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NEW ROUTE TO 3-(SUBSTITUTED) METHYL 1-OXA- AND (1-THIA)CEPHEMS FROM 3-EXOMETHYLENE INTERMEDIATES VIA SULFENYL CHLORIDE ADDUCTS

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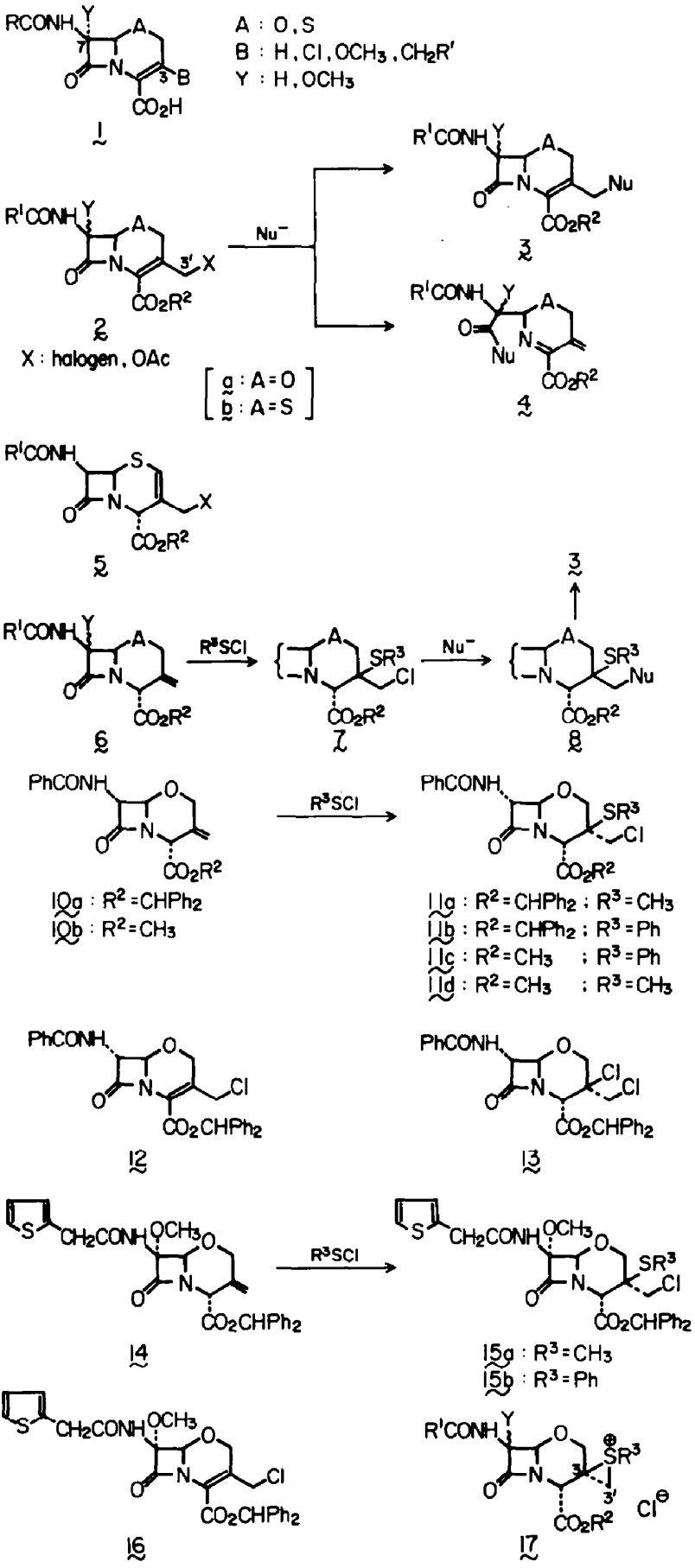
Abstract—Addition of methane- and benzenesulfenyl chlorides to 3-exomethylene-1-oxacephams **10** and **14** gave 3β-sulfenyl-3α-chloromethyl adducts **11** and **15**. Nucleophilic substitution of the adducts proceeded facilely to afford compounds **18–23**, which were converted into Δ^3-derivatives **26** and **27** by oxidative elimination. This new route, as illustrated by the sequence **6**→**7**→**8**→**3**, has an essential advantage in using the saturated intermediates **7** and **8** with a stabler β-lactam ring which is compatible in nucleophilic substitution, alkaline ester hydrolysis and further manipulations. These synthetic features are well demonstrated by successful synthesis of 1-oxacefamandol **35** and 7β-(2-thienylacetylamino)-3-(1-methyl-1*H*-tetrazol-5-yl)thiomethyl-3-cephem-4-carboxylic acid (**45**).

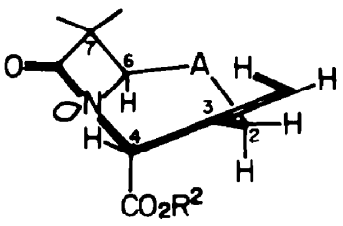
To date a number of semisynthetic cephem and 1-oxacephem antibiotics **1** have been prepared for clinical evaluation. Modifications at C-3′, like those at C-7, are critical in discovering β-lactam derivatives with good antibacterial and pharmacological properties. These chemical modifications are hindered often by the presence of the 3(4)-double bond attached to the β-lactam N (an enamide system). Being essential for furnishing the β-lactam ring with an elevated reactivity to acylate the bacterial transpeptidase,[1] this double bond, in turn, is responsible for the facile cleavage of the ring to make chemical manipulation of both cephem derivatives extremely difficult in many cases. This difficulty is much serious in the reaction of 1-oxacephems with the more reactive β-lactam ring than that of cephalosporins.[2] For example, nucleophilic substitution of 3-halomethyl-1-oxacephems **2a** giving **3a** is successful only with limited soft nucleophiles such as tetrazolylthiols.[3] With hard oxy nucleophiles such as acetoxy and methoxy anions, the replacement does not proceed smoothly, only to be dominated by the ring cleavage giving **4a** or their further decomposition products. An indirect route using Δ^2-isomers **5** involving Δ^3-reconversion via 1-sulfoxides has been applied to the cephalosporin modifications.[4] This Δ^2-route is not applicable to 1-oxacephem derivatives, because no practical reconversion to Δ^3-isomers has been known in the 1-oxacephem system. Thus, we have searched for 1-oxa and (1-thia) cepham substrates which can be modified at C-3′ and be derived to Δ^3-compounds after completion of necessary chemical manipulation. Hitherto unknown 3′-chloro-3-sulfenyl compounds **7** were selected as the most promising candidate from the following considerations: (1) the 3′-Cl atom would be activated by the neighboring S participation[5] to facilitate the nucleophilic substitution to **8**; (2) the sulfenyl group in **8** can be eliminated[6] to generate the Δ^3-bond; (3) compounds **7** might be prepared by the addition of sulfenyl chlorides[7] to exomethylene derivatives **6** which are easily available, especially in the 1-oxacepham system.[3] We report here successful preparation of 3-(substituted)methyl 1-oxa- and (1-thiacephems by the sulfenyl chloride route. The investigation on this route was pursued intensively in the 1-oxacepham system because of a practical importance and easy availability of the 3-exomethylene substrate in our laboratory.

Addition of sulfenyl chlorides to 3-exomethylene-1-oxacephams

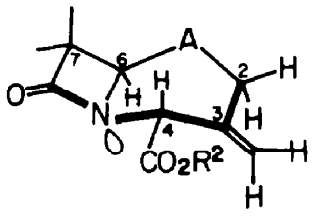
Methanesulfenyl chloride smoothly reacted at room temperature with diphenylmethyl 7α-benzoylamino-3-methylene-1-oxacepham-4α-carboxylate (**10a**), a key intermediate in our industrial synthesis of 1-oxacephem antibiotics,[3] giving a single adduct **11a** as good crystals in nearly quantitative yield. The 3α-chloromethyl-3β-methylthio structure was assigned to the adduct on the basis of the following NMR evidence supported by oxidative elimination (see a later section) to the known 3-chloro-1-oxacephem **12**.[3] In the ^{13}C-NMR spectrum[8] of the adduct **11a**, the C-3 and C-3′ carbon signals appeared at 49.8 and 45.3 ppm, respectively. The corresponding signals at 67.9 and 47.3 ppm for the known 3β-chloro-3α-chloromethyl-1-oxacepham derivative **13**[9] indicate that the C-3 substituent is not Cl and thus should be methylthio. The α-configuration of the 3-chloromethyl group and hence the 3β-methylthio configuration were determined from the anisotropic effect of the diphenylmethyl group in the ^{1}H-NMR spectrum.[8]

Addition of benzenesulfenyl chloride to **10a** also proceeded smoothly to give a single adduct **11b** in 88% yield. A 7β-acylamino substrate **14** and a less bulky ester **10b** underwent the sulfenyl chloride addition to afford adducts **15a, 15b, 11c** and **11d** in 83, 88, 45 and 85% yields, respectively. The structures of the adducts **11b, 15a** and **15b** were confirmed by the ^{1}H-NMR spectroscopic[8] and chemical (conversion into **12** and **16**) evidence as mentioned above, and the


A : O, S
B : H, Cl, OCH3, CH2R'
Y : H, OCH3
X : halogen, OAc
a : A=O
b : A=S
Nu⁻
R³SCl



(A)



(B)

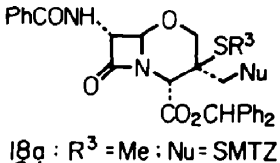
methyl ester **11c** was proved identical with an authentic sample prepared by deprotection of diphenylmethyl ester **11b** with trifluoroacetic acid and anisole followed by esterification with diazomethane.

The seemingly unusual β-side attack of sulfenyl chlorides could be predicted from the known β-side attack of molecular chlorine to the exomethylene substrate **10a** giving the 3β-chloro-3α-chloromethyl adduct **13**.[8] In supporting this prediction, examination of Dreiding models indicates that the tetrahydrooxazine ring in the exomethylene compounds **6** can take either a half chair-like conformation **A**, in which 2α-H and most importantly 4α-CO_2R^2 block the α-face of the double bond, or a less favorable boat-like conformation **B** in which this α-face is sterically hindered by 2α-H, 6α-H and the nitrogen lone pair. The preferred β-side attack is not affected by the α- or β-configuration of the 7-amide group oriented too far or by the size of R^2 (see the addition to **14** and **10b**). The regioselective, anti-Markownikoff addition to give 3′-chloro-3β-sulfenyl adducts can be rationalized by intermediacy of an episulfonium ion **17**, to which the chloride anion attacks at the less-hindered C-3′.

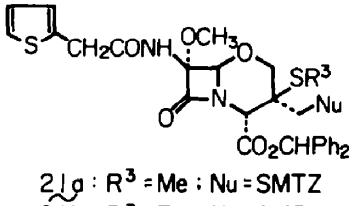
Nucleophilic substitution of 3α-chloromethyl-3β-sulfenyl-1-oxacephams

The reactivity of the C-3′ Cl atom in the methanesulfenyl chloride adducts turned out to be very high as expected from the neighboring sulfur participation. Thus, methylthio adducts **11a**, **11d** and **15a** reacted with sodium 1-methyl-1*H*-tetrazole-5-thiolate (Na-SMTZ) in acetone-methanol under gentle reflux for 1–2 hr to give crystalline 3-(tetrazolylthio)methyl derivatives **18a**, **18c** and **21a** in 98, 83, and 98% yields, respectively. The adducts **11a** and **15a** underwent also substitution with less nucleophilic methanol or dimethylacetamide at room temperature for 1–4 hr in the presence of silver tetrafluoroborate or perchlorate and calcium carbonate, giving 3-methoxymethyl derivatives **19a** (75%) and **22a** (96%) or 3-acetoxymethyl compounds **20a** (76%) and **23a** (71%). Apparently, intermediates for the 3-acetoxymethyl products **20** and **23** are iminium ions **24** formed by the chlorine substitution of **11** and **15** with dimethylacetamide. Alternatively, the 3-acetoxymethyl product **20a** was obtained in 86% yield on treatment of **11a** with sodium acetate and acetic acid in dimethylformamide at 65° for 4 hr.

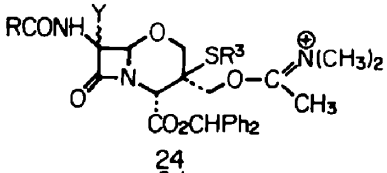
The benzenesulfenyl chloride adducts **11b** and **15b** were found less reactive than the methylthio analogs but still vulnerable to the substitution with sulfur and oxygen nucleophiles: 3-(tetrazolylthio)methyl derivatives **18b** (70%) and **21b** (59%) as well as 3-acetoxymethyl compounds **23b** (67%) were obtained under similar substitution conditions to those



18a : R^3 = Me ; Nu = SMTZ
18b : R^3 = Ph ; Nu = SMTZ
19a : R^3 = Me ; Nu = OCH_3
20a : R^3 = Me ; Nu = OAc



21a : R^3 = Me ; Nu = SMTZ
21b : R^3 = Ph ; Nu = SMTZ
22a : R^3 = Me ; Nu = OCH_3
23a : R^3 = Me ; Nu = OAc
23b : R^3 = Ph ; Nu = OAc



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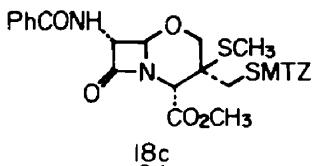


18c

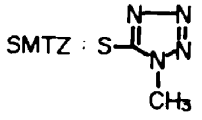


Table 1. Oxidative elimination of 3β-methylthio and phenylthio 1-oxacepham derivatives to 1-oxa-Δ³-cephems

Sulfide	Oxidizing agent	Δ³-Product	Yield (%)
18a	*m*-CPBA	**26a**	90
20a	*m*-CPBA	**26b**	80
21a	*m*-CPBA	**27a**	90
23a	*m*-CPBA	**27b**	82
21b	*m*-CPBA	**27a**	79
11a	*m*-CPBA	**12**	68
11b	*m*-CPBA	**12**	89
15a	*m*-CPBA	**16**	81
15b	*m*-CPBA	**16**	79
18a	CH_3CO_3H	**26a**	79

used for the methylthio analogs except for longer reaction times (15–24 hr). The observed lower reactivity of the phenylthio adducts can be accounted for by lesser participation of the sulfur bonded to the electron-withdrawing phenyl in a reactive intermediate similar to the episulfonium ion **17**.

The above successful substitution of the sulfenyl chloride adducts with the oxygen nucleophiles is especially significant as compared with the failure of the 3′-chloromethyl-Δ³ analog **12** in the reaction under similar conditions which gave only non-β-lactam products.[10]

Oxidative elimination of the 3β-methyl- or phenylthio group to generate the 1-oxa-3-cephem skeleton

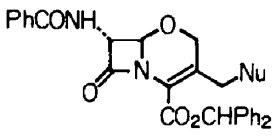
With 3β-configuration of the 3-methyl- or phenylthio group *cis* to the 4β-H, more acidic than 2β-H, in the substitution products, their sulfoxides **25** were expected to undergo thermal *cis*-2,3-sigmatropic elimination to generate the Δ³-bond. In an attempt to prepare the sulfoxide, the 3β-methylthio compound **18a** was treated with *m*-chloroperbenzoic acid (*m*-CPBA) at 0°. The TLC monitoring showed that the oxidation was complete in 30 min to give a polar compound, most likely the sulfoxide of **18a**. The product obtained by usual workup, however, was found to be a mixture of this polar compound and the expected elimination compound **26a**. This result indicating a facile sulfoxide elimination led to a general procedure for oxidative elimination which consists of treating the sulfide with *m*-CPBA or peracetic acid followed by heating a product solution in ethyl acetate or acetone at gentle reflux for 10–30 min to complete the elimination. Table 1 summarizes the results on the oxidative elimination of the substitution products **18**, **20**, **21** and **23** as well as the initial sulfenyl chloride adducts **11** and **15**. Significantly, no other double-bond isomers were isolated in this reaction.

From an unknown reason, oxidation of 3α-methoxymethyl-3β-methylthio derivatives **19a** and **22a** with *m*-CPBA (1.2 molar equiv) gave sulfones **28** and **29** accompanied with the starting materials. Therefore, the Δ³-compounds **26c** and **27c** were derived in 81 and 53% overall yields by oxidation of **19a** and **22a** with 2 molar equivalents of *m*-CPBA followed by elimination with 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) at a low temperature (−30°).

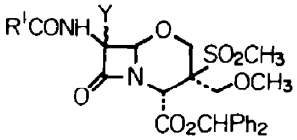
Compatibility of 3α-(substituted)methyl-3β-methylthio-1-oxacepham derivatives in further chemical manipulation

With the absence of the enamide structure, the 3α-(substituted)methyl-3β-methylthio-1-oxacepham system **8** is expected to be well compatible in further manipulations such as deacylation, new acylation, α to β epimerization etc at the C-7 side chain and deprotection of the C-4 ester by acid solvolysis or even by alkaline hydrolysis. This compatibility was tested by synthesis of 1-oxacefamandol and alkaline hydrolysis of the C-4 esters followed by oxidative elimination of the 3-methylthio group.

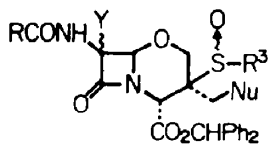
Synthesis of 1-oxacefamandol. The side-chain cleavage of 7α-benzolylamino-3β-methylthio-3α-(tetrazolylthio)methyl-1-oxacepham **18a** by the conventional PCl_5 method gave 7α-amine **30** in 92% yield, which was converted into 7β-amine **32** in 50% yield by our four-step procedure[11] consisting of stereospecific hydride-reduction of dichlorovinyl imine **31**. The amine **32** was acylated with D-4-phenyl-2,5-dioxo-1,3-dioxolane in a usual manner to give 7β-(D-mandelylamino)-1-oxacepham **33** in 88% yield. Oxidative elimination of **33** as described in the preceding section smoothly proceeded to give 1-oxacefamandol ester **34** in 82% yield. This ester was



26a : Nu = SMTZ
26b : Nu = OAc
26c : Nu = OCH_3



28 : R^1 = Ph ; Y = β-H
29 : R^1 =  ; Y = α-OCH_3



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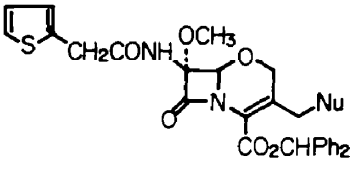
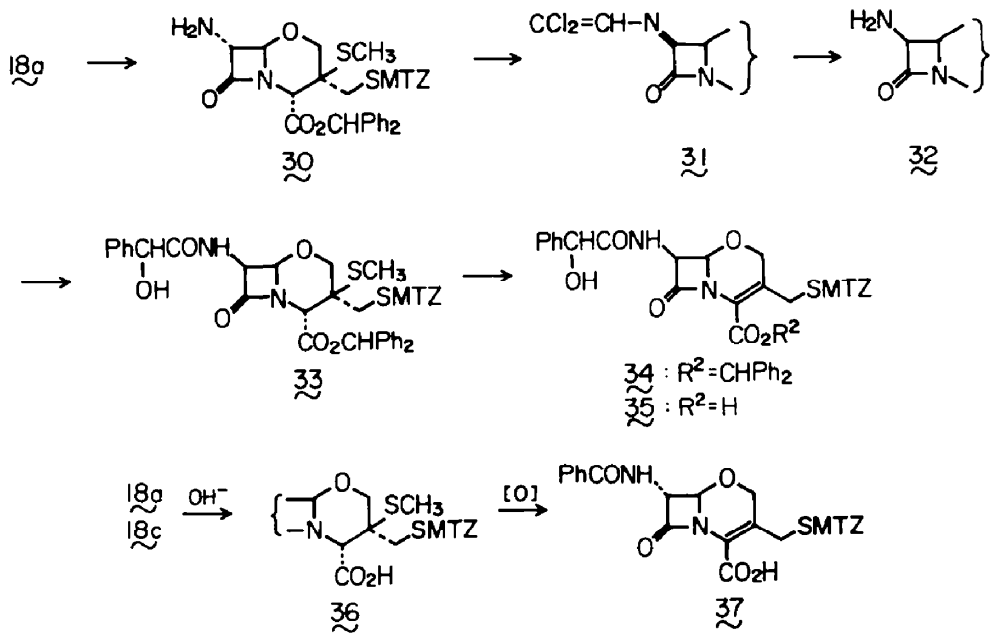


27a : Nu = SMTZ
27b : Nu = OAc
27c : Nu = OCH_3



deprotected with trifluoroacetic acid and anisole to 1-oxacefamandol **35** which was identical with an authentic sample of the antibiotic.[12]

Alkaline hydrolysis of 3β-methylthio-3α-(tetrazolylthio)methyl-1-oxacepham-4α-carboxylic acid esters followed by oxidative elimination. Esters **18a** and **18c** underwent smooth hydrolysis on treatment with an equimolar amount of 0.1 N NaOH in aqueous acetone at −5 to −10° for 0.5–1 hr to give acid **36** in 91 and 88% yields, respectively. Oxidative elimination of this acid **36** with peracetic acid or 30% hydrogen peroxide catalyzed by sodium tungstate proceeded as facilely as its esters, giving 3-(tetrazolylthio)methyl-1-oxa-3-cephem-4-carboxylic acid **37** in 81% yield. This facile sulfoxide elimination of acid **36** is significant and crucial in providing a route to Δ^3-acids in the final step after completing necessary chemical manipulation.

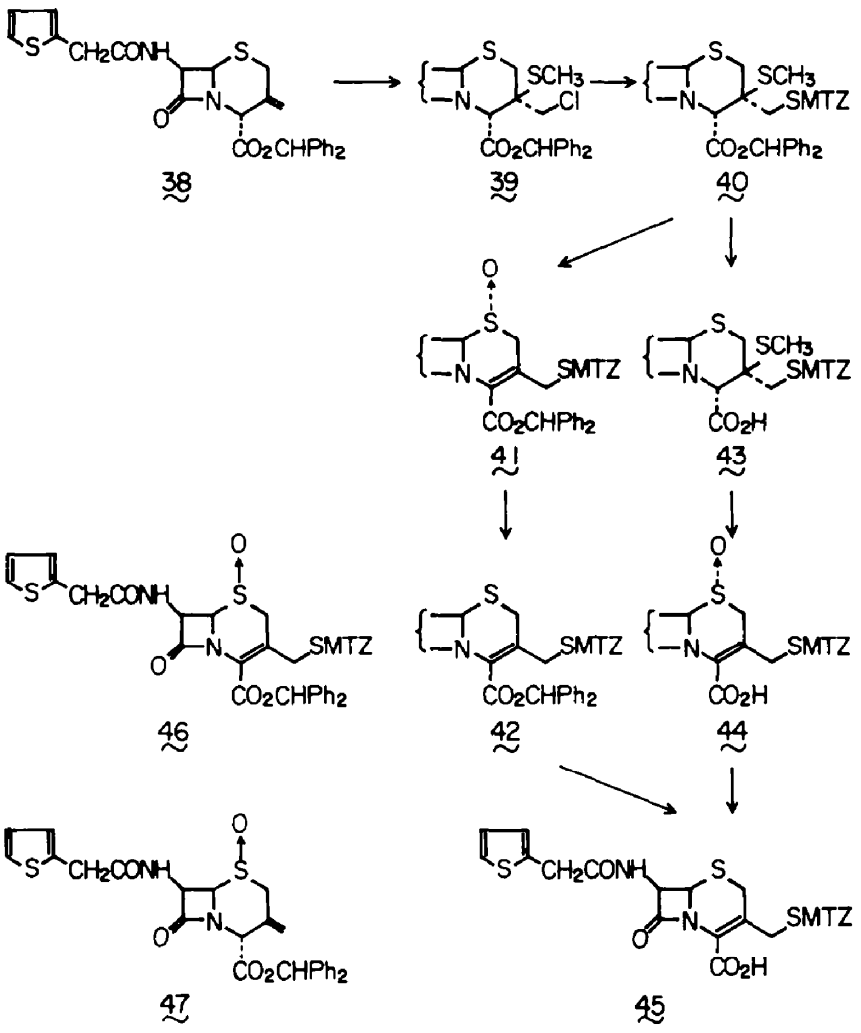
Application of the sulfenyl chloride route in the cephalosporin series

In contrast to the reported formation of the 3′-phenylthio-3-chloro adduct **9** from the corresponding 3-exomethylene derivative,[7] methanesulfenyl chloride added at 0° to 3-exomethylenecepham **38** in a stereo- and regioselective manner, as in the 1-oxacepham series, to give 3α-chloromethyl-3β-methylthio adduct **39**. Substitution of this adduct with Na-SMTZ also proceeded smoothly under similar conditions to those used for 1-oxacephams, affording 3α-(tetrazolylthio)methylcepham **40** in 82% overall yield from **38**. The 3β-methylthio configuration of **40** and consequently of the adduct **39** was established from NMR analysis and conversion into the following 3-(tetrazolylthio)methyl-3-cephem derivatives. With the presence of the incompatible S atom at position 1, oxidative elimination of the 3β-methylthiocepham **40** with *m*-CPBA gave crystalline 3-cephem α-sulfoxide **41** in 70% yield. This was reduced with stannous chloride and acetyl chloride to 3-cephem ester **42** (97%), which was identified with an authentic sample prepared by acylation of diphenylmethyl 7β-amino-3-(tetrazolylthio)methyl-3-cephem-4-carboxylate with 2-thiopheneacetyl chloride. The α-sulfoxide structure in the elimination product **41** was deduced from nonidentity with β-sulfoxide **46** prepared by *m*-CPBA oxidation of **42**. Alternatively, the 3β-methylthiocepham ester **40** was deprotected with trifluoroacetic acid and anisole or with aqueous alkali to acid **43**, which underwent oxidative elimination with peracetic acid to give the 3-cephem-carboxylic acid α-sulfoxide **44** in 78% overall yield. Esterification of **44** gave **41** in supporting the α-sulfoxide structure. Both ester **42** and acid **44** are convertible to 7β-(2-thienylacetylamino)-3-(1-methyl-1*H*-tetrazol-5-yl)thiomethyl-3-cephem-4-carboxylic acid (**45**) by the known deprotection or reduction process, respectively.

Exomethylenecepham sulfoxide **47** seemed an attractive substrate in this sulfenyl chloride route because of easy availability from inexpensive penicillin by the Lilly process[13] coupled with the inevitable formation of sulfoxide **41** or **44** in the oxidative elimination. However, the sulfoxide **47** turned out to be reluctant to the addition of methanesulfenyl chloride, most likely owing to steric hindrance of the S→O bond: the substrate was recovered unchanged on treatment with an excess of the reagent at 0° for 2 hr and the addition of boron trifluoride or perchloric acid or irradiation with a tungsten lamp was not effective, only to yield unidentified decomposition products.

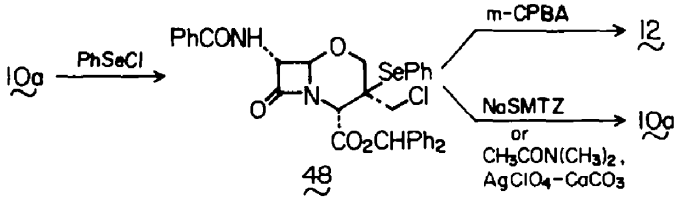
Use of phenylselenenyl chloride in place of sulfenyl chlorides

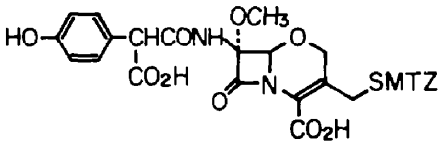
Like sulfenyl chlorides, phenylselenenyl chloride added to 3-exomethylene-1-oxacephem **10a** at room



temperature in 1.5 hr to give a crystalline adduct **48** in 87% yield. As expected from the reported better leaving ability,[14] the phenylseleno group underwent a more facile oxidative elimination: 3-chloromethyl-Δ^3-1-oxacephem **12** was obtained in 60% yield on treatment with *m*-CPBA at 0° for 10 min followed by usual workup. In contrast to this advantage, nucleophilic substitution of the adduct **48** with NaSMTZ or dimethylacetamide in the presence of silver perchlorate and calcium carbonate was unsuccessful, affording the starting 3-exomethylene material **10a** in 75–80% yields. Thus, the selenenyl chloride adducts are not usable for synthesis of 3-(substituted)methyl 1-oxacephem derivatives.

In conclusion, the sulfenyl chloride route as illustrated in the sequence **6**→**7**→**8**→**3** will be very useful





Latamoxef (6059-S, Moxalactam)

for synthesizing 3-(substituted)methyl 1-oxa- and (1-thia)cephem antibiotics from 3-exomethylene intermediates. It is especially suitable to the C-3′ modification in the 1-oxacephem series because of easy availability of the 3-exomethylene intermediates coupled with simple oxidative elimination to Δ^3-derivatives. The route has a vital advantage in that the saturated derivatives **8** can undergo a variety of otherwise destructive chemical manipulations including alkaline ester-hydrolysis and thus the biologically active but chemically susceptible Δ^3-4-carboxylic acid form can be constructed in the final elimination step.

This sulfenyl chloride route has been successfully applied to an efficient, practical synthesis of latamoxef (6059-S, moxalactam) which will be published elsewhere.

EXPERIMENTAL

M.ps were determined on a YANAGIMOTO m.ps apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian T-60A spectrometer with TMS as an internal standard. Optical rotations were measured on a Perkin–Elmer 141 polarimeter at ambient temperature. IR spectra were recorded on a HITACHI 260-10 spectrophotometer. Elemental analysis values obtained were within 0.3% of those calculated for the formula given.

Reagents and solvents were of reagent grade and anhyd solvents were prepared by drying with molecular sieves. All reactions were conducted under N_2.

General procedure for preparation of 3β-methylthio- or 3β-phenylthio-3α-chloromethyl-1-oxacephams

To a stirred soln of dimethyl- or diphenyl disulfide (0.6–1 mmol) in CCl_4 (1–3 ml) was added 1 M soln of Cl_2 in CCl_4 (0.6–1 mmol) at 0° and the mixture was stirred for 20 min at 0°. A soln of a 3-methylene substrate (1 mmol) in CH_2Cl_2–EtOAc (1:2–1:3) (5–7.5 ml) was added to this sulfenyl chloride soln. After being stirred for 1–2 hr at room temp or at 0°, the mixture was poured into a cold $Na_2S_2O_3$ aq and extracted with EtOAc. The organic layer was washed with water, dried with Na_2SO_4 and evaporated to give a crude product, which was crystallized or chromatographed on silica gel giving a pure adduct.

Diphenylmethyl 7α-benzoylamino-3β-methylthio-3α-chloromethyl-1-oxacepham-4α-carboxylate (**11a**). Compound **10a** gave **11a** in nearly quantitative yield as white crystals, m.p. 155–156° (ether). IR ($CHCl_3$): 3400, 1785, 1745, 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$): 2.12 (s, 3H, SCH_3), 3.21, 3.52 (ABq, 2H, J = 13 Hz, H-3′), 3.89, 4.14 (ABq, 2H, J = 13 Hz, H-2), 4.28 (s, 1H, H-4), 5.02 (d, 1H, J = 7 Hz, H-7), 5.42 (s, 1H, H-6), 6.87 (s, 1H, $CHPh_2$), 7.2–7.9 (m, 16H, C_6H_5, NH); Anal. ($C_{29}H_{27}O_5N_2SCl$) C, H, N: $[\alpha]_D^{23.5} - 13.0 \pm 0.5$ (c = 1.094, $CHCl_3$).

Diphenylmethyl 7α-benzoylamino-3β-phenylthio-3α-chloromethyl-1-oxacepham-4α-carboxylate (**11b**). Compound **10a** gave **11b** in 88% yield as white crystals, m.p. 195–196° (dec) (CH_2Cl_2–ether). IR ($CHCl_3$): 3430, 1785, 1745, 1675 cm^{-1}; ^{1}H NHR ($CDCl_3$): 3.08, 3.31 (ABq, 2H, J = 12 Hz, H-3′), 3.82, 4.18 (ABq, 2H, J = 12 Hz, H-2), 4.67 (s, 1H, H-4), 5.17 (d, 1H, J = 7 Hz, H-7), 5.15 (s, 1H, H-6), 6.85 (s, 1H, $CHPh_2$), 7.1–8.0 (m, 16H, C_6H_5, NH); Anal. ($C_{22}H_{21}O_5N_2SCl$) C, H, N, S, Cl; $[\alpha]_D^{23.5} - 11.2 \pm 0.5$ (c = 1.003, $CHCl_3$).

Diphenylmethyl 7α-methoxy-7β-(2-thienylacetylamino)-3β-methylthio-3α-chloromethyl-1-oxacepham-4α-carboxylate (**15a**). Compound **14** gave **15a** in 76% yield as a white foam. IR ($CHCl_3$): 3390, 1790, 1745, 1697 cm^{-1}; ^{1}H NMR ($CDCl_3$): 2.05 (s, 3H, SCH_3), 3.26, 3.58 (ABq, 2H, J = 13 Hz, H-3′), 3.45 (s, 3H, OCH_3), 3.78, 4.18 (ABq, 2H, J = 12 Hz, H-2), 3.88 (s, 2H, CH_2CO), 4.55 (s, 1H, H-4), 5.43 (s, 1H, H-6), 6.8–7.8 (m, 14H, C_6H_5, NH).

Diphenylmethyl 7α-methoxy-7β-(2-thienylacetylamino)-3β-phenylthio-3α-chloromethyl-1-oxacepham-4α-carboxylate (**15b**). Compound **14** gave **15b** in 88% yield as a white foam. IR ($CHCl_3$): 3380, 1780, 1740, 1695 cm^{-1}; ^{1}H NMR ($CDCl_3$): 3.21, 2.99 (ABq, 2H, J = 12 Hz, H-3′), 3.50 (s, 3H, OCH_3), 3.93 (s, 2H, CH_2CO), 3.80, 4.18 (ABq, 2H, J = 13 Hz, H-2), 4.53 (s, 1H, H-4), 5.41 (s, 1H, H-6), 6.6–7.9 (m, 20H, $CHPh_2$, ArH, NH).

Methyl 7α-benzoylamino-3β-phenylthio-3α-chloromethyl-1-oxacepham-4α-carboxylate (**11c**). Methyl ester **10b** gave **11c** in 45% yield as white crystals, m.p. 179–180° (ether–pentane). IR ($CHCl_3$): 3430, 1785, 1750, 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$): 3.39, 3.57 (ABq, 2H, J = 12 Hz, H-3′), 3.70 (s, 3H, CH_3), 3.86, 4.31 (ABq, 2H, J = 12 Hz, H-2), 4.52 (s, 1H, H-4), 5.20 (d, 1H, J = 7 Hz, H-7), 5.47 (s, 1H, H-6), 7.2–7.9 (m, 11H, C_6H_5, NH); Anal. ($C_{22}H_{21}O_5N_2SCl$) C, H, N, S, Cl; $[\alpha]_D^{23.5} - 28.7 \pm 0.7$ (c = 0.995, $CHCl_3$). This compound was identical with a sample obtained from **11b** in the following way. A solution of **11b** (2 g), anisole (1.5 ml) and CF_3COOH (1.5 ml) in CH_2Cl_2 (8 ml) was stirred at room temp for 40 min and concentrated *in vacuo*. The resulting oily product was triturated with n-pentane to give the corresponding acid (686 mg) as a white powder. IR (Nujol): 3380, 1776, 1758, 1738, 1676 cm^{-1}; ^{1}H NMR (acetone-d_6): 3.56 (s, 2H, H-3′), 3.90, 4.36 (ABq, 2H, J = 14 Hz, H-2), 4.45 (s, 1H, H-4), 5.28 (d, 1H, J = 8 Hz, H-7), 5.48 (s, 1H, H-6), 7.1–8.1 (m, 11H, C_6H_5, NH). To a soln of this acid (150 mg) in acetone (5 ml) was added a soln of diazomethane in ether at 0°. After stirring for 5 min, the mixture was evaporated to a crystalline residue, which was recrystallized from ether to give **11c** (123 mg, m.p. 181–182°).

Preparation of 3-methylene-1-oxacepham methyl ester **10b**

To a cold (−25°) soln of **10a** (3.0 g, 6.4 mmol) in CH_2Cl_2 (40 ml)-anisole (9 ml) was added dropwise a soln of $AlCl_3$ (2.8 g, 21.1 mmol) in nitromethane (40 ml) with stirring. After being stirred for 45 min at −20°, the mixture was poured into cold 1 N HCl aq (25 ml) and extracted with EtOAc. The organic layer was extracted with 5% $NaHCO_3$ aq. The aq layer was adjusted to pH 2 with 1 N HCl aq and extracted with EtOAc. The organic layer was washed with brine, dried with $MgSO_4$ and evaporated to give a viscous oil. To a stirred soln of the residue in MeOH (10 ml) was added a soln of CH_2N_2 in ether (excess amount) at 0°. After stirring for 20 min, the mixture was evaporated to a pale yellow foam, which was chromatographed on silica gel affording **10b** (1.83 g, 90%) as a white foam.

Methyl 7α-benzoylamino-3α-chloromethyl-3β-methylthio-1-oxacepham-4α-carboxylate (**11d**)

A mixture of **10b** (210 mg, 0.664 mmol), α-picoline (0.078 ml, 0.796 mmol), 1.6 M soln of CH_3SCl in CCl_4 (0.83 ml, 1.328 mmol) and CH_2Cl_2 (2.1 ml) was stirred for 2 days at 0°. The mixture was poured into a cold $Na_2S_2O_3$ aq and extracted with CH_2Cl_2. The organic layer was washed with cold 1 N HCl aq, 10% $Na_2S_2O_3$ aq and water, dried with Na_2SO_4 and evaporated to a foam. The crude product was chromatographed on silica gel [benzene–EtOAc (2:1)] to give the desired product **11d** (183 mg, 69%) as a white foam and a less polar compound (53 mg, 18%) as a white foam. The latter compound, the N-methylthio derivative of **11d**, was converted to **11d** (43 mg, 91%) on treatment with a 3.4 N ether solution of HCl (0.007 ml) in CH_2Cl_2 (1 ml) at 0° overnight followed by usual workup. IR ($CHCl_3$): 3430, 1775, 1743, 1663 cm^{-1}; ^{1}H NMR ($CDCl_3$): 2.11 (s, 3H, SCH_3), 3.59, 3.73 (ABq, 2H, J = 12 Hz, H-3′), 3.73 (s, 3H, OCH_3), 3.89, 4.29 (ABq, 2H, J = 12 Hz, H-2), 4.40 (s, 1H, H-4), 5.06 (d, 1H, J = 7.5 Hz, H-7), 5.44 (s, 1H, H-6), 7.25–8.00 (m, 5H, C_6H_5).

General procedure for the nucleophilic substitution of sulfenyl chloride adducts

(1) *With sodium 1-methyl-1H-tetrazole-5-thiolate* (Na-SMTZ)

A soln of 3β-methyl- or phenylthio-3α-chloromethyl-1-oxacepham (1 mmol) and Na-SMTZ·$2H_2O$ (2–3 mmol) in MeOH–acetone (2:1) (15–25 ml) was gently refluxed for 1–24 hr. The mixture was concentrated to leave a semi solid, which was dissolved in EtOAc. This soln was washed with water, dried with Na_2SO_4 and evaporated to give a crude product, which was purified by crystallization or column chromatography on silica gel.

Diphenylmethyl 7α-benzoylamino-3β-methylthio-3α-(1-methyl-1H-tetrazol-5-yl)thiomethyl-1-oxacepham-4α-carboxylate (**18a**). Compound **11a** (reaction time: 2 hr) gave **18a** in 98% yield as white crystals, m.p. 204–205° (CH_2Cl_2–ether). IR ($CHCl_3$): 3440, 1785, 1743, 1675 cm^{-1}; ^1H NMR ($CDCl_3$): 2.05 (s, 3H, SCH_3), 3.41 (s, 2H, H-3′), 3.81 (s, 3H, NCH_3), 3.82, 4.14 (ABq, 2H, J = 12 Hz, H-2), 4.67 (s, 1H, H-4), 5.03 (d, 1H, J = 8 Hz, H-7), 5.40 (s, 1H, H-6), 6.93 (s, 1H, $CHPh_2$), 7.0–7.9 (m, 16H, C_6H_5, NH); Anal. ($C_{36}H_{32}O_5N_6S_2$)C, H, N, S; $[\alpha]_D^{23.5} - 26.2 \pm 0.7$ (c = 1.005, $CHCl_3$).

Methyl 7α-benzoylamino-3α-(1-methyl-1H-tetrazol-5-yl)thiomethyl-3β-methyltio-1-oxacepham-4α-carboxylate (**18c**). Compound **11d** (reaction time: 6 hr at room temp) gave **18c** in 83% yield as white crystals, m.p. 219–221° (MeOH–ether). IR (Nujol): 3395, 1763, 1736, 1670 cm^{-1}; ^1H NMR (DMSO-d_6): 2.11 (s, 3H, SCH_3), 3.68 (s, 2H, H-3′), 3.75 (s, 3H, OCH_3), 4.00 (s, 3H, NCH_3), 4.00, 4.23 (ABq, 2H, J = 12.5 Hz, H-2), 4.54 (s, 1H, H-4), 4.96 (d, 1H, J = 9 Hz, H-7), 5.39 (s, 1H, H-6), 7.4–8.1 (m, 5H, C_6H_5), 9.34 (d, 1H, J = 9 Hz, NH); Anal. ($C_{19}H_{22}O_6N_5S_2 \cdot 1/2H_2O$) C, H, N, S; $[\alpha]_D^{24.0} + 15.7 \pm 0.6$ (c = 1.007, pyridine).

Diphenylmethyl 7α-methoxy-7β-(2-thienylacetyldmino)-3α-(1-methyl-1H-tetrazol-5-yl)thiomethyl-3β-methylthio-1-oxacepham-4α-carboxylate (**21a**). Compound **15a** (reaction time: 40 min) gave **21a** in 98% yield as a white foam. IR ($CHCl_3$): 3400, 1790, 1745, 1705 cm^{-1}; ^1H NMR ($CDCl_3$): 1.98 (s, 3H, SCH_3), 3.45 (s, 3H, OCH_3), 3.81 (s, 3H, NCH_3), 3.7–4.3 (m, 6H, H-2, H-3′, CH_2CO), 4.60 (s, 1H, H-4), 5.47 (s, 1H, H-6), 6.8–7.7 (m, 14H, C_6H_5, NH).

Diphenylmethyl 7α-benzoylamino-3β-phenylthio-3α-(1-methyl-1H-tetrazol-5-yl)thiomethyl-1-oxacepham-4α-carboxylate (**18b**). Compound **11b** (reaction time: 16 hr) gave **18b** in 70% yield as white crystals, m.p. 175–176° (CH_2Cl_2–ether). IR ($CHCl_3$): 3430, 1797, 1746, 1680 cm^{-1}; ^1H NMR ($CDCl_3$): 3.31 (s, 2H, H-3′), 3.69, 4.14 (ABq, 2H, J = 12 Hz, H-2), 3.76 (s, 3H, NCH_3), 4.78 (s, 1H, H-4), 5.18 (d, 1H, J = 7 Hz, H-7), 5.48 (s, 1H, H-6), 6.80 (s, 1H, $CHPh_2$), 7.2–8.0 (m, 16H, C_6H_5, NH); Anal. ($C_{36}H_{32}O_5N_6S_2$) C, H, N, S; $[\alpha]_D^{23.5} - 3.5 \pm 0.4$ (c = 1.052, $CHCl_3$).

Diphenylmethyl 7α-methoxy-7β-(2-thienylacetylamino)-3α-(1-methyl-1H-tetrazol-5-yl)thiomethyl-3β-phenylthio-1-oxacepham-4α-carboxylate (**21b**). Compound **15b** (reaction time: 15 hr) gave **21b** in 59% yield as a white foam. IR ($CHCl_3$): 3390, 1780, 1740, 1695 cm^{-1}; ^1H NMR ($CDCl_3$): 3.33 (s, 2H, H-3′), 3.50 (s, 3H, OCH_3), 3.80 (s, 3H, NCH_3), 3.95 (s, 2H, CH_2CO), 3.8–4.3 (m, 2H, H-2), 4.70 (s, 1H, H-4), 5.48 (s, 1H, H-6), 6.8–7.9 (m, 19H, ArH, NH).

(2) *With silver perchlorate or perfluoroborate in methanol*

A mixture of diphenylmethyl 3α-chloromethyl-3β-methyl- or phenylthio-1-oxacepham-4α-carboxylate (1 mmol), silver salt (2–2.3 mmol), $CaCO_3$ (3–3.5 mmol) and MeOH (5–8 ml) was stirred at room temp for 1–1.5 hr. The mixture was diluted with AcOEt and filtered to remove the precipitate. The filtrate was washed with H_2O, dried with Na_2SO_4 and concentrated to give a crude product, which was purified by column chromatography on silica gel to obtain the 3α-methoxymethyl cepham.

Diphenylmethyl 7α-benzoylamino-3α-methoxymethyl-3β-methylthio-1-oxacepham-4α-carboxylate (**19a**). Chloride **11a** (salt: $AgBF_4$; reaction time: 1 hr) gave **19a** in 75% yield as a foam. IR ($CHCl_3$): 3425, 1778, 1743, 1672 cm^{-1}; ^1H NMR ($CDCl_3$): 2.13 (s, 3H, SCH_3), 2.85 (s, 3H, OCH_3), 3.25, 3.38 (ABq, 2H, J = 10 Hz, H-3′), 3.80, 4.33 (ABq, 2H, J = 14 Hz, H-2), 4.57 (s, 1H, H-4), 5.08 (d, 1H, J = 7 Hz, H-7), 5.43 (s, 1H, H-7), 6.90 (s, 1H, $CHPh_2$), 7.2–8.0 (m, 16H, C_6H_5, NH).

Diphenylmethyl 7α-methoxy-7β-(2-thienylacetylamino)-3α-methoxymethyl-3β-methylthio-1-oxacepham-4α-carboxylate (**22a**). Chloride **15a** (salt: $AgClO_4$; reaction time: 1.5 hr) gave **22a** in 96% yield as a foam. IR ($CHCl_3$): 3400, 1783, 1743, 1695 cm^{-1}; ^1H NMR ($CDCl_3$): 2.02 (s, 3H, SCH_3), 2.83 (s, 3H, C_3-OCH_3), 3.21, 3.35 (ABq, 2H, J = 10 HZ, H-2), 3.45 (s, 3H, C_7-OCH_3), 3.74, 4.29 (ABq, 2H, J = 13 Hz, H-3′), 4.50 (s, 1H, H-4), 5.38 (s, 1H, H-6), 6.7–7.5 (m, 14H, C_6H_5, NH).

(3) *With silver perchlorate or tetrafluoroborate in dimethylacetamide (DMA)*

A soln of 3-chloromethyl-1-oxacepham-4-carboxylic acid ester (1 mmol), Ag salt (2–2.3 mmol) and $CaCO_3$ (4–4.5 mmol) in DMA (5–10 ml) was stirred at room temp for 3–24 hr. The mixture was diluted with EtOAc and filtered to remove the ppt. The filtrate was washed with water, dried with Na_2SO_4 and concentrated *in vacuo* to give a residue, which was chromatographed on silica gel to afford the 3α-acetoxymethyl-1-oxacepham-4α-carboxylic acid ester.

Diphenylmethyl 7α-benzoylamino-3α-acetoxymethyl-3β-methylthio-1-oxacepham-4α-carboxylate (**20a**). Chloride **11a** (salt: $AgBF_4$; reaction time: 3 hr) gave **20a** in 76% yield as a foam. IR ($CHCl_3$): 3435, 1785, 1750, 1683 cm^{-1}; ^1H NMR ($CDCl_3$): 1.76 (s, 3H, $COCH_3$), 2.25 (s, 3H, SCH_3), 3.73, 4.18 (ABq, 2H, J = 13 Hz, H-3′ or H-2), 3.86, 4.13 (ABq, 2H, J = 13 Hz, H-2 or H-3′), 4.63 (s, 1H, H-4), 5.05 (d, 1H, J = 7 Hz, H-7), 5.47 (s, 1H, H-6), 6.92 (s, 1H, $CHPh_2$), 7.3–8.1 (m, 16H, C_6H_5, NH).

Diphenylmethyl 7α-methoxy-7β-(2-thienylacetylamino)-3α-acetoxymethyl-3β-methylthio-1-oxacepham-4α-carboxylate (**23a**). Chloride **15a** (salt: $AgClO_4$; reaction time: 3.5 hr) gave **23a** in 71% yield as a foam. IR ($CHCl_3$): 3400, 1790, 1750, 1695 cm $^{-1}$; ^1H NMR ($CDCl_3$): 1.72 (s, 3H, $COCH_3$), 2.00 (s, 3H, SCH_3), 3.40 (s, 3H, OCH_3), 3.67, 4.14 (ABq, 2H, J = 14 Hz, H-3′ or H-2), 3.85, 4.14 (ABq, 2H, J = 12 Hz, H-2 or H-3′), 3.82 (s, 2H, CH_2CO), 4.50 (s, 1H, H-4), 5.43 (s, 1H, H-6), 6.8–7.3 (m, 14H, C_6H_5, NH).

Diphenylmethyl 7α-methoxy-7β-(2-thienylacetylamino)-3α-acetoxymethyl-3β-phenylthio-1-oxacepham-4α-carboxylate (**23b**). Chloride **15b** (salt: $AgClO_4$; reaction time: 24 hr) gave **23b** in 67% yield as a white foam. IR ($CHCl_3$): 3400, 1780, 1745, 1695 cm^{-1}; ^1H NMR ($CDCl_3$): 1.66 (s, 3H, $COCH_3$), 3.45 (s, 3H, OCH_3), 3.90 (s, 4H, CH_2CO, H-3′), 3.83, 4.18 (ABq, 2H, J = 13 Hz, H-2), 4.60 (s, 1H, H-4), 5.48 (s, 1H, H-6), 6.8–7.7 (m, 20H, $CHPh_2$, ArH, NH).

(4) *With sodium acetate in dimethylformamide*

A mixture of **11a** (276 mg, 0.5 mmol), NaOAc (62 mg, 0.75 mmol), HOAc (0.29 ml, 5 mmol) and dimethylformamide (1.4 ml) was stirred for 4 hr at 65°. The mixture was poured into cold water and extracted with EtOAc. The organic layer was washed with 5% $NaHCO_3$ aq and water, dried with $MgSO_4$ and evaporated to give a yellow oil, which was chromatographed on silica gel [benzene-EtOAc (4:1)] giving the 3-acetoxymethyl derivative **20a** (246 mg, 86%) as a white foam. This compound was identical with the acetate **20a** prepared by the reaction with $AgBF_4$ and DMA as described above.

General procedure for the oxidative elimination of the 3β-methyl- or phenylthio group to generate the 1-oxa-3-cephems

A soln of 3-methyl- or phenylthio cepham (1 mmol) and

m-CPBA (1.1–1.5 mmol) in CH_2Cl_2 (8–10 ml) was stirred for 15 min at 0°. The mixture was diluted with CH_2Cl_2 and washed successively with 10% $Na_2S_2O_3$ aq, 5% $NaHCO_3$ aq and water. After being dried with Na_2SO_4, the CH_2Cl_2 solution was concentrated to give a residue. A solution of this crude sulfoxide in EtOAc (12–24 ml) was refluxed for 10–30 min to complete the elimination and then washed with 5% $NaHCO_3$ aq and water. The organic layer was dried with Na_2SO_4 and concentrated to give a crude 3-cephem. The crude cephem was chromatographed on silica gel eluting with benzene–EtOAc.

Diphenylmethyl 7α-benzoylamino-3-(1-methyl-1H-tetrazol-5-yl)thiomethyl-1-oxa-3-cephem-4-carboxylate (**26a**). 3α-Methylthio cepham **18a** gave **26a** in 90% yield as white crystals, m.p. 203–205° (ether–pentane). IR ($CHCl_3$): 3450, 1792, 1725, 1680 cm^{-1}; ^1H NMR ($CDCl_3$): 3.77 (s, 3H, NCH_3), 4.20 (s, 2H, H-3′), 4.57 (s, 2H, H-2), 4.90 (d, 1H, J = 7 Hz, H-7), 5.07 (s, 1H, H-6), 6.93 (s, 1H, $CHPh_2$), 7.2–7.9 (m, 16H, C_6H_5, NH); Anal. ($C_{20}H_{26}O_5N_6S$) C, H, N, S; $[\alpha]_D^{22} - 116.1 \pm 3.2$ (c = 0.492 dioxane). This compound was identical with an authentic sample prepared previously.[9]

Diphenylmethyl 7α-benzoylamino-3-acetoxymethyl-1-oxa-3-cephem-4-carboxylate (**26b**). Compound **20a** gave 80% yield as a white foam. IR ($CHCl_3$): 3380, 1785, 1735, 1665 cm^{-1}; ^1H NMR ($CDCl_3$): 2.00 (s, 3H, $COCH_3$), 4.41 (s, 2H, H-2), 4.92 (s, 3H, H-3′, H-6), 5.06 (d, 1H, J = 8 Hz, H-7), 6.88 (s, 1H, $CHPh_2$), 7.15–7.90 (m, 16H, C_6H_5, NH). This compound was identical with an authentic sample prepared previously.[9]

Diphenylmethyl 7α-methoxy-7β-(2-thienylacetylamino)-3-(1-methyl-1H-tetrazol-5-yl)thiomethyl-1-oxa-3-cephem-4-carboxylate (**27a**). 3-Methyl- and phenylthiocephams **21a** and **21b** gave **27a** in 90 and 76% yields respectively, as white crystals, m.p. 175–176° (acetone–ether). IR ($CHCl_3$): 3400, 1790, 1705 cm^{-1}; ^1H NMR ($CDCl_3$): 3.48 (s, 3H, OCH_3), 3.80 (s, 3H, NCH_3), 3.83 (s, 2H, CH_2CO), 4.27 (s, 2H, H-3′), 4.62 (s, 2H, H-2), 5.05 (s, 1H, H-6), 6.48 (s, 1H, NH), 6.9–7.6 (m, 14H, $CHPh_2$, ArH); Anal. ($C_{30}H_{28}O_6N_6S_2$) C, H, N; $[\alpha]_D^{23.5} - 86.6 \pm 1.2$ (c = 1.061, $CHCl_3$).

Diphenylmethyl 7α-methoxy-7β-(2-thienylacetylamino)-3-acetoxymethyl-1-oxa-3-cephem-4-carboxylate (**27b**). Compound **23a** gave **27b** (82%) as a white foam. IR ($CHCl_3$): 3400, 1793, 1736, 1701 cm^{-1}; ^1H NMR ($CDCl_3$): 2.00 (s, 3H, $COCH_3$), 3.48 (s, 3H, OCH_3), 3.87 (s, 2H, CH_2CO), 4.45 (s, 2H, H-2), 5.05 (s, 3H, H-3′, H-6), 6.57 (s, 1H, NH), 6.9–7.6 (m, 14H, $CHPh_2$, ArH).

Diphenylmethyl 7α-methoxy-7β-(2-thienylacetylamino)-3-chloromethyl-1-oxa-3-cephem-4-carboxylate (**16**). 3-Chloromethyl compounds **15a** and **15b** gave **16** in 81 and 79% yields respectively, as white crystals, m.p. 158–160° (CH_2Cl_2–MeOH). IR (Nujol): 3250, 1775, 1730, 1690, 1665 cm^{-1}; ^1H NMR ($CDCl_3$): 3.48 (s, 3H, OCH_3), 3.83 (s, 2H, CH_2CO), 4.43 (s, 2H, H-3′ or H-2), 4.48 (s, 2H, H-2 or H-3′), 5.06 (s, 1H, H-6), 6.6–7.6 (m, 15H, $CHPh_2$, ArH, NH); Anal. ($C_{28}H_{25}O_6N_2SCl$) C, H, N, S, Cl; $[\alpha]_D^{24.0} + 6.1 \pm 0.5°$ (c = 1.013, $CHCl_3$).

Diphenylmethyl 7α-benzoylamino-3-chloromethyl-1-oxa-3-cephem-4-carboxylate (**12**). Compounds **11a** and **11b** gave **12** in 68 and 89% yields respectively, as white crystals, m.p. 129–130° (CH_2Cl_2-ether). IR ($CHCl_3$): 3375, 1790, 1728, 1670 cm^{-1}; ^1H NMR ($CDCl_3$): 4.35 (s, 2H, H-2 or H-3′), 4.48 (s, 2H, H-3′ or H-2), 4.98 (s, 1H, H-6), 5.02 (d, 1H, J = 6 Hz, H-7), 6.90 (s, 1H, $CHPh_2$), 7.1–7.95 (m, 16H, C_6H_5, NH). This compound was identical with an authentic sample prepared previously.[9]

Diphenylmethyl 7α-benzoylamino-3-(1-methyl-1H-tetrazol-5-yl)thiomethyl-1-oxa-3-cephem-4-carboxylate (**26a**)

To a stirred soln of **18a** (175 mg, 0.277 mmol) in CH_2Cl_2 (2.6 ml) was added 40% peracetic acid (0.08 ml, 0.415 mmol) at 0° and the mixture was stirred for 20 min at 0°. After addition of dimethyl sulfide (0.01 ml), the mixture was refluxed for 65 min and then evaporated to an oily residue. The crude product was chromatographed on silica gel [benzene–EtOAc (4:1)] to give 3-cephem **26a** (127 mg, 79%) as white crystals, which was identical with a sample prepared by the oxidation with *m*-CPBA.

Diphenylmethyl 7α-methoxy-7β-(2-thienylacetylamino)-3α-methoxymethyl-3β-methanesulfonyl-1-oxacepham-4α-carboxylate (**29**)

A soln of **22a** (300 mg, 0.5 mmol) and *m*-CPBA (200 mg, 1 mmol) in CH_2Cl_2 (3 ml) was stirred for 40 min at 0° and then diluted with EtOAc. The mixture was washed with cold 10% $Na_2S_2O_3$ aq, 5% $NaHCO_3$ aq and water. The organic layer was dried with Na_2SO_4 and evaporated to afford the crude product, which was chromatographed on silica gel [benzene–EtOAc (4:1)] to give **29** (234 mg, 75%) as a white foam. IR ($CHCl_3$): 3400, 1790, 1745, 1700 cm^{-1}; ^1H NMR ($CDCl_3$): 2.85 (s, 3H, OCH_3 or SO_2CH_3), 2.92 (s, 3H, SO_2CH_3 or OCH_3), 3.19, 3.45 (ABq, 2H, J = 12 Hz, H-2), 3.43 (s, 3H, C_7-OCH_3), 3.82 (s, 2H, CH_2CO), 4.22, 4.45 (ABq, 2H, J = 13 Hz, H-3′), 5.07 (s, 1H, H-4), 5.42 (s, 1H, H-6), 6.7–7.5 (m, 14H, $CHPh_2$, ArH, NH).

Diphenylmethyl 7α-methoxy-7β-(2-thienylacetylamino)-3-methoxymethyl-1-oxa-3-cephem-4-carboxylate (**27c**)

To a stirred soln of **29** (230 mg, 0.365 mmol) in CH_2Cl_2 (2.5 ml) was added DBU (0.082 ml, 0.53 mmol) at −30°. After being stirred for 25 min at −30°, the mixture was poured into ice-water and the resulting mixture was extracted with EtOAc. The organic layer was washed with 2N HCl aq, 5% $NaHCO_3$ aq, and water, dried with Na_2SO_4, and concentrated to afford a foam. The crude product was chromatographed on silica gel [benzene–EtOAc (9:1)] to give cephem **27c** (164 mg, 82%) as white crystals, m.p. 155–156° (CH_2Cl_2–ether). IR ($CHCl_3$): 3420, 1790, 1725, 1700 cm^{-1}; ^1H NMR ($CDCl_3$): 3.25 (s, 3H, C_3-OCH_3), 3.50 (s, 3H, C_7-OCH_3), 3.87 (s, 2H, CH_2CO), 4.42 (s, 2H, H-2 or H-3′), 4.53 (s, 2H, H-2 or H-3′), 5.05 (s, 1H, H-6), 6.50 (s, 1H, NH), 6.8–7.7 (m, 14H, $CHPh_2$, ArH); Anal. ($C_{29}H_{28}O_7N_2S$) C, H, N, S; $[\alpha]_D^{23.5} + 22.8 \pm 0.6$ (c = 1.008, $CHCl_3$).

Diphenylmethyl 7α-benzoylamino-3α-methoxymethyl-3β-methanesulfonyl-1-oxacepham-4α-carboxylate (**28**)

In the same way as described for **29**, compound **28** was obtained from **19a** in 90% yield as a foam. IR ($CHCl_3$): 3425, 1785, 1742, 1672 cm^{-1}; ^1H NMR ($CDCl_3$): 2.82 (s, 3H, OCH_3), 2.98 (s, 3H, SO_2CH_3), 3.08, 3.42 (ABq, 2H, J = 12 Hz, H-3′), 4.21, 4.49 (ABq, 2H, J = 14 Hz, H-2), 4.93 (d, 1H, J = 7 Hz, H-7), 5.18 (s, 1H, H-4), 5.52 (s, 1H, H-6), 6.92 (s, 1H, $CHPh_2$), 7.2–8.1 (m, 16H, C_6H_5, NH).

Diphenylmethyl 7α-benzoylamino-3-methoxymethyl-1-oxa-3-cephem-4-carboxylate (**26c**)

In the same way as described for **27c**, compound **26c** was obtained from **28** in 89% yield as a white foam. IR ($CHCl_3$): 3430, 1790, 1725, 1673 cm^{-1}; ^1H NMR ($CDCl_3$): 3.18 (s, 3H, OCH_3), 4.27 (s, 2H, H-3′), 4.36, 4.57 (ABq, 2H, J = 19 Hz, H-2), 4.93 (s, 1H, H-6), 5.02 (d, 1H, J = 7 Hz, H-7), 6.88 (s, 1H, $CHPh_2$), 7.2–7.9 (m, 16H, C_6H_5, NH).

Synthesis of 1-oxacefamandol

Diphenylmethyl 7α-amino-3α-(1-methyl-1H-tetrazol-5-yl)-thiomethyl-3β-methylthio-1-oxacephan-4α-carboxylate (**30**)

To a stirred soln of **18a** (1.5 g, 2.38 mmol) in CH_2Cl_2 (15 ml) were added pyridine (0.29 ml, 3.57 mmol) and PCl_5 (0.76 g, 3.57 mmol) at 0°, and the stirring was continued for 2 hr at 0°. The resulting mixture was mixed with i-BuOH (7.8 ml) and stirred for 0.5 hr at 0° and for 3 hr at room temp. After addition of MeOH (1 ml) and water (0.8 ml),

the mixture was concentrated to give a viscous oil. Crystallization from MeOH (4 ml)-ether (6 ml) gave 7α-amino-1-oxacephem hydrochloride (1.23 g, 92%) as white crystals, m.p. 135–137°. IR (Nujol): 3615, 1784, 1740 cm^{-1}; ^1H NMR (DMSO-d_6): 2.10 (s, 3H, SCH_3), 3.2–3.7 (m, 4H, H-3′, NH_2), 3.87 (s, 3H, NCH_3), 4.00, 4.15 (ABq, 2H, J = 12.5 Hz, H-2), 4.43 (s, 1H, H-4), 4.26 (s, 1H, H-7), 5.48 (s, 1H, H-6), 6.90 (s, 1H, $CHPh_2$), 7.2–7.6 (m, 10H, C_6H_5); Anal. ($C_{24}H_{27}O_4N_6S_2Cl \cdot H_2O$) C, H, N, S, Cl; $[\alpha]_D^{24.0} - 4.8 \pm 0.5°$ (c = 1.001, $CHCl_3$). A suspension of this hydrochloride in CH_2Cl_2 was washed with 5% $NaHCO_3$ aq to give amine **30** as white crystals, m.p. 156–157° (CH_2Cl_2–ether). IR (Nujol): 3380, 1760, 1725 cm^{-1}; ^1H NMR ($CDCl_3$): 1.68 (s, 2H, NH_2), 2.05 (s, 3H, SCH_3), 3.46 (s, 2H, H-3′), 3.80 (s, 3H, NCH_3), 3.95 (s, 1H, H-7), 4.05, 4.21 (ABq, 2H, J = 8 Hz, H-2), 4.61 (s, 1H, H-4), 5.08 (s, 1H, H-6), 6.87 (s, 1H, $CHPh_2$), 7.3–7.5 (m, 10H, C_6H_5); Anal. ($C_{24}H_{26}O_4N_6S_2$) C, H, N; $[\alpha]_D^{22.5} - 32.9 \pm 0.7°$ (c = 1.01, $CHCl_3$).

Diphenylmethyl 7β-amino-3α-(1-methyl-1H-tetrazol-5-yl)-thiomethyl-3β-methylthio-1-oxacepham-4α-carboxylate (**32**)

Compound **30** was treated with chloral to give its Schiff base as yellow crystals, m.p. 179–181°. IR (Nujol): 1770, 1720, 1645 cm^{-1}; ^1H NMR ($CDCl_3$): 2.08 (s, 3H, SCH_3), 3.43 (s, 2H, H-3′), 3.80 (s, 3H, NCH_3), 3.92, 4.17 (ABq, 2H, J = 12 Hz, H-2), 4.65 (s, 2H, H-4), 4.93 (d, 1H, J = 2 Hz, H-7), 5.47 (s, 1H, H-6), 6.87 (s, 1H, $CHPh_2$), 7.2–7.4 (m, 10H, C_6H_5), 7.94 (d, 1H, J = 2 Hz, CH = N); Anal. ($C_{26}H_{25}O_4N_6S_2Cl_2$) C, H, N, S, Cl; $[\alpha]_D^{22.5} + 58.4 \pm 1.0$ (c = 1.013, $CHCl_3$). The Schiff base was converted into **31** on treatment with the Hünig base. IR ($CHCl_3$): 1785, 1740 cm^{-1}; ^1H NMR ($CDCl_3$): 2.05 (s, 3H, SCH_3), 3.50 (s, 2H, H-3′), 3.82 (s, 3H, NCH_3), 3.97, 4.08 (ABq, 2H, J = 12 Hz, H-2), 4.78 (s, 1H, H-4), 5.78 (s, 1H, H-6), 6.95 (1H, s, $CHPh_2$), 72–7.4 (m, 10H, C_6H_5), 7.95 (s, 1H, = CHN). Reduction of **31** with KBH_4 and successive hydrolysis with HCl aq gave **32** as white crystals, m.p. 92–95°. IR (Nujol): 3150, 1760, 1720 cm^{-1}; ^1H NMR ($CDCl_3$): 1.95 (s, 2H, NH_2), 2.15 (s, 3H, SCH_3), 3.42, 3.58 (ABq, 2H, H-3′), 3.77 (s, 3H, NCH_3), 3.93, 4.23 (ABq, 2H, J = 12 Hz, H-2), 4.27 (d, 1H, J = 4 Hz, H-7), 4.62 (s, 1H, H-4), 5.27 (d, 1H, J = 4 Hz, H-6), 6.83 (s, 1H, $CHPh_2$), 7.2–7.4 (m, 10H, C_6H_5); Anal. ($C_{24}H_{26}O_4N_6S_2$) C, H, N; $[\alpha]_D^{22.5} - 31.6 \pm 0.7$ (c = 1.010, $CHCl_3$).

Diphenylmethyl 7β-(D-mandelylamino)-3α-(1-methyl-1H-tetrazol-5-yl)thiomethyl-3β-methylthio-1-oxacephem-4α-carboxylate (**33**)

To a stirred soln of **32** (263 mg, 0.5 mmol) in EtOAc (10 ml) were added a soln of $NaHSO_3$ (235 mg, 2.26 mmol) in water (4 ml) and D-4-phenyl-2,5-dioxo-1,3-dioxolane (178 mg, 1 mmol). After being stirred for 20 min at room temp, the reaction mixture was diluted with EtOAc, and washed with 5% $NaHCO_3$ aq and water. The organic layer was dried with Na_2SO_4, concentrated to give a crude product, which was chromatographed on silica gel [benzene–EtOAc (1:1)] to afford pure **33** (292 mg, 88%) as a white foam. IR (Nujol): 3370, 1775, 1730, 1670 cm^{-1}; ^1H NMR ($CDCl_3$): 1.95 (s, 3H, SCH_3), 3.42 (s, 2H, H-3′), 3.57 (s, 3H, NCH_3), 3.92, 4.18 (ABq, 2H, J = 12 H , H-2), 4.58 (s, 1H, H-4), 5.07 (br d, 1H, PhCHCO), 5.3–5.6 (m, 2H, H-6, H-7), 6.88 (s, 1H, $CHPh_2$), 7.2–7.5 (m, 16H, C_6H_5, NH).

Diphenylmethyl 7β-(D-mandelylamino)-3-(1-methyl-1H-tetrazol-5-yl)thiomethyl-1-oxa-3-cephem-4-carboxylate (**34**)

A soln of **33** (330 mg, 0.5 mmol) and *m*-CPBA (120 mg, 0.576 mmol) in CH_2Cl_2 (6 ml) was stirred for 30 min at 0°. The mixture was diluted with CH_2Cl_2, and washed with 10% $Na_2S_2O_3$ aq, 5% $NaHCO_3$ aq and water. The organic layer was dried with Na_2SO_4 and evaporated to dryness. A solution of the residue in acetone (6 ml) was refluxed for 15 min and evaporated to afford a crude product, which was chromatographed on silica gel to give **34** (249 mg, 82%) as a white foam. IR (Nujol): 3150 (br), 1770, 1705, 1660 cm^{-1}; ^1H NMR ($CDCl_3$-CD_3OD): 3.73 (s, 3H, NCH_3), 4.18 (s, 2H, H-3′), 4.55 (s, 2H, H-2), 5.00 (d, 1H, J = 4 Hz, H-6), 5.03 (s, 1H, PhCHCO), 5.47, 5.63 (dd, 1H, J = 10, 4 Hz, H-7), 6.87 (s, 1H, $CHPh_2$), 7.2–7.5 (m, 15H, C_6H_5, NH).

7α-Benzoylamino-3α-(1-methyl-1H-tetrazol-5-yl)thiomethyl-3β-methylthio-1-oxacephem-4α-carboxylic acid (**36**)

From **18a**. To a stirred cold (−20°) soln of **18a** (563 mg, 0.893 mmol) in acetone (11.3 ml) was added dropwise a soln of 0.1 N NaOH aq (10 ml, 1 mmol) and the mixture was stirred for 20 min at −10°. After addition of 1 N HCl aq (1 ml), the mixture was evaporated and extracted with EtOAc. The organic layer was washed with water, dried with Na_2SO_4, and concentrated to a yellow oily residue, which was crystallized from MeOH–acetone–CH_2Cl_2–ether to give acid **36** (338 mg, 82%) as white crystals, m.p. 194–195°. The mother liquor was condensed to an oily residue. A soln of the residue in methyl ethyl ketone (MEK) was shaken with 5% $NaHCO_3$ aq. The organic layer was washed with water and evaporated to a foam, which was chromatographed on silica gel [benezene–EtOAc (2:1)] to give the starting ester **18a** (43 mg, 7.6%) as crystals. A second crop of **36** (12 mg, 2.9%) was obtained from the alkaline layer by acidification followed by the workup as described above. IR (Nujol): 3340, 1764, 1735, 1655, 1630 cm^{-1}; ^1H NMR (acetone-d_6): 2.18 (s, 3H, SCH_3), 3.78 (s, 2H, H-3′), 4.03 (s, 3H, NCH_3), 4.11, 4.38 (ABq, 2H, J = 13 Hz, H-2), 4.55 (s, 2H, H-4), 5.20 (d, 1H, J = 8 Hz, H-7), 5.47 (s, 1H, H-6), 7.4–8.2 (m, 16H, C_6H_5, NH); Anal. ($C_{18}H_{20}N_6O_5S_2 \cdot H_2O$) C, H, N, S; $[\alpha]_{436}^{23.5} + 12.5 \pm 0.5°$ (c = 0.998, acetone).

From methyl ester **18c**. To a stirred cold (−7°) suspension of ester **18c** (500 mg, 1.045 mmol) in acetone (25 ml) was added dropwise 0.1 N NaOH aq (10.5 ml, 1.05 mmol) and the mixture was stirred for 30 min at −5°. After addition of 1 N HCl aq (1.05 ml), the reaction mixture was concentrated to an oily residue and then triturated with water. The resulting crystals were filtered, washed with water, ether, and cold acetone, and dried to give acid **36** (428 mg, 88%).

7α-Benzoylamino-3-(1-methyl-1H-tetrazol-5-yl)thiomethyl-1-oxa-3-cephem-4-carboxylic acid (**37**)

To a mixture of **36** (232 mg, 0.5 mmol), $NaHCO_3$ (84 mg, 1 mmol), $Na_2WO_4 \cdot 2H_2O$ (20 mg), acetone (5 ml) and water (1 ml) was added 30% H_2O_2 aq (0.3 ml, 2.6 mmol) with stirring at 0°. After stirring for 1 hr at 0°, the mixture was poured into cold $Na_2S_2O_3$ aq. The mixture was adjusted to pH 2 with conc HCl aq and extracted with MEK. The organic layer was washed with water, dried with Na_2SO_4 and evaporated to a foam. A soln of the residue in acetone (6 ml) was refluxed for 20 min and then evaporated to dryness. An acidic product was separated from the crude product in a usual way to give **37** (168 mg, 81%) as a white powder. IR (Nujol): 3300, 1780, 1710, 1640 cm^{-1}; ^1H NMR (acetone-d_6-CD_3OD-D_2O): 4.03 (s, 3H, NCH_3), 4.32 (s, 2H, H-3′), 4.70 (s, 2H, H-2), 4.97 (s, 1H, H-7), 5.28 (s, 1H, H-6), 7.4–8.1 (m, 5H, C_6H_5).

Diphenylmethyl 7β-(2-thienylacetylamino)-3α-chloromethyl-3β-methylthiocepham-4α-carboxylate (**39**)

To a stirred soln of dimethyl disulfide (0.373 ml, 4.14 mmol) in CCl_4 (4 ml) was added 1 M soln of Cl_2 in CCl_4 (4.4 ml, 4.4 mmol) at 0° and the resulting soln was stirred for 20 min at 0°. A soln of **38** (1 g, 2 mmol) in CH_2Cl_2 (8 ml) was added to the above methane-sulfenyl chloride soln. The mixture was stirred for 2.5 hr at room temp, diluted with

EtOAc, washed with 10% $Na_2S_2O_3$ aq and water, dried with Na_2SO_4, and evaporated to a foam. The crude product was chromatographed on silica gel to give the pure **39** (776 mg, 66%) as a white foam. IR ($CHCl_3$): 3400, 1783, 1742, 1691 cm^{-1}; ^1H NMR ($CDCl_3$): 2.00 (s, 3H, SCH_3), 2.70, 3.53 (ABq, 2H, J = 12 Hz, H-2), 3.27, 3.56 (ABq, 2H, J = 12 Hz, H-3'), 3.83 (s, 2H, CH_2CO), 4.58 (s, 1H, H-4), 5.20 (d, 1H, J = 5 Hz, H-6), 5.58 (dd, 1H, J = 11, 5 Hz, H-7), 6.66 (d, 1H, J = 11 Hz, NH), 6.9–7.5 (m, 13H, ArH).

Diphenylmethyl 7β-(2-thienylacetylamino)-3α-(1-methyl-1H-tetrazol-5-yl)thiomethyl-3β-methylthiocepham-4α-carboxylate (**40**)

A soln of crude **39** (prepared from 1.27 g **38**) and Na-SMTZ·$2H_2O$ (900 mg, 5.2 mmol) in MeOH (30 ml)–acetone (15 ml) was refluxed for 20 min. The solvent was evaporated, and the residue was dissolved in EtOAc and washed with water. The organic layer was dried with Na_2SO_4 and evaporated to a foam, which was chromatographed on silica gel [benzene–EtOAc (4:1)] to give pure **40** (1.39 g, 82% from **38**) as a white foam. IR ($CHCl_3$): 3380, 1781, 1740, 1686 cm^{-1}; ^1H NMR ($CDCl_3$): 1.92 (s, 3H, SCH_3), 2.73, 3.57 (ABq, 2H, J = 16 Hz, H-2), 3.58 (s, 2H, H-3'), 3.67 (s, 5H, NCH_3, CH_2CO), 4.65 (s, 1H, H-4), 5.27 (d, 1H, J = 5 Hz, H-6), 5.58 (dd, 1H, J = 10, 5 Hz, H-7), 6.72 (d, 1H, J = 10 Hz, NH), 6.9–7.5 (m, 14H, $CHPh_2$, ArH).

Diphenylmethyl 7β-(2-thienylacetylamino)-3-(1-methyl-1H-tetrazol-5-yl)thiomethyl-3-cephem-4-carboxylate 1α-oxide (**41**)

A soln of **40** (150 mg, 0.225 mmol) and *m*-CPBA (110 mg, 0.528 mmol) in CH_2Cl_2 (1.5 ml) was stirred for 30 min at 0°. After dilution with CH_2Cl_2, the mixture was washed with 10% $Na_2S_2O_3$ aq, 5% $NaHCO_3$ aq and water, dried with Na_2SO_4 and concentrated to a foam. A soln of the residue in acetone (6 ml) was refluxed for 20 min and then concentrated to an oily residue, which was chromatographed on silica gel (EtOAc) to give cephem oxide **41** (81 mg, 70%) as white crystals, m.p. 121–123° (acetone–ether). IR ($CHCl_3$): 3475, 1803, 1727, 1685 cm^{-1}; ^1H NMR ($CDCl_3$): 3.79, 4.16 (ABq, 2H, J = 15 Hz, H-2), 3.80 (s, 2H, CH_2CO), 3.83 (s, 3H, NCH_3), 4.19, 4.67 (ABq, 2H, J = 13 Hz, H-3'), 4.43 (d, 1H, J = 5 Hz, H-6), 5.27 (dd, 1H, J = 8, 5 Hz, H-7), 6.9–7.5 (m, 15H, $CHPh_2$, NH, ArH); Anal. ($C_{29}H_{26}O_5N_6S_3 \cdot H_2O$) C, H, N; $[\alpha]_D^{23.5} - 230.1 \pm 2.5°$ (c = 1.066, $CHCl_3$).

Diphenylmethyl 7β-(2-thienylacetylamino)-3-(1-methyl-1H-tetrazol-5-yl)thiomethyl-3-cephem-4-carboxylate (**42**)

To a stirred soln of **41** (63.5 mg, 0.095 mmol) in DMF (2 ml) were added $SnCl_2 \cdot 2H_2O$ (90 mg, 0.4 mmol) and acetylchloride (0.3 ml, 4.25 mmol) at 0°. After stirring for 1 hr at room temp, the mixture was poured into ice-water and extracted with EtOAc. The organic layer was washed with 5% $NaHCO_3$ aq and water, dried with Na_2SO_4 and concentrated to a foam. The crude product was chromatographed on silica gel to give **42** (59 mg, 97%) as a white foam. IR ($CHCl_3$): 1788, 1720, 1685 cm^{-1}; ^1H NMR ($CDCl_3$): 3.60 (s, 2H, H-2), 3.73 (s, 3H, NCH_3), 3.80 (s, 2H, CH_2CO), 4.27 (s, 2H, H-3'), 4.93 (d, 1H, J = 5 Hz, H-6), 5.87 (dd, 1H, J = 9, 5 Hz, H-7), 6.8–7.5 (m, 15H, $CHPh_2$, NH, ArH).

7β-(2-Thienylacetylamino)-3α-(1-methyl-1H-tetrazol-5-yl)-thiomethyl-3β-methylthiocepham-4α-carboxylic acid (**43**)

A mixture of **40** (200 mg, 0.28 mmol), anisole (0.2 ml), CF_3COOH (0.2 ml) and CH_2Cl_2 (2 ml) was stirred for 40 min at 0° and then at room temp for 2 hr. After evaporation, the residue was triturated with ether to give **43** (150 mg, ~ 100%) as a white powder. IR ($CHCl_3$): 3380, 1780, 1735, 1685 cm^{-1}; ^1H NMR (acetone-d_6): 2.03 (s, 3H, SCH_3), 3.07, 3.79 (ABq, 2H, J = 15 Hz, H-2), 3.85 (s, 2H, CH_2CO), 3.92 (s, 2H, H-3'), 4.00 (s, 3H, NCH_3), 4.53 (s, 1H, H-4), 5.33 (d, 1H, J = 5 Hz, H-6), 5.67 (dd, 1H, J = 9, 5 Hz, H-4), 6.9–7.4 (m, 3H, ArH), 8.00 (d, 1H, J = 9 Hz, NH). This compound was also prepared by the alkaline hydrolysis of **40** in the same way as used for **18a**.

7β-(2-Thienylacetylamino)-3-(1-methyl-1H-tetrazol-5-yl)-thiomethyl-3-cephem-4-carboxylic acid 1α-oxide (**44**)

A soln of **43** (141 mg, 0.282 mmol) and 40% peracetic acid (0.2 ml, 1 mmol) in CH_2Cl_2 (1.5 ml)–acetone (0.5 ml) was stirred for 30 min at 0°. After addition of $(CH_3)_2S$ (0.1 ml), the mixture was evaporated to an oil, which was triturated with ether. A soln of the crude product in acetone (6 ml) was refluxed for 20 min and evaporated to an oily residue. A solution of the residue in MEK was extracted with 5% $NaHCO_3$ aq. The aq layer was adjusted to pH 2 with conc HCl aq, saturated with NaCl and extracted with MEK. The organic layer was washed with brine, dried with Na_2SO_4 and evaporated to give a white foam, which was triturated with acetone–ether affording **44** (107 mg, 78%) as a white powder. IR (Nujol): 3125–3400, 1790, 1713, 1673 cm^{-1}; ^1H NMR (acetone-d_6-CD_3OD): 3.84, 4.36 (ABq, 2H, J = 16 Hz, H-2), 3.95 (s, 3H, NCH_3), 4.00 (s, 2H, CH_2CO), 4.29, 4.73 (ABq, 2H, J = 14 Hz, H-3'), 4.60 (d, 1H, J = 5 Hz, H-6), 5.57 (d, 1H, J = 5 Hz, H-7), 6.9–7.4 (m, 3H, ArH).

Diphenylmethyl 7α-benzoylamino-3β-phenylseleno-3α-chloromethyl-1-oxacepham-4α-carboxylate (**48**)

To a stirred soln of **10a** (1.17 g, 2.5 mmol) in CH_2Cl_2 (10 ml) was added benzeneselenenyl chloride (955 mg, 5 mmol) with ice-cooling. After stirring for 1.5 hr at room temp, the mixture was diluted with EtOAc and washed with 10% $Na_2S_2O_3$ aq, 5% $NaHCO_3$ aq and water. The organic layer was dried with Na_2SO_4 and concentrated to a crystalline residue, which was recrystallized from ether giving **48** (1.435 g, 87%) as white crystals, m.p. 160–161° (dec). IR ($CHCl_3$): 3430, 1790, 1750, 1680 cm^{-1}; ^1H NMR ($CDCl_3$): 3.18, 3.45 (ABq, 2H, J = 12 Hz, H-3'), 3.91, 4.19 (ABq, 2H, J = 14 Hz, H-2), 4.72 (s, 1H, H-4), 5.17 (d, 1H, J = 7 Hz, H-7), 5.50 (s, 1H, H-6), 6.83 (s, 1H, $CHPh_2$), 7.1–8.0 (m, 21H, C_6H_5, NH); Anal. ($C_{34}H_{29}O_3N_2SeCl$) C, H, N, Cl; $[\alpha]_D^{23.5} - 12.4 \pm 0.5°$ (c = 1.051, $CHCl_3$).

Diphenylmethyl 7α-benzoylamino-3-chloromethyl-1-oxa-3-cephem-4-carboxylate (**12**) *from seleno adduct* **48**

A soln of **48** (132 mg, 0.2 mmol) and *m*-CPBA (49 mg, 0.235 mmol) in CH_2Cl_2 (3 ml) was stirred for 10 min at 0°. After dilution with EtOAc, the mixture was washed with 10% $Na_2S_2O_3$ aq, 5% $NaHCO_3$ aq and water. The organic layer was dried with Na_2SO_4 and concentrated to a crude product, which was chromatographed on silica gel [benzene–EtOAc (9:1)] to give crystalline **12** (63 mg, 60%). This compound was identical with an authentic sample prepared previously.[9]

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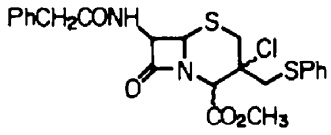
[7]Although patent literature (*Jpn. Kokai Tokkyo Koho JP* 77-59,185) describes the formation of an undesired isomeric adduct **9** by the addition of benzenesulfenyl chloride to the corresponding 3-exomethylene compound, we found no reliable data to support the structure.



9

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