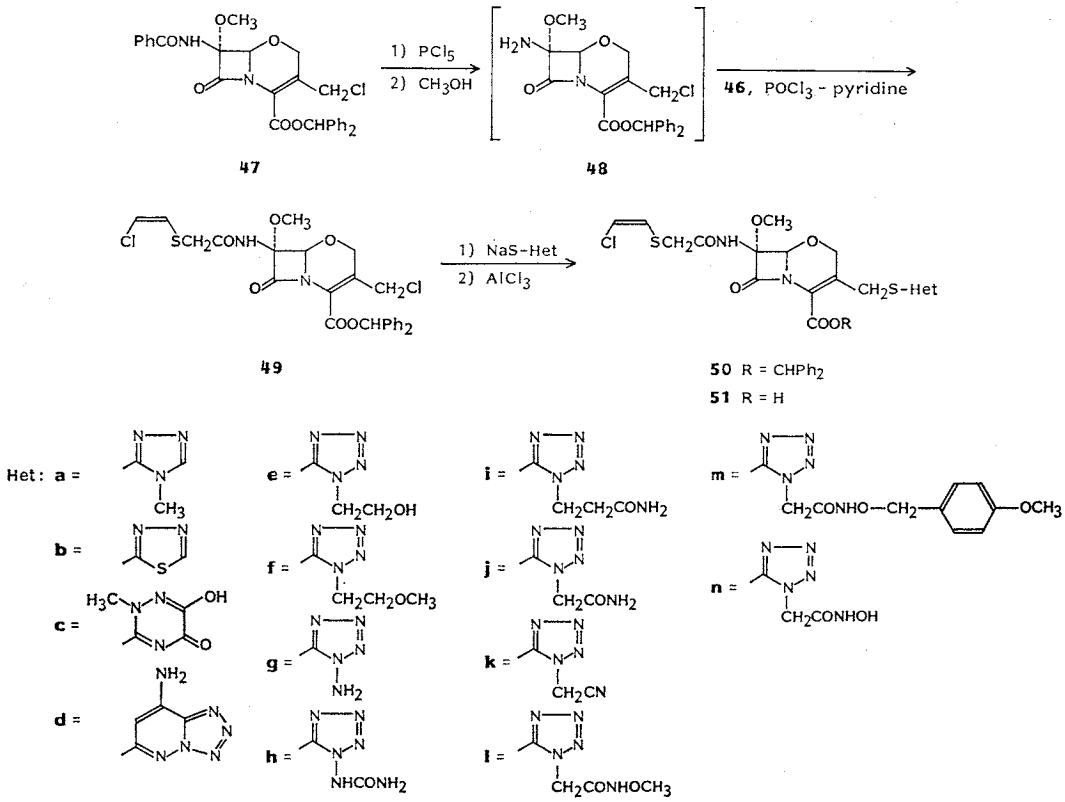


Fig. 7.



reasonable yield. Introduction of various heterocyclylthio groups into the C-3′ position was effected by reaction of **49** with sodium heterocyclylthiolates (NaS-Het) in *N*,*N*-dimethylformamide or in a two-phase system using tetrabutyl ammonium bromide as a catalyst to give **50a**~**50m** which upon ester deprotection with either $AlCl_3$ or CF_3COOH and anisole in methylene chloride gave **51a**~**51l** and **51n** (Fig. 7). Bioassay results of these oxacephem antibiotics are discussed below.

Biology

The MICs of the 1-oxacephem antibiotics prepared are listed in Tables 1 and 2 in comparison with those of latamoxef (LMOX) and cefazolin (CEZ).

The antibacterial activities of four chloro- or dichlorovinylthioacetamido-1-oxacephems **16a**~**16d** were excellent as expected. Especially of interest is **16d**, in which chlorine and sulfur in the C-7 side chain have a *cis* alignment. This oxacephem **16d** shows superior overall activity compared with **16c** which has an isomeric *trans* chlorovinylthioacetamido side chain. This structure-activity relationship is similar to that observed by NANNINI *et al.*[12,13] with cephalosporins bearing the *cis*- or *trans*-oriented cyano- or carboxy-vinylthioacetamido side chain. Another characteristic of **16d** is that its antibacterial activity is well balanced, that is, its MIC values are equally low against both Gram-positive and Gram-negative bacteria. This feature in activity is evident from comparison of the MICs between **16d**, structurally related **16e**, LMOX and CEZ. LMOX is mainly active against Gram-negative bacteria, and CEZ and **16e** against Gram-positive bacteria.

To our disappointment, none of the other vinylthioacetamido-1-oxacephems **16f**~**16j** substituted with groups other than chlorine exhibited better activity than the parent oxacephem **16d**. The superiority of oxacephem compound with the *cis*-substituted vinylthioacetamido side chain over that with the *trans*-oriented side chain is also seen in the pair of oxacephems **16i** and **16j**.

Effects of the introduction of a polar group onto the *cis*-chlorovinylthioacetamido side chain were investigated with the series of **16k**~**16m**. While introduction of a carbamoyl or hydroxymethyl group does not effectively improve the pharmacokinetic properties of **16d**, the introduction of carboxyl does,

Table 1. MIC values (μg/ml) of 1-oxacephem antibiotics.

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
LMOX	6.3	6.3	0.1	0.4	0.1	0.1	0.2
CEZ	0.2	0.4	1.6	25	>100	3.1	50
16a	0.05	0.1	0.1	1.6	0.1	0.8	0.8
16b	0.1	0.1	0.05	0.8	0.1	0.8	0.8
16c	0.2	0.2	0.2	0.8	0.2	0.4	0.8
16d	0.1	0.1	0.02	0.1	0.05	0.1	0.2
16e	0.05	0.2	6.25	12.5	1.56	3.13	6.25
16f	0.1	0.2	0.8	1.6	0.4	0.8	0.8
16g	0.4	0.4	0.2	0.2	0.2	0.8	0.8
16h	0.2	0.4	0.2	1.6	0.2	0.8	0.8
16i	0.1	0.2	0.1	1.6	0.4	0.8	1.6
16j	0.2	0.2	0.2	6.3	0.8	3.1	6.3
16k	0.8	0.8	0.02	0.05	0.02	0.05	0.1
16l	0.2	0.4	0.05	0.1	0.02	0.2	0.2
16m	0.2	0.4	0.1	0.2	0.05	0.4	0.4

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

Table 2. MIC values (μg/ml) of 1-oxacephem antibiotics.

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
51a	0.2	0.4	0.2	0.4	0.2	0.4	0.8
51b	0.1	0.1	0.4	0.8	0.05	0.4	0.8
51c	0.4	0.8	0.4	0.8	0.2	0.1	0.4
51d	1.6	1.6	0.05	1.6	0.2	0.4	0.8
51e	0.1	0.2	0.02	0.2	0.05	0.1	0.2
51f	0.1	0.2	0.2	0.8	0.1	0.8	0.2
51g	0.1	0.1	0.05	0.1	0.05	0.1	0.1
51h	0.1	0.4	0.05	0.2	0.05	0.1	0.4
51i	0.1	0.2	0.1	0.2	0.1	0.1	0.2
51j	0.1	0.2	0.02	0.2	0.05	0.1	0.2
51k	0.05	0.1	0.02	0.2	0.05	0.1	0.2
51l	0.2	0.4	0.1	0.2	0.1	0.1	0.2
51n	0.1	0.2	0.1	0.2	0.1	0.1	0.2

Abbreviations: See foot note in Table 1.

Table 3. Plasma levels of 1-oxacephem antibiotics in mice.

Compound	**16d**	**16k**	**16l**	**16m**	**51b**	**51e**	**51f**	**51g**	**51h**	**51i**	**51j**	**51k**	**51l**	**51n**
AUC (μg·hour/ml)	6.2	8.6	3.9	3.8	6.3	6.2	4.1	8.6	7.7	6.0	6.1	4.7	25.5	11.8
Half life (minutes)	15	18	12	12	15	15	9	20	10	14	12.4	14	18.5	15.3

Dose: 20 mg/kg, sc.

but only at the expense of the antibacterial activity against Gram-positive bacteria.

Table 2 lists MIC values of **51a**~**51l** and **51n**. Although somewhat enhanced antibacterial activity is seen for **51g**, **51j** and **51k**, there was no particular improvement from the pharmacokinetic viewpoint. However, an extraordinarily large AUC value was observed for **51l**, which bears a characteristic hydroxamate moiety on the C-3-tetrazole nitrogen (Table 3). The improved pharmacokinetics might sufficiently cover its reduced antibacterial activity. The unusual pharmacokinetic properties of **51l** are due to its high affinity for serum protein.

Experimental

MP and BP were uncorrected. ^{1}H NMR spectra were recorded at 60 MHz on a Varian T-60 NMR Spectrometer. Chemical shifts are given in ppm downfield from TMS as an internal (in organic solvent) or external (in D_2O) standard. IR spectra were taken on a Hitachi 260-10 Spectrometer. All reactions under anhydrous conditions were carried out using anhydrous solvents dried over Molecular Sieves type 4A in nitrogen atmosphere.

Materials: The heterocyclic thiols used for modification of the C-3′ position were prepared by modifying the known synthetic methods.

Antibacterial Activity

All the *in vitro* antibacterial activities are given as the MIC in μg/ml required to prevent growth of bacterial culture. MICs were determined by the serial agar dilution method after incubation at 37°C for 18~20 hours with an inoculum size of about 10^6 cells/ml.

Ethyl (2,2-Dichlorovinylthio)acetate (6)

Ethyl thioglycolate (18.6 ml, 170 mmol) was added to a solution of chloral (25 g, 170 mmol) in benzene (200 ml) with triethylamine (0.7 ml, 5 mmol) at room temp. After stirring for 1.5 hours,

additional triethylamine (1.5 ml, 10.8 mmol) and methyl isocyanate (10.2 ml, 173 mmol) were added and the mixture was stirred for 3 hours at the same temp. The reaction mixture was diluted with EtOAc, washed with aqueous sodium hydroxide and water, and evaporated to give an oil, which was chromatographed on silica gel to give a fraction (10.9 g) with a singlet peak at δ 6.47 in NMR spectrum ($CDCl_3$). The fraction was dissolved in AcOH (45 ml) and reduced with zinc powder (10 g) at room temp. The reaction mixture was worked up in a usual way and chromatographed on silica gel to afford 3.0 g (8.2%) of **6**: IR ($CHCl_3$) 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (3H, t, J=7.5 Hz), 3.40 (2H, s), 4.20 (2H, q, J=7.5 Hz), 6.50 (1H, s).

Ethyl (1,2-Dichlorovinylthio)acetate (**9**)

To a sodium ethoxide solution prepared from sodium (2.7 g) and anhydrous EtOH (20 ml) were successively added ethyl thioglycolate (9.0 ml, 82 mmol) and trichloroethylene (35 ml) at room temp and the mixture was heated under reflux for 1.5 hours, cooled to room temp, and then partitioned between ether and water. The organic layer was washed with brine and evaporated *in vacuo*. Chromatography of the residue on silica gel gave 1.94 g of **9** (11%) as a colorless oil: IR ($CHCl_3$) 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (3H, t, J=7 Hz), 3.62 (2H, s), 4.15 (2H, J=7 Hz), 6.40 (2H, s).

Ethyl (2,2-Dichloroethylthio)acetate (**11**)

Triethylamine (15 ml) was added to a mixture of ethyl thioglycolate (12 g, 100 mmol) and 1,1,2-trichloroethane (20 ml) in DMF (20 ml) at room temp. After being stirred for 1 hour at 70°C and 15 hours at 20°C, the reaction mixture was partitioned between water and EtOAc. The organic layer was successively washed with dilute HCl, water, 5% NaOH and brine, dried and evaporated *in vacuo*. The residue was distilled to give 5.7 g of **11** (26.3%): BP 87~94°C/2 mmHg; IR ($CHCl_3$) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (3H, t, J=7 Hz), 3.37 (2H, s), 3.40 (2H, d, J=6 Hz), 4.23 (2H, q, J=7 Hz), 5.92 (1H, t, J=6 Hz).

Ethyl (*cis*- and *trans*-Chlorovinylthio)acetate (**12**)

DBU (1.53 g, 10 mmol) was added to a solution of **11** (2.17 g, 10 mmol) in benzene (10 ml). The mixture was heated at 80°C for 30 minutes, then cooled, washed with dilute HCl and evaporated to give a mixture **12** (1.15 g, 63.7%); IR ($CHCl_3$) 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (3H, t, J=7 Hz), 3.33, 3.38 (2H, s), 4.18 (2H, q, J=7 Hz), 6.15 (1H, d, J=13 and 4 Hz), 6.48, 6.38 (1H, d, J=13 and 4 Hz).

(*cis*-Methylthiovinylthio)acetic Acid (**17**)

25% $NaOCH_3$ - MeOH (5.65 ml, 25.7 mmol) was added to a mixture of **46** (1.40 g, 9.18 mmol), 30% CH_3SH - MeOH (2.08 ml, 13 mmol) and water (2 ml) at room temp. After heating under reflux for 40 minutes, the reaction mixture was poured into dilute HCl and extracted with EtOAc. The usual work-up afforded 1.30 g of **17** (86.4%) as an oil; ^1H NMR ($CDCl_3$) δ 2.32 (3H, s), 3.43 (2H, s), 6.15 (2H, s), 11.23 (1H, s); **17** could be characterized further as its methyl ester prepared by the treatment of diazomethane. Methyl ester of **17**: ^1H NMR ($CDCl_3$) δ 1.83 (3H, s), 3.03 (2H, s), 3.32 (3H, s), 5.83 (1H, d, J=8 Hz), 6.10 (1H, d, J=8 Hz).

Methyl (*cis*-Hydroxymethylvinylthio)acetate (**19**)

A mixture of methyl thioglycolate (4.47 ml, 50 mmol), propargyl alcohol (5 ml, 85.9 mmol) and 25% $NaOCH_3$ - MeOH (0.2 ml, 0.93 mmol) was stirred at 100°C for 6 hours and at room temp for 2 days. The reaction mixture was diluted with EtOAc, washed with water, dried and concd. The residue (2.3 g) was purified by chromatography on silica gel to give 1.25 g of **19** (15.4%): IR ($CHCl_3$) 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.67 (2H, s), 3.73 (3H, s), 4.10~4.40 (3H, m), 5.63~5.98 (1H, m), 6.13 (1H, d, J=10 Hz).

Ethyl (*cis*- and *trans*-Methylvinylthio)acetate (**23**)

A mixture of diethoxypropane (25 ml, 155 mmol) and ethyl thioglycolate (10 ml, 91.2 mmol) in anhydrous toluene (25 ml) with a catalytic amount of *p*-toluenesulfonic acid was heated at 130°C for 3 hours. The reaction mixture was distilled under reduced pressure to give 2.5 g of **23** (18.8%): BP 70~75°C/4 mmHg; IR ($CHCl_3$) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (3H, t, J=7 Hz), 1.62~1.87 (3H,

m), 3.33 (2H, s), 4.17 (2H, q, J=7 Hz), 5.40~6.20 (2H, m).

Ylide **28**

To a solution of diethyl 2,2'-dithioacetate (**26**) (1.2 g, 5 mmol) in THF (15 ml) was slowly added a solution of chlorine (1.25 M solution in CCl_4, 4 ml, 5 mmol) at −20°C, and the mixture was stirred at −20~0°C for 10 minutes. Then **25** (2.7 g, 9.94 mmol) in THF (10 ml) was added at 0°C. After being stirred for 10 minutes, the reaction mixture was poured into dilute aq $NaHCO_3$ solution and extracted with CH_2Cl_2. The extract was washed with water and evaporated to give the crystalline residue, which was recrystallized from CH_2Cl_2 - ether to afford 4.0 g of **28** (82%): IR ($CHCl_3$) cm^{-1} 1720, 1555; ^1H NMR ($CDCl_3$) δ 1.20 (3H, t, J=7 Hz), 2.70 (2H, br s), 4.00 (2H, q, J=7 Hz), 7.37~7.93 (15H, m).

Ethyl (*cis*- and *trans*-Trifluoromethylvinylthio)acetate (**29** and **31**)

Compound **28** (3.0 g, 6.1 mmol) was dissolved in AcOH (30 ml) and $NaCNBH_3$ (3.0 g, 47.7 mmol) was added portionwise during 30 minutes at room temp. The reaction mixture was stirred for an additional 4 hours, concd *in vacuo* to *ca.* 10 ml, poured into a suspension of $NaHCO_3$ (30 g) in H_2O (300 ml) and extracted with EtOAc. The usual work-up followed by chromatography on silica gel gave **29** (370 mg, 28.3%): IR ($CHCl_3$) cm^{-1} 1725, 1615; ^1H NMR ($CDCl_3$) δ 1.28 (3H, t, J=7 Hz), 3.40 (2H, s), 4.22 (2H, q, J=7 Hz), 5.63 (1H, dq, J=9, 10 Hz), 6.82 (1H, d, J=10 Hz); and **31** (960 mg, 73.5%); IR ($CHCl_3$) cm^{-1} 1730, 1615; ^1H NMR ($CDCl_3$) δ 1.30 (3H, t, J=7 Hz), 3.50 (2H, s), 4.23 (2H, q, J=7 Hz), 5.67 (1H, dq, J=7 and 16 Hz), 7.07 (1H, dq, J=1.16 Hz).

(*Z*)- and (*E*)-(2-Benzhydroxycarbonyl-2-chlorovinylthio)acetic Acid (**35**)

A mixture of thioglycolic acid (0.7 ml, 10.1 mmol) and pyridine (1.6 ml, 20 mmol) in anhydrous THF (20 ml) was treated with trimethylsilylchloride (1.3 ml, 10.2 mmol) at 0°C for 30 minutes. To the resultant mixture was added the benzhydryl ester of **33** (1.53 g, 4.06 mmol). After 20 hours at room temp, the mixture was partitional between water and EtOAc. The organic layer was evaporated to give an oily residue, which was dissolved in CH_2Cl_2 and washed 3 times with water to remove the excess thioglycolic acid. Evaporation *in vacuo* gave 1.49 g of crude **35** (101.2%) as a mixture of *Z*- and *E*-isomers: IR ($CHCl_3$) cm^{-1} 3300~3100, 1710; ^1H NMR ($CDCl_3$) δ 3.52, 3.72 (2H, s), 6.93 (1H, s), 7.2~7.5 (10H, m), 7.90, 7.98 (1H, s), 9.77 (1H, s).

Methyl ((*Z*)- and (*E*)-2-Carboxy-2-chlorovinylthio)acetate (**36**)

Trimethylsilylchloride (7.9 g, 72.7 mmol) was slowly added to a mixture of tetrachloropropionic acid (**33**) (12 g, 56.6 mmol) and pyridine (5.43 ml, 67.9 mmol) in anhydrous DMF (30 ml) at −30°C. After 30 minutes at −40~−30°C, methyl thioglycolate (12.3 ml, 137.5 mmol) and pyridine (14 ml, 175 mmol) were added, and the mixture was gradually warmed to room temp and stirred overnight. The reaction mixture was partitioned between EtOAc and dilute HCl. The organic layer was washed twice with water and evaporated to give 8.3 g of **36** (70%) as a mixture of *Z*- and *E*-isomers: ^1H NMR ($CDCl_3$) δ 3.50, 3.63 (1H, s), 3.80 (3H, s), 7.47, 8.03 (1H, s), 11.15 (1H, s).

Methyl ((*Z*)-2-Carbamoyl-2-chlorovinylthio)acetate (**37a**)

Ethyl chloroformate (0.46 ml, 4.8 mmol) was added to a mixture of **36** (1.0 g, 4.75 mmol) and triethylamine (0.78 ml, 5.6 mmol) in anhydrous CH_2Cl_2 (15 ml) at −30°C. After being stirred for 20 minutes at the same temp, NH_3 gas was gently bubbled for 10 minutes and then the mixture was gradually warmed to room temp to complete the reaction. The reaction mixture was washed with dilute HCl and water, and evaporated. The residue was chromatographed on silica gel to give **37a** (786 mg, 79%): IR ($CHCl_3$) cm^{-1} 3540, 3420, 1745, 1680, 1575; ^1H NMR ($CDCl_3$) δ 3.58 (2H, s), 3.77 (3H, s), 7.27 (1H, s).

Methyl ((*Z*)-2-Hydroxymethyl-2-chlorovinylthio)acetate (**37b**)

Methyl chloroformate (0.7 ml, 7.3 mmol) was added to a solution of **36** (1.48 g, 7 mmol) in anhydrous THF (20 ml) with pyridine (0.65 ml, 8.1 mmol) at −30°C. After stirring 10 minutes at 0°C, $NaBH_4$ (0.8 g, 21 mmol) was added and the mixture was stirred for 2 hours at the same temp, and then partitioned between EtOAc and dilute HCl. The organic layer was washed with aq $NaHCO_3$

solution and evaporated *in vacuo*. The residue was chromatographed to give 492 mg of **37b** (35.8%): IR ($CHCl_3$) cm^{-1} 3580, 3440, 1730; ^1H NMR ($CDCl_3$) δ 3.48 (2H, s), 3.57~3.83 (1H, m), 3.73 (3H, s), 4.18 (2H, s), 6.50 (1H, s).

General Procedure for the Hydrolysis of Esters **6**, **9**, **12**, **20**, **23**, **29**, **31** and **37**

To a stirred solution of ester (2 mmol) in MeOH or Me_2CO (5~10 ml) was added 1 N NaOH (2~2.2 ml, 2~2.2 mmol) and the mixture was stirred at −10~0°C for 20~30 minutes. The reaction mixture was condensed *in vacuo* to *ca.* 3 ml and partitioned between EtOAc and water. The aq layer was neutralized with 1 N HCl (2~2.2 ml, 2~2.2 mmol) and extracted with EtOAc under salting-out condition. The extract was washed with brine, dried and evaporated *in vacuo* to give the corresponding carboxylic acid in a good yield. It was characterized by its NMR spectrum and transformation into the starting methyl or ethyl ester with diazomethane or diazethane, and then was used for the next coupling reaction without further purification.

7: Oil; ^1H NMR ($CDCl_3$) δ 3.43 (2H, s), 6.43 (1H, s), 10.17 (1H, s).

10: Oil; ^1H NMR ($CDCl_3$) δ 3.68 (2H, s), 6.40 (1H, s), 10.10 (1H, s).

13: Oil; IR ($CHCl_3$) cm^{-1} 1710; ^1H NMR ($CDCl_3$) δ 3.40, 3.45 (2H, s), 6.17, 6.20 (1H, d, J=15 and 7 Hz), 6.48, 6.43 (1H, d, J=15 and 7 Hz), 11.33 (1H, s).

21: To a solution of **19** (0.45 g, 2.78 mmol) in CH_2Cl_2 (3.5 ml) were added dihydropyran (0.3 ml, 3.3 mmol) and a catalytic amount of *p*-toluenesulfonic acid at 0°C. After stirring for 10 minutes at 0°C and another 10 minutes at room temp, the reaction mixture was washed with aq $NaHCO_3$ solution and water, dried and evaporated to give the residue (0.67 g). It was hydrolyzed according to the general procedure to yield **21** (0.61 g, 94.6% from **19**), which was immediately coupled with methoxyamine **14**.

24: Oil; ^1H NMR ($CDCl_3$) δ 1.63~1.83 (3H, m), 3.35 (2H, s), 5.40~6.17 (2H, m).

30: Oil; ^1H NMR ($CDCl_3$) δ 3.47 (2H, s), 5.63 (1H, dq, J=11 and 9 Hz), 6.77 (1H, d, J=11 Hz), 10.97 (1H, s).

32: Oil; ^1H NMR ($CDCl_3$) δ 3.55 (2H, s), 5.68 (1H, dq, J=16 and 6 Hz), 7.07 (1H, dq, J=16 and 1 Hz), 10.71 (1H, s).

38a: MP 205~206°C; IR (Nujol) cm^{-1} 3410, 3200, 1690, 1640; ^1H NMR (DMSO-d_6) δ 3.78 (2H, s), 7.45 (2H, br s), 7.82 (1H, s).

38c: Tetrahydropyranylation of **38b** (490 mg, 2.5 mmol) followed by hydrolysis afforded 450 mg of an acidic fraction (crude **38c**), which was immediately used for the coupling reaction without characterization.

General Procedure for Acylation of Methoxyamine **14** with Carboxylic Acids **7**, **10**, **13**, **17**, **21**, **24**, **30**, **32**, **35**, **38a** and **38c**

To a mixture of methoxyamine **14** (1 mmol), carboxylic acid (1 mmol) and pyridine (1.1~1.3 mmol) in anhydrous CH_2Cl_2 (5~10 ml) was added phosphorous oxychloride (1.05~1.1 mmol) at −10°C and the resultant mixture was washed with dilute HCl and water, dried and evaporated. The residue, chromatographed on silica gel, gave the product in good yield.

15a: IR ($CHCl_3$) cm^{-1} 3350, 1785, 1700; ^1H NMR ($CDCl_3$) δ 3.45 (2H, s), 3.57 (3H, s), 3.82 (3H, s), 4.27 (2H, s), 4.60 (2H, s), 5.08 (1H, s), 6.40 (1H, s), 6.88 (1H, s), 7.22~7.68 (11H, m).

15b: IR ($CHCl_3$) cm^{-1} 3350, 1785, 1700; ^1H NMR ($CDCl_3$) δ 3.55 (3H, s), 3.70 (2H, s), 3.77 (3H, s), 4.23 (2H, s), 4.62 (2H, s), 5.05 (2H, s), 6.47 (1H, s), 6.90 (1H, s), 7.10~7.67 (11H, m).

15c: IR ($CHCl_3$) cm^{-1} 3360, 1790, 1700; ^1H NMR ($CDCl_3$) δ 3.42 (2H, s), 3.57 (3H, s), 3.80 (3H, s), 4.28 (2H, s), 4.68 (2H, s), 5.08 (1H, s), 6.10 (1H, d, J=14 Hz), 6.42 (1H, d, J=14 Hz), 6.92 (1H, s), 7.20~7.67 (11H, m).

15d: IR ($CHCl_3$) cm^{-1} 3360, 1790, 1700; ^1H NMR ($CDCl_3$) δ 3.43 (2H, br s), 3.57 (3H, s), 3.72 (3H, s), 4.20 (2H, br s), 4.62 (2H, br s), 5.05 (1H, s), 6.05 (1H, d, J=6.5 Hz), 6.45 (1H, d, J=6.5 Hz), 6.90 (1H, s), 7.10~78.73 (11H, m).

15f: IR ($CHCl_3$) cm^{-1} 3340, 1780, 1710, 1690; ^1H NMR ($CDCl_3$) δ 2.30 (3H, s), 3.43 (2H, br s), 3.58 (3H, s), 3.85 (3H, s), 4.27 (2H, s), 4.65 (2H, s), 4.65 (2H, s), 5.07 (1H, s), 6.00 (1H, d, J=8 Hz), 6.30 (1H, d, J=8 Hz), 6.92 (1H, s), 7.20~7.68 (11H, m).

15g: IR ($CHCl_3$) cm^{-1} 3350, 1780, 1710, 1695; ^1H NMR ($CDCl_3$) δ 1.93~2.33 (2H, m), 3.42 (2H, s), 3.55 (3H, s), 3.82 (3H, s), 4.10~4.30 (4H, m), 4.67 (2H, s), 5.08 (1H, s), 5.63~6.27 (2H, m), 6.92 (1H, s), 7.13~7.67 (10H, m).

15h: IR ($CHCl_3$) cm^{-1} 3350, 1785, 1710, 1695; ^1H NMR ($CDCl_3$) δ 1.60~1.90 (3H, m), 3.40 (2H, s), 3.55 (3H, s), 3.82 (3H, s), 4.27 (2H, s), 4.65 (2H, s), 5.07 (1H, s), 5.43~6.07 (2H, m), 6.92 (1H, s), 7.17~7.70 (11H, m).

15i: IR ($CHCl_3$) cm^{-1} 3350, 1785, 1700; ^1H NMR ($CDCl_3$) δ 3.47 (2H, br s), 3.52 (3H, s), 3.70 (3H, s), 4.07~4.33 (2H, m), 4.43~4.77 (2H, m), 5.07 (1H, s), 5.17~5.95 (1H, m), 6.73~6.98 (1H, m), 6.90 (1H, s), 7.07~7.87 (11H, m).

15j: IR ($CHCl_3$) cm^{-1} 3360, 1785, 1705; ^1H NMR ($CDCl_3$) δ 3.52 (5H, s), 3.72 (3H, s), 4.10~4.32 (2H, m), 4.45~4.72 (2H, m), 5.05 (1H, s), 5.23~5.95 (1H, m), 6.88 (1H, s), 7.08~7.68 (12H, m).

15k: IR ($CHCl_3$) cm^{-1} 3160, 1780, 1705, 1650; ^1H NMR ($CDCl_3$) δ 3.35 (3H, s), 3.43 (2H, s), 3.83 (3H, s), 4.18 (2H, br s), 4.55 (2H, br s), 5.20 (1H, s), 6.92 (1H, s), 6.95 (1H, s), 7.30~7.80 (10H, m), 8.48 (1H, s), 9.57 (1H, s).

15l: IR ($CHCl_3$) cm^{-1} 3260, 1775, 1700, 1635; ^1H NMR (DMSO-d_6) δ 3.45 (3H, s), 3.70 (2H, s), 3.72 (3H, s), 4.22 (2H, s), 4.40 (2H, s), 5.15 (1H, s), 6.87 (1H, s), 7.2~7.6 (12H, m), 7.87 (1H, s), 9.25 (1H, s).

15m: The crude product obtained from **14** and **41c** was dissolved in Me_2CO (8 ml) and 1 N HCl (2 ml) was added at room temp to remove the THP group. After 1.5 hours, the reaction mixture was partitioned between EtOAc and water. The organic layer was washed with aq $NaHCO_3$ solution and brine, and evaporated. The residue was chromatographed to give **42c** (350 mg) as crystals: MP 171~178°C (from EtOH - CH_2Cl_2); IR ($CHCl_3$) cm^{-1} 3350, 1780, 1717, 1698; ^1H NMR ($CDCl_3$) δ 3.42 (2H, br s), 3.50 (3H, s), 3.77 (3H, s), 3.90~4.33 (5H, m), 4.47~4.73 (2H, m), 5.03 (1H, s), 6.43 (1H, br s), 6.87 (1H, s), 7.07~7.67 (1H, m).

Methyl (2-Chloroethylthio)acetate (**40**)

The alcohol **39** (476 g, 3.17 mol) was added to $SOCl_2$ (250 ml, 3.42 mol) at 30±2°C over 50 minutes. The mixture was stirred for 30 minutes and then distilled to give **40** (429.1 g, 80.3%): BP 104~105°C/7 mmHg; IR ($CHCl_3$) 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.97 (2H, t, J=7 Hz), 3.27 (2H, s), 3.67 (2H, t, J=7 Hz), 3.72 (3H, s).

Methyl Vinylthioacetate (**41**)

DBU (419 ml, 2.80 mol) was added to a solution of the chloride **45** (429.1 g, 2.55 mol) in benzene (820 ml) and the mixture was heated under reflux for 1.5 hours. After cooling, the reaction mixture was diluted with EtOAc, washed with dilute HCl and water. Distillation gave 247 g of **41** (73.4%): BP 59~65.5°C/4 mmHg; IR ($CHCl_3$) 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.45 (2H, s), 3.75 (3H, s), 5.17 (1H, d, J=17 Hz), 5.27 (1H, d, J=10 Hz), 6.40 (1H, dd, J=10 and 17 Hz).

Methyl (*cis*- and *trans*-Chlorovinylthio)acetate (**43**) *via* **42**

To a solution of **41** (11.65 g, 88.26 mmol) in CH_2Cl_2 (220 ml) was added a solution of chlorine (1.25 M Cl_2 - CCl_4, 1 ml, 1.25 mmol) at −20°C. After the disappearance of the yellowish color, the mixture was cooled to −60°C and another solution of chlorine (74 ml, 92.5 mmol) was slowly added. After being stirred for 15 minutes, the reaction mixture was washed with aqueous sodium sulfate solution and brine, and evaporated *in vacuo*, leaving an oily residue **42**, which was heated with dried lithium chloride (10 g, 236 mmol) in anhydrous DMF (50 ml) at 65~70°C for 30 minutes. After cooling to room temp, the reaction mixture was partitioned between EtOAc and water. The organic layer was washed twice with water, dried and distilled under reduced pressure to give **43** (11.8 g, 80.3%) as a mixture of *cis*- and *trans*-isomers in a ratio of 4 to 1: BP 78~85°C (2 mm); IR ($CDCl_3$) 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.38, 3.42 (2H, s), 3.75 (3H, s), 6.10, 6.19 (1H, d, J=13 and 7 Hz), 6.47, 6.48 (1H, d, J=13 and 7 Hz).

(*cis*-Chlorovinylthio)acetic Acid (**46**)

The ester **43** (6.7 g, 40.24 mmol) was hydrolyzed by the general procedure to afford carboxylic acid **44**, from which was obtained *cis*-isomer **46** (4.2 g, 68.4%) in pure state by crystallization from

benzene - hexane, 1 : 3; IR ($CHCl_3$) 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.48 (2H, s), 6.08 (1H, d, J=6.5 Hz), 6.40 (1H, d, J=6.5 Hz), 10.70 (1H, br s).

7α-Methoxy-7β-*cis*-chlorovinylthioacetamido-3-chloromethyl-1-oxacephem **49**

Phosphorus pentachloride (10.4 g, 49.94 mmol) was added to a mixture of **47** (13.4 g, 25.16 mmol) and pyridine (4 ml, 50 mmol) in anhydrous CH_2Cl_2 (130 ml) at 0°C and the mixture was stirred for 2 hours at the same temp. After cooling to −40°C, chilled (−40°C) methanol (140 ml) was added. The mixture was further stirred at 0°C for 2 hours and then diethylamine (21 ml) was slowly added at −20°C. After being gradually warmed to 0°C over 20 minutes, the reaction mixture was successively washed with H_2O (2 times), 1% HCl (2 times), H_2O, aq $NaHCO_3$ solution and brine, dried and condensed *in vacuo* to *ca.* 70 ml to give a solution of the methoxy-amine **48** in CH_2Cl_2. The solution was cooled at −30°C, and pyridine (3.56 ml), the carboxylic acid **46** (2.65 g, 17.4 mmol) in anhydrous CH_2Cl_2 (10 ml) and phosphorous oxychloride (1.62 ml, 17.38 mmol) were successively added. After 30 minutes at −20°C the reaction mixture was washed with dilute HCl and water and then evaporated to afford a solid residue which was crystallized from EtOAc to give **49** (4.60 g, 47% from **47**); IR ($CHCl_3$) cm^{-1} 3350, 1785, 1725, 1695; ^1H NMR ($CDCl_3$) δ 3.43 (3H, s), 3.53 (2H, s), 4.50 (4H, br s), 5.20 (1H, s), 6.30 (1H, d, J=6.5 Hz), 6.70 (1H, d, J=6.5 Hz), 6.87 (1H, s), 7.03~7.63 (11H, m),

Preparation of **50a~50m**

Compound **50a~50m** were prepared by method A or B. Method A: To a solution of **49** (1 mmol) in CH_2Cl_2 (10 ml) with a catalytic amount of tetrabutylammonium bromide was added a solution of sodium heterocyclylthiolate (1.2 mmol) in H_2O (3 ml) and the mixture was stirred at room temp for 0.5~2 hours (monitored by TLC). The organic layer was separated and evaporated to afford **50** in good yield, which, if necessary, was purified by chromatography on silica gel. Method B: Sodium heterocyclylthiolate (1.0~1.2 mmol) was added to a solution of **49** (1 mmol) in DMF (3 ml) under ice-cooling. After being stirred for 30 minutes at the same temp, the reaction mixture was partitioned between EtOAc and water, and the organic layer was washed twice with water and evaporated. The residue was chromatographed to afford **50** in a good to quantitative yield.

50a: IR ($CHCl_3$) cm^{-1} 3350, 1785, 1710, 1695; ^1H NMR ($CDCl_3$) δ 3.42 (3H, s), 3.50 (2H, s), 3.53 (3H, s), 3.90~4.27 (2H, m), 4.57 (2H, br s), 5.02 (1H, s), 6.07 (1H, d, J=6 Hz), 6.45 (1H, d, J=6 Hz), 6.77 (1H, s), 7.13~7.60 (10H, m), 7.88 (2H, br s).

50b: IR ($CHCl_3$) cm^{-1} 3350, 1785, 1720, 1695; ^1H NMR ($CDCl_3$) δ 3.42 (2H, s), 3.53 (3H, s), 4.20, 4.77 (2H, ABq, J=13 Hz), 4.58 (2H, br s), 5.03 (1H, s), 6.05 (1H, d, J=7 Hz), 6.42 (1H, d, J=7 Hz), 6.90 (1H, s), 7.08~7.60 (10H, m), 8.92 (1H, s).

50c: IR ($CHCl_3$) cm^{-1} 3375, 1790, 1720, 1695, 1650; this compound gave poor ^1H NMR spectra.

50d: IR (Nujol) cm^{-1} 3320, 3180, 1783, 1715, 1665, 1630; ^1H NMR (DMSO-d_6) δ 3.40 (3H, s), 3.48 (2H, s), 3.98, 4.35 (2H, ABq, J=14 Hz), 4.57 (2H, br s), 5.13 (1H, s), 6.20 (1H, s), 6.25 (1H, d, J=6 Hz), 6.68 (1H, d, J=6 Hz), 6.88 (1H, s), 7.05~8.0 (12H, m).

50e: IR ($CHCl_3$) cm^{-1} 3350, 1780, 1705; ^1H NMR ($CDCl_3$) δ 2.43~3.03 (1H, m), 3.45 (2H, br s), 3.55 (3H, s), 3.80~4.37 (6H, m), 4.58 (2H, br s), 5.03 (1H, s), 6.12 (1H, d, J=7 Hz), 6.38 (1H, d, J=7 Hz), 6.87 (1H, s), 7.10~7.63 (11H, m).

50f: IR ($CHCl_3$) cm^{-1} 3350, 1780, 1710, 1700; ^1H NMR ($CDCl_3$) δ 3.27 (3H, s), 3.47 (2H, br s), 3.55 (3H, s), 3.70 (2H, t, J=5 Hz), 4.23 (2H, br s), 4.32 (2H, t, J=5 Hz), 4.62 (2H, s), 5.05 (1H, s), 6.12 (1H, d, J=7 Hz), 6.37 (1H, d, J=7 Hz), 6.88 (1H, s), 7.10~7.67 (11H, m).

50g: IR (Nujol) cm^{-1} 3280, 3190, 1780, 1710, 1660; ^1H NMR (DMSO-d_6) δ 3.28 (3H, s), 3.43 (3H, s), 4.57 (2H, br s), 4.60 (2H, br s), 5.17 (1H, s), 6.33 (1H, d, J=7 Hz), 6.75 (1H, d, J=7 Hz), 6.90 (3H, br s), 7.17~7.73 (10H, m), 9.13 (1H, br s).

50h: IR ($CHCl_3$) cm^{-1} 3380, 3350, 1780, 1720, 1690; this compound gave poor ^1H NMR spectra.

50i: IR ($CHCl_3$) cm^{-1} 3340, 1780, 1700; ^1H NMR ($CDCl_3$ - CD_3OD) δ 3.43 (2H, s), 3.53 (3H, s), 4.18 (2H, s), 4.54 (2H, s), 4.92 (2H, s), 5.04 (1H, s), 6.12 (1H, d, J=6.5 Hz), 6.49 (1H, d, J=6.5 Hz), 6.87 (1H, s), 7.3~7.6 (10H, m).

50j: IR ($CHCl_3$) cm^{-1} 3340, 1780, 1700; ^1H NMR ($CDCl_3$ - CD_3OD) δ 3.43 (2H, s), 3.53 (3H, s),

4.18 (2H, s), 4.54 (2H, s), 4.92 (2H, s), 5.04 (1H, s), 6.12 (1H, d, J=6.5 Hz), 6.49 (1H, d, J=6.5 Hz), 6.87 (1H, s), 7.3~7.6 (10H, m).

50k: IR ($CHCl_3$) cm^{-1} 3350, 3200, 1785, 1700; ^1H NMR ($CDCl_3$ - CD_3OD) δ 3.58 (3H, s), 3.72 (3H, s), 4.22 (2H, s), 4.58 (2H, s), 4.87 (2H, s), 5.11 (2H, s), 5.33 (1H, s), 6.19 (1H, d, J=6.5 Hz), 6.53 (1H, d, J=6.5 Hz), 6.92 (1H, s), 7.2~7.7 (12H, m).

50l: IR ($CHCl_3$) cm^{-1} 3350, 3200, 1785, 1700; ^1H NMR ($CDCl_3$) δ 3.40 (2H, s), 3.52 (3H, s), 3.70 (3H, s), 4.16 (2H, s), 4.53 (2H, s), 4.77 (4H, s), 5.96 (1H, s), 6.11 (1H, d, J=6.5 Hz), 6.41 (1H, d, J=6.5 Hz), 6.90 (1H, s), 7.2~7.8 (16H, m).

50m: IR ($CHCl_3$) cm^{-1} 3350, 3200, 1785, 1700; ^1H NMR ($CDCl_3$) δ 3.40 (2H, s), 3.52 (3H, s), 3.70 (3H, s), 4.16 (2H, s), 4.53 (2H, s), 4.77 (4H, s), 5.96 (1H, s), 6.11 (1H, d, J=6.5 Hz), 6.41 (1H, d, J=6.5 Hz), 6.90 (1H, s), 7.2~7.8 (16H, m).

General Procedures for Removal of the Protecting Group of **15** and **50**

Deprotection of BH-ester was carried out using one of the following procedures. Method A: A solution of ester (1 mmol) in anhydrous CH_2Cl_2 (10 ml) with anisole (1 ml) and TFA (1 ml) was stirred at ice-cooling temperature for 30~120 minutes. The reaction was monitored by TLC. The reaction mixture was concd *in vacuo* to dryness and the residue was purified by: (1) Trituration with ether or (2) partition between aqueous $NaHCO_3$ solution and EtOAc followed by extraction of the acidified aqueous layer with EtOAc and subsequent evaporation of the extract *in vacuo*. Method B: The ester (1 mmol) in anhydrous CH_2Cl_2 (5~10 ml) was added to a mixture of $AlCl_3$ (5~10 ml) and anisole (5~10 ml) in nitromethane (5~10 ml) at −10°C. After 30 minutes at the same temp, the reaction mixture was partitioned between water and EtOAc. The organic layer was extracted twice with aq $NaHCO_3$ solution. The extracts were combined, acidified (pH 2) with dilute HCl and re-extracted with EtOAc. The extract was washed with brine, dried and evaporated *in vacuo* to give a residue in a good yield, which was triturated with ether. Some of the free acids obtained were neutralized with sodium bicarbonate and further purified by chromatography on Diaion HP-20 followed by freeze-drying to give the corresponding sodium salts. These acids (or sodium salt) were characterized by IR and NMR spectra or by transformation into the corresponding pivaloyloxymethyl ester with pivaloyloxymethyl iodide and K_2CO_3 in DMF.

16a: IR (Nujol) cm^{-1} 3200, 1770, 1710, 1665, 1625; ^1H NMR (Me_2CO-d_6) δ 3.50 (3H, s), 3.65 (2H, s), 4.00 (3H, s), 4.35 (2H, s), 4.68 (2H, s), 5.12 (1H, s), 6.85 (1H, s), 6.58~7.08 (1H, m).

16b: IR (Nujol) cm^{-1} 1765, 1705, 1670, 1625; ^1H NMR (Me_2CO-d_6) δ 3.48 (3H, s), 3.85 (2H, s), 3.98 (3H, s), 4.33 (2H, s), 4.50 (2H, s), 5.08 (1H, s), 6.73 (1H, s), 7.78~8.33 (2H, m).

16c: IR (Nujol) cm^{-1} 3200, 1770, 1710, 1680, 1625; ^1H NMR (Me_2CO-d_6) δ 3.50 (3H, s), 3.58 (2H, s), 4.00 (3H, s), 4.35 (2H, s), 4.68 (2H, s), 5.12 (1H, s), 6.48 (1H, d, J=14 Hz), 6.68 (1H, d, J=14 Hz), 7.13~7.70 (1H, m).

Sodium salt of **16d**: IR (Nujol) cm^{-1} 3250, 1675, 1670, 1630, 1600; ^1H NMR (D_2O) δ 4.00 (3H, s), 4.07 (2H, s), 4.50 (3H, s), 4.62 (2H, br s), 5.02 (2H, br s), 5.65 (1H, s), 6.75 (1H, d, J=6.5 Hz), 7.07 (1H, d, J=6.5 Hz).

16f: IR (Nujol) cm^{-1} 1780, 1710, 1680; ^1H NMR (Me_2CO-d_6) δ 2.30 (3H, s), 3.48 (5H, s), 3.98 (3H, s), 4.32 (2H, s), 4.65 (2H, s), 5.08 (1H, s), 5.73~6.33 (2H, m), 6.20 (2H, s).

16g: IR (Nujol) cm^{-1} 1760, 1700, 1630, 1610; ^1H NMR (Me_2CO-d_6) δ 3.47 (5H, s), 4.00 (3H, s), 4.17 (2H, dd, J=1.0 and 6.0 Hz), 4.33 (2H, s), 4.67 (2H, s), 5.10 (1H, s), 5.50~6.03 (1H, m) 6.20 (2H, dd, J=1.0 and 9.0 Hz), 6.07~6.70 (2H, m).

16h: IR (Nujol) cm^{-1} 3250, 1775, 1710, 1680, 1625; ^1H NMR (Me_2CO-d_6) δ 1.60~1.83 (3H, m), 3.47 (5H, s), 3.97 (3H, s), 4.33 (2H, s), 4.67 (2H, s), 5.08 (1H, s), 5.28~6.35 (2H, m), 6.95~7.63 (2H, m).

16i: IR (Nujol) cm^{-1} 3200, 1775, 1700, 1670, 1610; ^1H NMR (as Na salt, D_2O) δ 3.93 (3H, s), 4.05 (2H, s), 4.43 (3H, s), 4.57 (2H, s), 4.95 (2H, br s), 5.58 (1H, s), 5.77~6.60 (1H, m), 7.25~7.60 (1H, m).

16j: IR (Nujol) cm^{-1} 3200, 1775, 1710, 1680, 1615; ^1H NMR (Me_2CO-d_6) δ 3.48 (3H, s), 3.77 (2H, s), 3.98 (3H, s), 4.33 (2H, s), 4.63 (2H, s), 5.10 (1H, s), 5.53~6.48 (3H, m), 7.12~7.52 (1H, m).

16k: IR (KBr) cm^{-1} 3420, 1780, 1705 (br); ^1H NMR (Me_2CO-d_6) δ 3.50 (3H, s), 3.80 (2H, s),

4.02 (3H, s), 4.35 (2H, s), 4.68 (2H, s), 5.13 (1H, s), 8.15 (1H, s).

16l: IR (Nujol) cm^{-1} 3150, 1770, 1655; ^1H NMR (Me_2CO-d_6) δ 3.50 (3H, s), 3.83 (2H, s), 4.00 (3H, s), 4.36 (2H, s), 4.67 (2H, s), 5.10 (1H, s), 6.97 (2H, br s), 7.98 (1H, s), 8.37 (1H, br s).

16m: IR (Nujol) cm^{-1} 3250, 1770, 1670, 1620; ^1H NMR (as Na-salt, D_2O) δ 3.97 (2H, s), 4.07 (2H, s), 4.50 (3H, s), 4.63 (5H, br s), 5.00 (2H, s), 5.62 (1H, s), 7.05 (1H, s).

51a: ^1H NMR (Me_2CO-d_6) δ 3.48 (3H, s), 3.58 (2H, s), 3.78 (2H, s), 4.10 4.35 (2H, ABq, J=13 Hz), 4.63 (2H, s), 5.07 (1H, s), 6.23 (1H, d, J=6.5 Hz), 6.73 (1H, d, J=6.5 Hz), 6.92 (2H, br s), 8.68 (1H, s).

51b: This compound gave poor ^1H NMR spectra and was characterized by transformation into the starting BH-ester with diphenyldiazomethane.

51c: ^1H NMR (Me_2CO-d_6) δ 3.48 (3H, s), 3.56 (2H, s), 3.70 (3H, s), 4.18, 4.45 (2H, ABq, J= 13 Hz), 4.63 (2H, s), 5.10 (1H, s), 4.93~5.67 (2H, m), 6.23 (1H, d, J=7 Hz), 6.73 (1H, d, J=7 Hz), 7.93~8.33 (1H, m).

51d: IR (Nujol) cm^{-1} 3300, 1770, 1680, 1630; ^1H NMR (Me_2CO-d_6) δ 3.47 (3H, s), 3.57 (2H, s), 4.15, 4.52 (2H, ABq, J=14 Hz), 4.67 (2H, s), 5.10 (1H, s), 4.83~5.63 (2H, m), 6.18 (1H, d, J=7 Hz), 6.72 (1H, d, J=7 Hz), 7.03~7.43 (1H, m).

51e: IR (Nujol) cm^{-1} 3380, 3250, 1770, 1700, 1650, 1630 (sh); ^1H NMR (DMSO-d_6) δ 3.40 (3H, s), 3.53 (2H, s), 4.43 (2H, t, J=5 Hz), 4.03~4.93 (8H, m), 5.08 (1H, s), 6.35 (1H, d, J=6 Hz), 6.77 (1H, d, J=6 Hz), 9.13 (1H, m).

POM ester of **51f**: IR ($CHCl_3$) cm^{-1} 3360, 1790, 1750, 1700; ^1H NMR ($CDCl_3$) δ 1.22 (9H, s), 3.30 (3H, s), 3.48 (2H, br s), 3.52 (3H, s), 3.77 (2H, t, J=5 Hz), 7.60 (2H, br s), 4.43 (2H, t, J=5 Hz), 4.63 (2H, br s), 5.07 (1H, s), 5.92, 6.03 (2H, ABq, J=6 Hz), 6.15 (1H, d, J=6 Hz), 6.50 (1H, d, J=6 Hz), 7.40~7.63 (1H, m).

51g: IR (Nujol) cm^{-1} 3270, 1775, 1675, 1630; ^1H NMR (as Na-salt, D_2O) δ 3.97 (3H, s), 4.03 (2H, s), 4.63 (2H, br s), 4.97 (2H, br s), 5.58 (1H, s), 6.68 (1H, d, J=6 Hz), 6.97 (1H, d, J=6 Hz).

51h: IR (Nujol) cm^{-1} 3250, 1775, 1665; ^1H NMR (DMSO-d_6) δ 3.37 (3H, s), 3.53 (2H, s), 3.67~ 4.60 (8H, m), 5.07 (1H, s), 6.32 (1H, d, J=7 Hz), 6.75 (1H, d, J=7 Hz).

51i: IR (Nujol) cm^{-1} 3250, 1775, 1665; ^1H NMR (DMSO-d_6) δ 3.37 (3H, s), 3.53 (2H, s), 3.67~ 4.60 (8H, m), 5.07 (1H, s), 6.32 (1H, d, J=7 Hz), 6.75 (1H, d, J=7 Hz).

51j: IR (KBr) cm^{-1} 3350, 1760, 1675, 1600; ^1H NMR (Me_2CO-d_6) δ 3.49 (3H, s), 3.60 (2H, s), 4.27, 4.36 (2H, ABq, J=16 Hz), 4.62 (2H, s), 5.11 (1H, s), 5.20 (2H, s), 6.23 (1H, d, J=6.5 Hz), 6.76 (1H, d, J=6.5 Hz).

51k: IR (KBr) cm^{-1} 3250, 2150, 1770, 1670; ^1H NMR (Me_2CO-d_6) δ 3.50 (3H, s), 3.58 (2H, s), 4.36 (2H, s), 4.67 (2H, s), 5.08 (1H, s), 5.70 (2H, s), 6.21 (1H, d, J=6.9 Hz), 6.74 (1H, d, J=6.9 Hz).

51l: IR (as Na-salt, KBr) cm^{-1} 3360 1760, 1670, 1600; ^1H NMR (Me_2CO-d_6) δ 3.50 (3H, s), 3.62 (2H, s), 3.78 (3H, s), 4.33 (2H, s), 4.63 (2H, s), 5.13 (3H, s), 6.26 (1H, d, J=7.5 Hz), 6.75 (1H, d, J=7.5 Hz).

51n: IR (as Na-salt, KBr) cm^{-1} 3350, 1760, 1660, 1600; ^1H NMR (DMSO-d_6) δ 3.48 (3H, s), 3.61 (2H, s), 4.32 (2H, s), 4.63 (2H, s), 5.11 (3H, s), 6.22 (1H, d, J=6 Hz), 6.75 (1H, d, J=6 Hz).

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