HETEROCYCLES, Vol 28, No 2, 1989

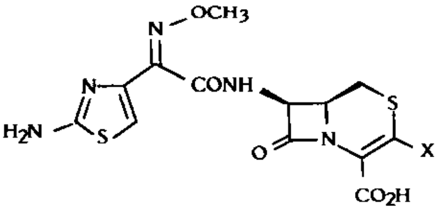
SYNTHESIS OF 3-(ALKYL AND ARYL)THIO-2-ISOCEPHEMS

Jozsef Aszodi*, Jean-François Chantot, Jeannine Collard, and Georges Teutsch
Centre de Recherche Roussel Uclaf
93230 Romainville (France)

Abstract-Synthesis of 3-S-substituted isocephems has been carried out in a convergent way using readily available intermediates such as 4-mercaptomethylazetidinone 3 and chloropyruvates 4 prepared by the reaction of sulfenyl chlorides with t-butyl diazopyruvate. During the synthesis, mild acid catalyzed decarboxylation of the β-carboxy ketene-dithioacetal moiety was observed as a side-reaction.

INTRODUCTION

The chemistry of nuclear analogues of cephalosporins has attracted much interest during the last 20 years[1]. However a rather limited effort has been devoted to the synthesis of 1-dethia-2-thia-cephalosporins, the so called isocephems[2,3]. The early compounds were characterized by low antibacterial potency on Gram positive strains, but compared favorably with their cephem counterparts on Gram negatives[3c]. The first molecule structurally related to third generation cephalosporins (1)[4,5] is highly potent against enterobacteriacea but is devoid of antistaphylococcal activity.



1 X = H
2 X = SR

In order to verify that the lack of activity against staphylococci is not an intrinsic property of the isocephem nucleus and as part of our ongoing research program for the synthesis of 3-substituted derivatives, we planned to synthesize compounds in which the substituent is attached to the 3-position of the isocephem nucleus via a sulfur atom, to give a penem-like structure (2).

DISCUSSION AND RESULTS

The synthetic approach was based on the reaction of the 4-mercaptomethylazetidinone 3 with bromo or chloropyruvates 4 according to a known methodology[3c], as outlined in Chart 1.

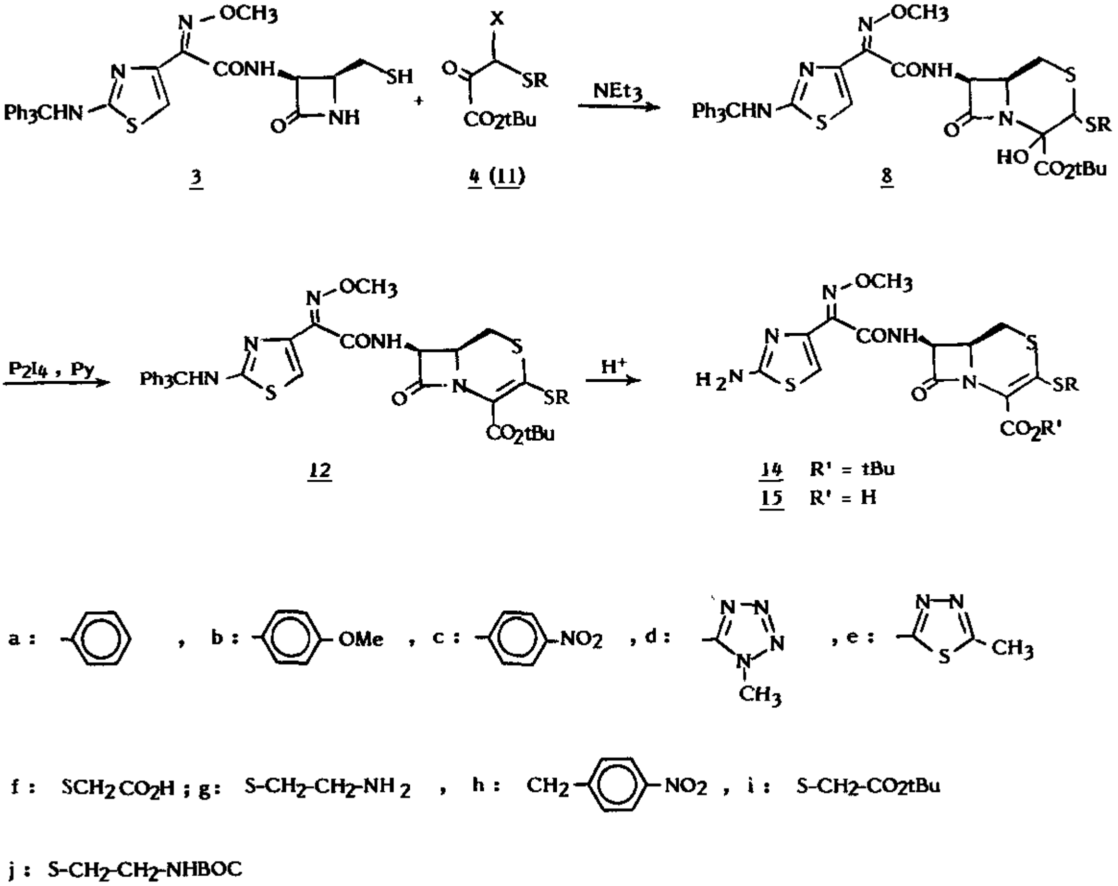
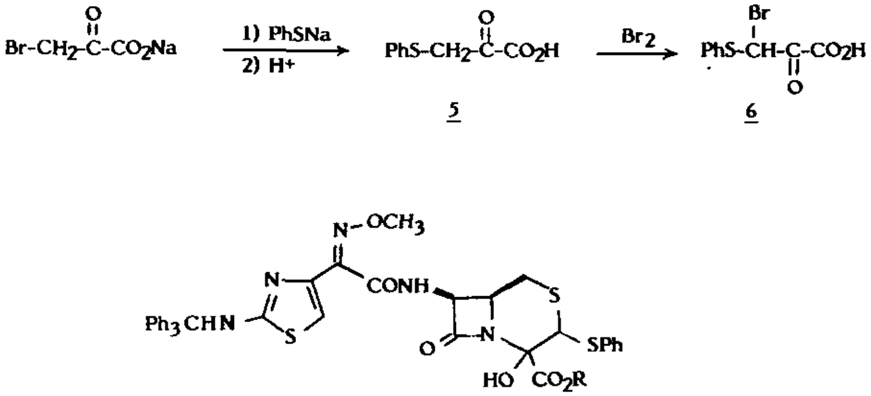


Chart 1

Two different pathways were tried for the preparation of substituted pyruvates of type 4. The first one (chart 2) is exemplified by the synthesis of 3-bromo-3-phenylthiopyruvic acid 6 via the substitution of sodium bromopyruvate by sodium thiophenoxide followed by bromination at -78°C with bromine in chloroform-ethyl ether. Reaction of 6 with the 4-mercaptomethylazetidinone synthon 3[6,7] in the presence of triethylamine afforded the cyclized aminal 7 in good yield, but attempts for the dehydration of the tertiary alcohol failed. Transformation of 7 into the corresponding t-butyl ester using O-t-butyl-N,N-diisopropylisourea afforded 8a in only 24% yield.



$$\mathrm{Br\text{-}CH_2\text{-}\overset{O}{\overset{\|}{C}}\text{-}CO_2Na} \xrightarrow[2)\ H^+]{1)\ PhSNa} \mathrm{PhS\text{-}CH_2\text{-}\overset{O}{\overset{\|}{C}}\text{-}CO_2H} \xrightarrow{Br_2} \mathrm{PhS\text{-}\overset{Br}{\overset{|}{C}H}\text{-}\underset{O}{\underset{\|}{C}}\text{-}CO_2H}$$

5

6

7 R = H

8a R = t-Bu

Chart 2

As this method was not satisfactory for the preparation of a large variety of isocephems, we turned our attention to a more straightforward way of preparingα-halo-α-arylthiopyruvates, based on the known reaction of diazoketones and esters with sulfenyl chlorides [8]. To this end, t-butyldiazopyruvate 9 was prepared in two steps from oxalyl chloride via monoesterification with t-butanol and reaction with diazomethane[9]. This rather stable compound could easily be prepared on a hundred gram scale.

$$\mathrm{N_2CH\text{-}\overset{O}{\overset{\|}{C}}\text{-}CO_2tBu} + \mathrm{RSCl} \longrightarrow \mathrm{RS\text{-}\underset{Cl}{\underset{|}{C}H}\text{-}\overset{O}{\overset{\|}{C}}\text{-}CO_2tBu}$$

9 10 (a-j)* 11 (a-j)*

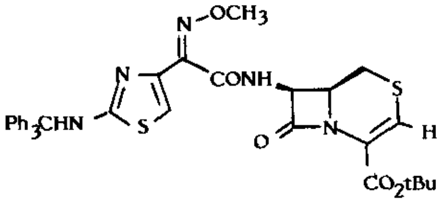
* see Chart 1

Chart 3

The diazopyruvate 9 reacted smoothly with phenylsulfenyl chloride [10] at room temp. in dichloromethane to give the chloropyruvate 11a. *The reaction can easily be followed by the end of* nitrogen evolution. Attempts to purify this compound by column chromatography resulted in partial decomposition of the product and yielded only 25 % of this highly reactive molecule which exists as a mixture of tautomers according to nmr and ir spectroscopies (see experimental part for a more stable analogue 11e). For convenience only the keto form is depicted in the scheme. The chloropyruvate reacted smoothly with 3 to give the cyclized product 8a in 67 % yield after chromatography (chart 1). *This compound is a mixture of a major and a minor diasteroisomer (ca.* 10 %), differring most probably by the relative configuration of the C-3 and (or) C-4 asymmetric centers. NOE experiments on the related compound 18a permitted to deduce that the relative configuration of the 3-phenylthio group in the major diastereoisomer is trans with respect to the C-7 side chain.

Indeed NOE enhancement was observed between H-1β (3.12 ppm) and H-3 (4.76 ppm) indicating a 1,3-diaxial interaction, as well as between H-1α (2.43 ppm) and H-6 (4.37 ppm), H-1α and H-1β, and finally H-6 and H-7α (5.30 ppm).

This convergent approach to the isocephem skeleton suffers from the presence of some unstable intermediates. Fortunately, the synthesis can be carried out without isolation of either the sulfenyl chlorides or the chloropyruvates. Thus reaction of aliphatic or aromatic mercaptans with N-chlorosuccinimide led to a solution of the sulfenyl chorides 10 which were treated successively with the diazopyruvate 9 followed by the β-lactam synthon 3 to give the cyclized compounds 8 in a one pot reaction. Alternatively, the first step can be carried out by chlorination of the corresponding disulfides as was performed for the in situ preparation of 11d, 11h and 11j.



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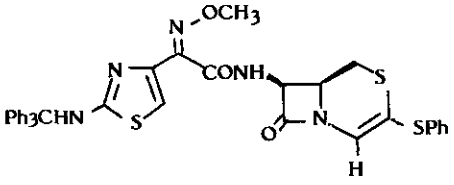

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Dehydration of the aminals 8 was attempted by literature methods[3c], i.e. thionyl chloride or trifluoroacetic anhydride in pyridine, but none of them gave rise to the desired compound 12. Eventually, it was found that the reaction could be achieved in the same solvent using diphosphorous tetraiodide to give 12 in moderate yields. In most cases, however, a small quantity (ca. 10%) of a *side product was isolated and identified as the 3-unsubstituted* isocephem 13. The formation of this molecule proceeds via a reductive elimination which is known as the predominant pathway during the reaction of P_2I_4 with acyclic β-hydroxy-thioethers under similar conditions (CH_2Cl_2,NEt_3) (Figure 1)[12]. In fact, both base catalyzed elimination of water or reductive elimination supposes that the C-3 hydrogen on the one hand or the RS-group on the other hand is in a trans diaxial *position with the OH group. Thus a relative* cis configuration of the C-3 substituent and C-4 hydroxy group in the major isomer of 8 could explain why in our case the dehydration pathway is preferred.

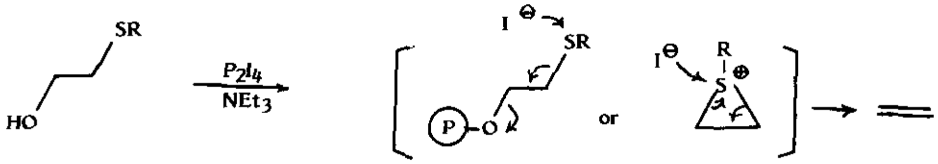


Figure 1 : Proposed mechanism for the reductive elimination of β-hydroxysulfides by P_2I_4 [12]

We attempted the verification of this hypothesis on 18b as this was one of the rare examples where the major and the minor isomers could be separated. Interestingly, while the major isomer upon reaction with P_2I_4 yielded only the desired compound 19b, the minor isomer afforded a mixture of 19b and the compound 20, resulting from reductive elimination. This result could be due to a partial epimerisation at C-4 of the minor component of 18b during the reaction via simple ring opening of the aminal moiety. A further consequence, taking into account the results of the NOE experiments on 18a and the necessity for trans stereochemistry of the 3-H and 4-OH groups for successful dehydration, is that the configuration of the major diastereoisomer must be 3α-SPh, 4α-OH.

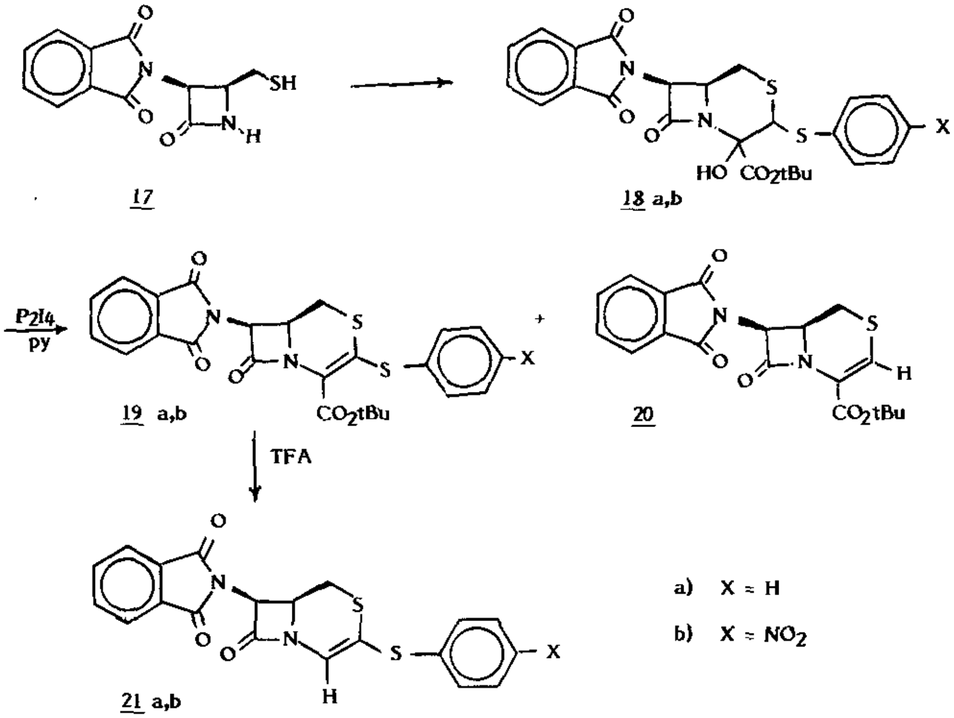


Chart 4

In the last step, double deprotection of 12 was attempted by the generally used trifluoroacetic acid treatment at room temperature. Surprisingly, under these conditions only the decarboxylated derivative 16 was obtained. In the hope that lowering the temperature would prevent this side reaction, the trityl group was first cleaved by aqueous formic acid at room temperature. The resulting amino ester on dissolution in trifluoroacetic acid at 0°C afforded after 1 hour the desired compound 15 with only traces of the decarboxylation product. The same result was achieved in one step when treating 14 with aqueous formic acid at 60°C for 5-7 hours.

This decarboxylation depends obviously on the acidic strength of the solvent, as well as on the temperature. Literature search showed that known decarboxylations of β-carboxyketenedithioacetals proceed under basic or neutral conditions and require high temperatures[13] or the presence of an additional carbonyl group[14]. In order to determine a possible mechanism for this reaction a qualitative kinetic analysis was carried out on model compounds 19a and b (Chart 4). When 19a was treated with trifluoroacetic acid at room temperature, complete decarboxylation occurred in less than 1 hour.

Conversely, when 19b was treated under the same conditions, only deprotection took place, and the decarboxylation needed a prolonged heating at 60°C. None of the two compounds, however, gave 21 when heated with aqueous (66%) formic acid at 60°C, though traces of 21a were observed when concentrated formic acid was used.

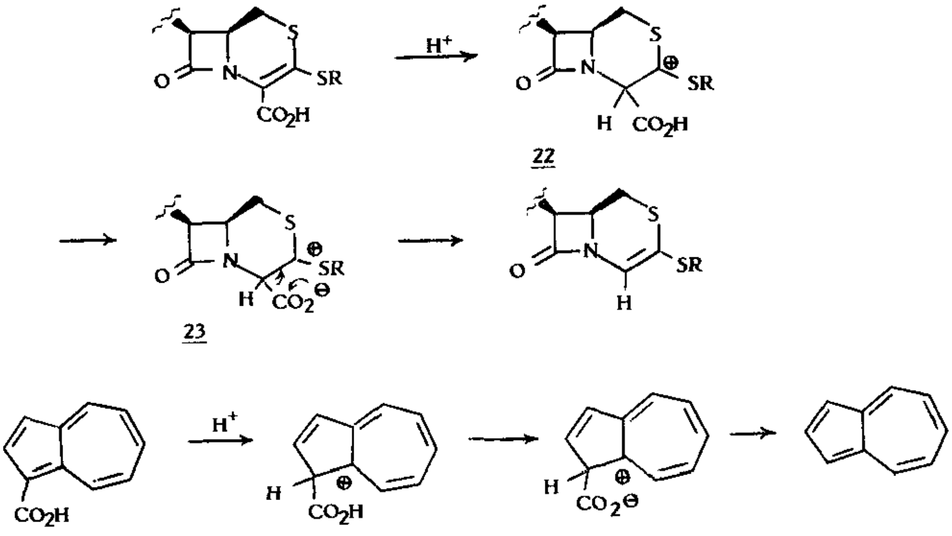
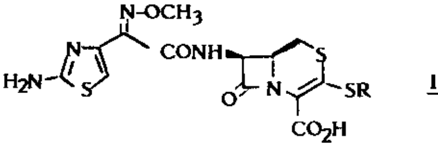


Figure 2 : Proposed mechanism for the acid catalyzed decarboxylation of carboxyketenedithioacetals and *azulene-1-carboxylic acid*[15].

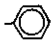
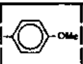
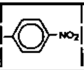
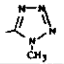
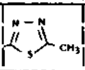
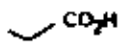
These observations are in agreement with the proposed mechanism (Figure 2), in which a rate determining protonation would lead to the intermediate <u>22</u>, in which the positive charge is stabilized by the presence of the two sulfur atoms, but destabilized when the aromatic ring contains a nitro group. The cation could either lose carbon dioxide directly or after deprotonation to <u>23</u>. This mechanism is also supported by the proposed pathway for the decarboxylation of azulene-1-carboxylic acid under similar mild conditions [15].

The above approach to isocephems led to the synthesis of compounds <u>15a-h</u>. The <u>in vitro</u> antibacterial activities are outlined in Table 1, in comparison with Cefotaxime. The MICs show that some compounds (<u>15c,d,h</u>) are more active than Cefotaxime against staphylococci, but all of them display only poor activity against Gram negative strains.

Table 1 : <u>In Vitro</u> antibacterial activity of some isocephems



<u>15</u> a,h

Compound	15a	15b	15c	15d	15e	15f	15g	15h	Cefotaxime
R								$-CH_2-\Phi-NO_2$	
MIC' s (μg/ ml) *									
S. aureus SG 511	5	5	0.6	1.2	2.5	> 40	5	0.6	1.2
S. aureus 285	5	10	1.2	1.2	2.5	> 40	40	2.5	2.5
S. aureus 54 146	10	10	1.2	5	2.5	> 40	> 40	1.2	2.5
Str. pyogenes A 561	≤ 0.04	≤ 0.04	≤ 0.04	≤ 0.04	≤ 0.04	0.6	≤ 0.04	≤ 0.04	≤ 0.04
Str. pyogenes 77 A	≤ 0.04	≤ 0.04	≤ 0.04	≤ 0.04	≤ 0.04	0.6	≤ 0.04	0.08	≤ 0.04
Str. faecium M 78 L	> 40	> 40	10	> 40	10	> 40	> 40	> 40	10
P. aeruginosa 1771	> 40	> 40	> 40	> 40	> 40	> 40	> 40	> 40	20
P. aeruginosa 1771 M	5	10	10	2.5	5	20	40	40	0.3
P. aeruginosa ATTC 9027	> 40	> 40	> 40	> 40	> 40	> 40	> 40	> 40	40
E. coli UC 1894	0.6	1.2	1.2	0.3	0.3	0.6	2.5	1.2	≤ 0.04
E. coli 078	5	10	10	0.6	1.2	5	5	10	≤ 0.04
E. coli TEM	20	20	20	2.5	10	5	10	20	0.08
E. coli 1507 E	1.2	1.2	1.2	0.6	0.6	5	5	2.5	≤ 0.04
E. coli DC 0	> 40	20	10	2.5	2.5	10	20	40	0.15
E. coli DC 2	1.2	5	1.2	0.3	1.2	5	10	0.3	≤ 0.04
Salm. typhy MZ 11	10	10	10	1.2	1.2	1.2	20	5	0.3
Klebs. pneu. 52 145	20	20	20	2.5	5	5	20	20	0.15
Klebs. aero. 1082 E	> 40	> 40	> 40	20	> 40	40	40	10	5
Klebs. aero. 1522 E	20	10	40	1.2	2.5	2.5	20	20	0.15
Ent. cloacae P 99	> 40	> 40	> 40	> 40	> 40	> 40	> 40	> 40	> 40
Ent. cloacae 1321 E	10	10	20	0.6	10	2.5	20	20	≤ 0.04
Serratia. RG 2532	> 40	> 40	> 40	> 40	> 40	> 40	> 40	40	2.5
Prot. mirabilis A 235	5	5	5	0.6	1.2	0.3	5	2.5	≤ 0.04
Prot. vulgaris A 232	> 40	10	20	2.5	10	1.2	10	1.2	0.15
Providencia DU 48	> 40	10	10	20	> 40	5	20	20	2.5

* MIC's were obtained by the two fold broth dilution method.

* All isocephems are racemic, MIC's should be halved for comparison with cefotaxime.

EXPERIMENTAL

Melting points were determined on a Koefler hot-plate. Spectral data were recorded on the following spectrometers : ir, Perkin-Elmer 580 ; nmr, Bruker WP or WH ; ms, MAT-311A or ZAB-HFQ ; For the nmr *chemical shifts* are given in ppm from tetramethylsilane as an internal standard.

Chromatographic separations were performed using 50 parts (w/w) of Merck silica gel (0.04-0.063 μ). Pyridine and dichloromethane were dried prior to use by standing over KOH and 3A molecular sieves respectively.

tert-Butyl 7β-[2-(2-tritylaminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido] -3-phenylthio-4-hydroxy-1-dethia-2-thiacepham-4-carboxylate *(8a)*

A solution of t-butyl diazopyruvate 9[9] (0.15 g, 1 mmol) in dichloromethane (0.5 ml) was stirred *under* N_2 at room temperature and a solution of freshly prepared phenylsulfenyl chloride 10 (0.17 g, 1 mmol) in dichloromethane (2 ml) was added dropwise over 5 min. The stirring was continued until nitrogen evolution ceased (about 15 min) and the reaction mixture was diluted with dichloromethane (5 ml). Solid mercaptomethylazetidinone 3[6] was added (0.56 g, 1 mmol) followed by triethylamine (0.1 g, 1 mmol). The stirring was continued for 30 min and the reaction mixture was successively washed with water, brine, dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography ($CHCl_3$-acetone 8:2) to give 8a (545 mg, 67 %) as a major compound containing *some minor isomer* : ^{1}H-Nmr(90 MHz)($CDCl_3$), δ: 1.53 (s,9H, t-Bu), 2.50-3.10 (m, 2H, S-CH_2), 4.03 (s, 3H, OCH_3), 4.20-4.40 (m, 1H, H-6), 4.55 (s, 1H,H-3), 4.90-5.00 (m, 1H, H-7), 6.52 (s, 1H, H-thiazole), 7.2-7.6 (m, 20H, aromatics) ; ir : ($CHCl_3$) 3570, 3490, 3410, 1770, 1740, 1675, 1598, 1585, 1530, 1495, 1480, 1373, 1158, 1050 cm^{-1} ; Anal. Calcd for $C_{42}H_{41}N_5O_6S_3$: C, 62.4 ; H, 5.1 ; N, 8.7 ; S, 11.9 ; Found: C, 62.2 ; H, 5.2 ; N, 8.8 ; S, 11.8

tert-Butyl 7β-[2-(2-tritylaminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido] -3-(4-methoxyphenylthio)-4 hydroxy-1-dethia-2-thiacepham-4-carboxylate (8b)

This compound was prepared in the same way as 8a using a slight excess (1.1 equiv) of 4-methoxyphenylsulfenyl chloride [16] 10b, to give 75 % of 8b without chromatography. After recrystallization of the crude product from ether, 8b was obtained as a single isomer. ^{1}H-Nmr (90 MHz) ($CDCl_3$), δ : 1.60 (s, 9H, t-Bu) 3.81 (s, 3H, CH_3O-), 3.84 (s, 1H, 3-H), 3.96 (s, 3H, CH_3-O-N), 4.94 (dd, J = 5Hz , 6Hz, 1H, H-7), 6.43 (s, 1H, H-thiazole), 7.28 (bs, 15H, trityl), 6.83-6.93 and 7.44-7.54 (m, 4H, aromatics) ; ir ($CHCl_3$) 3600, 3400, 2840, 1770, 1738, 1680, 1590, 1527, 1520, 1490, 1160, 1050 cm^{-1}. FAB-MS m/z : 838 $(M+H)^+$

tert-Butyl 7β-[2-(2-tritylaminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido] -3-(4-nitrophenylthio)-4-hydroxy-1-dethia-2-thiacepham-4-carboxylate (8c)

To a suspension of N-chlorosuccinimide (13.4 g, 0.1 mol) in benzene (80 ml) at 0-5°C 4-nitrothiophenol (15.5 g, 0.1 mmol) was added over 30 min and the suspension was stirred overnight. The reaction mixture was filtered and evaporated. A solution of this crude 4-nitrophenylsulfenyl chloride (1.33 g, ∿7 mmol) in dichloromethane (15 ml) was added dropwise under nitrogen to a stirred solution of t-butyl diazopyruvate 9 (0.8 g, 4.7 mmol) in dichloromethane (15 ml) at 0-5°C over 15 min. The stirring was maintained at room temp. for 30 min and 4-mercaptomethylazetidinone 3[6] (2.62 g, 4.7 mmol) and triethylamine (0.7 ml, 5 mmol) *were added. After 1 h the reaction mixture* was washed successively with 0.1N HCl, saturated $NaHCO_3$ solution, brine, dried over $MgSO_4$ and evaporated. Column chromatography ($CHCl_3$-acetone 9:1) afforded 2.5 g (62.5 %) of 8c containing one major *diastereoisomer* ^{1}*H-nmr*(90 MHz) ($CDCl_3$), δ : 1.47 (s, 9H, t-Bu), 4.06 (s, 3H, CH_3O), 4.62 (s, 1H, H-3), 4.97 (t, J =6Hz, 1H, H-7), 6.60 (s, 1H, H-thiazole), 7.30 (bs, 15H, trityl), 7.54-7.64 and 8.11-8.21 (m, 4H, aromatics) ; ir ($CHCl_3$) 3600, 3410, 2825, 1772, 1740, 1672, 1598, 1580, 1520, 1495, 1370, 1340, 1152, 1050, 850 cm^{-1}.

tert-Butyl 7β-[2-(2-tritylaminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido] -3-[(1-methyltetrazol-5-yl)thio]-4-hydroxydethia-2-thiacepham-4-carboxylate (8d)

A solution of chlorine (124 mg, 7.75 mmol) in CCl_4 (0.98 ml) was added over 5 min to a cooled suspension (-20°C) of bis-(1-methyltetrazol-5-yl)disulfide (437 mg, 3.9 mmol) in dichloromethane chloride (7.5 ml). The temperature was allowed to rise to 0°C over 10 min. After an additional 5 min, a solution of t-butyl diazopyruvate (596 mg, 3.5 mmol) in dichloromethane (5 ml) was added dropwise, leading to nitrogen evolution and discoloration of the *yellow sulfenyl chloride solution*. After further stirring (15 min at 0°C and 30 min at room temp. a solution of 4-mercaptomethylazetidinone 3 (2.16 g, 3.5 mmol) in methylene chloride (10 ml) was added, followed by triethylamine (0.61 ml, 4.37 mmol) and the reaction mixture was stirred at room temp. for 3 h. The insoluble was removed by filtration and the solute was washed successively with 0.1 N HCl and water, dried over $MgSO_4$ and evaporated under reduced pressure. The crude product (2.67 g) was purified by column chromatography (CH_2Cl_2-AcOEt, 3:1) to give 8d (1.39 g, 48.8 %), mp 210°C (decomp). ^{1}H-Nmr (90MHz)($CDCl_3$), δ : 1.51 (s, 9H, CO_2t-Bu), 2.55-3.33 (m, 2H, CH_2S), 3.95 (s, 3H, CH_3-tetrazole), 4.10 (s, 3H, OCH_3), 5.03 (m, 1H, H-7) 5.54 (s, 1H, H-3), 6.46 (s, 1H, H-thiazole), 7.28 (bs, 15H, trityl); ir : ($CHCl_3$) 3400, 2830, 1772, 1730, 1680, 1585, 1530, 1495, 1370, 1150, 1040 cm^{-1} ; uv (EtOH, HCl N/10) : 278 nm (ε = 14650). Anal.Calcd for $C_{38}H_{39}N_9O_6S_3$: C, 56.07 ; H, 4.83 ; N, 15.49 ; S, 11.82 ; Found : C, 56.2 ; H, 4.9 ; N, 14.6 ; S, 11.2.

tert-Butyl 7β-[2-(2-tritylaminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido] -3-[(5-methyl-1,3,4-thiadiazol-2 yl)thio]-4-hydroxy-1-dethia-2-thiacepham-4-carboxylate (8e)

A solution of chloropyruvate 11e (493 mg, 1.6 mmol), 4-mercaptomethylazetidinone 3[6] (685 mg, 1.23 mmol) and triethylamine (0.26 ml, 1.85 mmol) in dichloromethane (10 ml) was stirred at room temp. for 2 h. The reaction mixture was filtered, washed successively with 1 N HCl, saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$ and evaporated. Column chromatography (CH_2Cl_2-acetone 85:15) yielded two diastereoisomers in 65 % yield.

Major isomer : 605 mg (59.3 %), ^{1}H-nmr (250 MHz)($CDCl_3$), δ : 1.49 (s, 9H, t-Bu), 2.75, (s, 3H, CH_3-C), 4.11 (s, 3H, CH_3O), 5.01 (t, J = 5Hz, 1H, H-7), 5.61 (s, 1H, H-3), 6.36 (bs, 1H, H-thiazole), 7.21 (bs, 15H, trityl); ir : ($CHCl_3$) : 3480, 1771, 1740, 1680, 1372, 1154 cm^{-1}. Anal. Calcd for $C_{39}H_{39}N_7O_6S_4$: C, 56.4 ; H, 4.7 ; N, 11.8 ; S, 15.5. Found : C, 56.6 ; H, 4.6 ; N, 11.5 ; S, 15.2.

Minor isomer : 59 mg, 5.7 %, ^{1}H-nmr (90 MHz)($CDCl_3$), δ : 1.54 (s, 9H, t-Bu), 2.74 (s, 3H, CH_3-C), 4.13 (s, 3H, CH_3O), 5.12-5.25 (m, 1H, H-7), 5.35 (s, 1H, H-3), 6.73 (s, 1H, H-thiazole), 7.31 (bs, 15H, trityl).

tert-Butyl 7β-[2-(2-tritylaminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido] -3-(4-nitrobenzylthio)-4-hydroxy-1-dethia-2-thiacepham-4-carboxylate (8h)

A 1.1 M solution of chlorine in CCl_4 (2.5 ml) was added dropwise over 2 min to a stirred suspension of bis-4-nitrobenzyldisulfide (925 mg, 2.75 mmol) in dry dichloromethane (10 ml). After 10 min of stirring a yellow solution was obtained which was added dropwise to a solution of t-butyl diazopyruvate 9 (1.12 g, 6.6 mmol) in dichloromethane (5 ml). After a further 30 min a suspension of 4-mercaptomethylazetidinone 3 (1.22 g, 2.2 mmol) in dichloromethane (10 ml) and a solution of triethylamine (0.77 ml, 4.4 mmol) in dichloromethane (4 ml), were added simultaneously over a 20 min period. After 30 min of additional stirring the reaction mixture was washed successively with 0.1 N HCl, saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$ and evaporated. Column chromatography (CH_2Cl_2-acetone 9:1) *yielded 1.16 g (61 %) of* 8h *as a 4:1 mixture of diastereoisomers*, ^{1}*H-nmr* (90 MHz)($CDCl_3$), δ : 1.47 and 1.56 (2 x s, 9H, t-Bu), 3.88-4.44 (m, 6H, CH_3O + S-CH_2-ϕ+H-3), 4.88-5.02 and 5.13-5.26 (m, 1H, H-7), 6.71 (s, 1H, H-thiazole), 7.31 (bs, 15H, trityl), 7.43-7.53 and 8.14-8.24 (m, 4H, aromatics) ; ir : ($CHCl_3$) 3565, 3490, 3407, 1771, 1738, 1681, 1347 cm^{-1}.

tert-Butyl 7β-[2-(2-tritylaminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido] -3-[(tert-butoxycarbonylmethyl)thio]-4-hydroxy-1-dethia-2-thiacepham-4-carboxylate (8i)

t-Butylmercaptoacetate [17] (1.48 g, 10 mmol) was dissolved in carbon tetrachloride (3 ml) and was added under nitrogen to a stirred suspension of N-chlorosuccinimide [18] (1.47 g, 11 mmol) in CCl_4 (6 ml) over 1 h. The stirring was continued for additional 10 min and the reaction mixture was cooled down to -10°C. *A solution of t-butyldiazopyruvate* 9 *(1.7 g, 10 mmol) in dichloromethane* (5 ml) was added dropwise. The suspension was stirred at room temp. for 20 min and filtered. Mercaptomethylazetidinone 3 (2.78 g, 5 mmol) and triethylamine (1.68 ml, 12 mmol) in dichloromethane (20 ml) were added. The mixture was stirred for 1 h, filtered, washed successively with 1N HCl, saturated $NaHCO_3$ solution, brine, dried over $MgSO_4$ and evaporated. Chromatographic purification (CH_2Cl_2-acetone 9:1) afforded 8i (1.07 g, 25.3 %) as a major isomer containing a small quantity of an other diastereoisomer, ^{1}H-nmr (250MHz)($CDCl_3$), δ : 1.47 (s, 9H, S-C-CO_2tBu), 1.59 (s, 9H, O-C-CO_2tBu), 2.62 and 2.96 (m, 2H, CH_2-S cyclic), 3.31 and 3.38 (AB system, J = 15Hz, 2H, S-CH_2-CO_2), 4.07 (s, 3H, CH_3O), 4.52 (s, 1H, H-3), 4.96 (dd, J = 5Hz, 6Hz, 1H, H-7), 6.55 (s, 1H, H-thiazole), 7.29 (s, 15H, trityl) ; ir : ($CHCl_3$) 3560, 3404, 2820, 1770, 1734, 1680, 1598,; 1585, 1527, 1492, 1370, 1155 cm^{-1} ; FAB-MS m/z : 846 $(M+H)^+$.

tert-Butyl 7β-[2-(2-tritylaminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido]-3-[2-tert-butoxycarbonylaminoethyl)thio]-4-hydroxy-1-dethia-2-thiacepham-4-carboxylate (8j)

A solution of BOC-2-aminoethylsulfenyl chloride was prepared from the corresponding disulfide and chlorine according to the conditions described for the preparation of 8d and 8h. To this freshly prepared solution (4.5 mmol in theory) was added dropwise, at 5°C, a solution of t-butyl diazopyruvate (783 mg, 4.6 mmol) in dichloromethane (10 ml). The reaction is monitored by the nitrogen evolution. After it ceased, the temperature was allowed to rise to room temp. and 4-mercaptomethylazetidinone 3 (2.54 g, 4.6 mmol) was added at once, followed by triethylamine (0.8 ml, 5.75 mmol). After 15 min, the reaction mixture fluidified distinctly and after an additional hour, the insoluble material was removed by filtration, the filtrate was washed successively with 0.1 N HCl (50 ml) and water, dried over $MgSO_4$ and evaporated under reduced pressure. The crude product (3.85 g) was purified by column chromatography (CH_2Cl_2-AcOEt, 3:1) to give 8j (2.07 g, 51.3 %), mp 210°C (decomp.). ^{1}H-Nmr (90 MHz)($CDCl_3$), δ : 1.43 (s, 9H, t-Bu of BOC), 1.60 (s, 9H, CO_2-t-Bu) 2.45 to 3.50 (m, 6H, CH_2S and CH_2N), 4.11 (s, 3H, OCH_3), 4.37 (s, 1H, H-3), 4.97 (dd, J = 4.5 and 6Hz, 1H, H-7), 6.72 (s, 1H, H-thiazole), 7.31 (bs, 15H, trityl), ir : ($CHCl_3$) 3560, 3450, 3410, 3090, 3060, 2820, 1772, 1732, 1710, 1690, 1596, 1585, 1510, 1499, 1370, 1169, 1165, 1043 cm^{-1}, uv (EtOH, HCl N/10) 278 nm (ε = 14100). Anal. Calcd for $C_{43}H_{50}N_6O_8S_3$: C, 59.02 ; H, 5.76 ; N, 9.60 ; S, 10.99 Found : C, 59.2 ; H, 5.8 ; N, 9.5 ; S, 10.7

tert-Butyl 2-oxo-3-chloro-3-[(5-methyl-1,3,4-thiadiazol-2-yl)thio]propanoate (11e)

5-methyl-4-mercapto-1,3,4-thiadiazole (1.32 g, 10 mmol) was added under nitrogen to a stirred suspension a N-chlorosuccinimide (1.34 g, 10 mmol) in benzene (25 ml) below 10°C over 10 min. The mixture was stirred at 7°C for 15 min and a solution of t-butyldiazopyruvate 9 (1.7 g, 10 mmol) in dichloromethane (5 ml) was added dropwise over 10 min. The stirring was maintained at room temp. for 1 h. The reaction mixture was filtered, evaporated and the product was purified by column chromatography (CH_2Cl_2-acetone 8.7:1.3) to give 11e (820 mg, 26.5 %) as a yellow oil which exists as a mixture of tautomers. ^{1}H-Nmr (60 MHz)($CDCl_3$), δ : 1.53 and 1.60 (2 x s, 9H, t-Bu), 2.80 (s, 3H, CH_3), 6.21 and 6.86 (2 x s, 1H, CH + OH ?) ; ir : ($CHCl_3$) 3540, 3490, 1755, (sh), 1740, 1730 (sh), 1370, 1152 cm^{-1} ; uv : (EtOH) 230 nm, (sh), 263 nm, (ε = 5850) ; FD-MS m/z : 308 (M^+), EI - MS (m/z, %) : 252 (5), 234 (13), 207 (86), 180 (20), 145 (57), 132 (27), 57 (100).

General method for the dehydration of the cyclic aminals 8 and 18

The tertiary alcohol 8 was dissolved under nitrogen in 10 volumes of dry pyridine, 1.2-2.0 molar equivalents of P_2I_4 were added and the reaction mixture was stirred until disappearance of the starting material according to TLC (1-2h). The suspension was diluted with ethyl acetate, filtered and concentrated to remove the major part of the pyridine. The residue was diluted with ethyl acetate, washed with 0.1 N HCl until complete elimination of the pyridine, washed with saturated $NaHCO_3$ solution, brine, dried over magnesium sulfate and evaporated. Purification of the residue by column chromatography (CH_2Cl_2-acetone 95:5) and recrystallization from ether afforded the desired product.

tert-Butyl 7β-[2-(2-tritylaminotniazol-4-yl)-(Z)-2-methoxyiminoacetamido] -3-phenylthio-1-dethia-2-thia-3-cephem-4-carboxylate (12a)

P_2I_4 : 1 molar equivalent, yield : 40 %, mp 200-203°C (decomp.), ^{1}H-nmr (90 MHz)($CDCl_3$), δ : 1.53 (s, 9H, t-Bu), 2.90-3.00 (m, 2H, S-CH_2), 4.11 (s, 3H, OCH_3), 5.30-5.50 (m, 1H, H-7), 6.59 (s, 1H H-thiazole), 7.30-7.60 (m, 20H, aromatics), ir : ($CHCl_3$) 3405, 1773, 1713, 1682, 1596, 1582, 1525, 1492, 1480, 1370, 1155, 1050, 1040 cm^{-1}, uv : (EtOH) 235 nm (ε = 32400) and 310 nm (ε = 17100). Anal. Calcd for $C_{42}H_{39}N_5O_5S_3$: C, 63.8 ; H, 5.0 : N, 8.9 ; S, 12.2. Found : C, 63.5 ; H, 5.0 ; N, 8.7 , S, 12.1.

tert-Butyl 7β-[2-(2-tritylaminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido] -3-(4-methoxyphenylthio)-1-dethia-2-thia-3-cephem-4-carboxylate (12b)

P_2I_4 : 1.3 molar equivalents, yield : 43 %, ^{1}H-nmr (90 MHz)($CDCl_3$), δ : 1.57 (s, 9H, t-Bu), 2.82-2.94 (m, 2H, S-CH_2), 3.82 (s, 3H, CH_3O), 4.03 (s, 3H, CH_3ON=), 5.40 (t, J = 6Hz, 1H, H-7), 6.66 (s, 1H, H-thiazole), 6.83-6.92 (m, 2H, H-aromatic) 7.30 (bs, 15H, trityl), 7.44-7.53 (m, 2H, H-aromatic), ir : ($CHCl_3$) 3405, 2860, 2820, 1770, 1710, 1680, 1592, 1582, 1520, 1495, 1370, 1155, 1140, 1045, 831 cm^{-1}, uv : (EtOH) 238 nm (ε = 36600) and 315 nm (ε = 17600) FAB-MS m/z : 820 $(M+H)^+$

tert-Butyl 7β-[2-(2-tritylaminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido] -3-(4-nitrophenylthio)-1-dethia-2-thia-3-cephem-4-carboxylate (12c)

P_2I_4 : 1.5 molar equivalents, yield : 29 %, ^{1}H-nmr (90 MHz)($CDCl_3$),δ : 1.46 (s, 9H, t-Bu), 3.05-3.14 (m, 2H, S-CH_2), 4.06 (m, 1H, H-6), 4.06 (s, 3H, CH_3O), 5.46 (t, J = 5Hz, 1H, H-7), 6.63 (s, 1H, H-thiazole), 7.30 (bs, 15H, trityl) 7.44-7.54 (m, 2H, H-aromatic), 8.11-8.21 (m, 2H, H-aromatic) ; ir : ($CHCl_3$),3410, 2820, 1780, 1720, 1682, 1600, 1583, 1520, 1495, 1370, 1340, 1155, 1040, 852 cm^{-1}, uv : (EtOH, HCl N/10) 292 nm (ε = 23400) and 320-325 nm (ε = 18000). When using crude 8c for the reaction, 12c was obtained in 20.6 % yield, along with 6 % of 13 : ^{1}H-Nmr (90 MHz)($CDCl_3$), δ : 1.52 (s, 9H, t-Bu), 2.94-3.04 (m, 2H, S-CH_2), 4.00 (m, 1H, H-6), 4.06 (s, 3H, CH_3O), 5.58 (dd, J = 5Hz, 6Hz, 1H, H-7), 6.64 (s, 1H, H-thiazole), 6.92 (s, 1H, H-3), 7.31 (bs, 15H, trityl) ; ir ($CHCl_3$) : 3410, 1775, 1706, 1680, 1590, 1527, 1515, 1491, 1370, 1041 cm^{-1} ; FD-MS m/z : 682 (M^+).

tert-Butyl 7β-[2-(2-tritylaminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido] -3-[(1-methyltetrazol-5-yl)thio]-1-dethia-2-thia-3-cephem-4-carboxylate (12d)

P_2I_4 : 2 molar equivalents, yield : 32 %, ^{1}H-nmr ($CDCl_3$, 90 MHz) 1.55 (s, 9H, CO_2t-Bu), 3.03-3.12 (m, 2H, CH_2S) 4.05 (s, 3H, CH_3 tetrazole) 4.13 (s, 3H, OCH_3) 5.45 (t, J = 6Hz, 1H, H-7) 6.66 (s, 1H, H-thiazole), 7.30 (bs, 15H, trityl), ir : ($CHCl_3$) 3405, 2825, 1779, 1725, 1682, 1595, 1585, 1530, 1520, 1495, 1370, 1152, 1040 cm^{-1}, uv : (EtOH) 230 nm (ε = 29400) (sh) and 310nm (ε = 15400).

tert-Butyl 7β-[2-(2-tritylaminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido] -3-[(5-methyl-1,3,4 thiadiazol-2-yl)thio]-1-dethia-2-thia-3-cephem-4-carboxylate (12e)

P_2I_4 : 3 molar equivalents, yield : 26.7 %, ^{1}H-nmr (90 MHz)($CDCl_3$), δ : 1.52 (s, 9H, t-Bu), 2.75 (s, 3H, CH_3-C), 3.06-3.12 (m, 2H, S-CH_2), 4.08 (s, 3H, CH_3-O), 4.11 (m, 1H, H-6), 5.40-5.50 (m, 1H, H-7), 6.67 (s, 1H, H-thiazole), 7.28 (bs, 15H, trityl) ; ir : ($CHCl_3$) 3405, 2820, 1779, 1718, 1681, 1600, 1585, 1515, 1493, 1429, 1370, 1155, 1040 cm^{-1}, uv (EtOH) 235 nm (sh) (ε = 30800) and 310 nm (ε = 15700). The reaction also yielded 4.5 % of 13.

tert-Butyl 7β -[2-(2-tritylaminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido] -3-(4-nitrobenzylthio)-1-dethia-2-thia-3-cephem-4-carboxylate (12h)

P_2I_4 : 2 molar equivalents, yield : 37.5 %, ^{1}H-nmr (90 MHz)($CDCl_3$),δ : 1.53, (s, 3H, t-Bu), 3.00-3.06 (m, 2H, CH_2-S), 4.07-4.15 (m, 5H, OCH_3 and -S-CH_2), 5.33-5.45 (m, 1H, H-7), 6.66 (s, 1H, H-thiazole), 7.90, (bs, 15H, trityl), 6.72-6.80 and 7.32-7.40 (m, 4H, H-aromatic). Anal. Calcd for $C_{43}H_{40}N_6O_7S_3$: C, 60.8 ; H, 4.8 ; N, 9.9 ; S, 11.3. Found C, 60.6 ; H, 4.8 ; N, 10.0; S, 11.2 FAB-MS m/z : 849 $(M + H)^+$. The reaction also yielded 5.5 % of 13.

tert-Butyl 7β-[2-(2-tritylaminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido]-3-[(tert-butoxycarbonylmethyl)thio] -1-dethia-2-thia-3-cephem-4-carboxylate (12i)

P_2I_4 : 2 molar equivalents, yield : 47.2 %, ^{1}H-nmr (250 MHz)($CDCl_3$), δ : 1.46 (s, 9H, S-C-CO_2t-Bu), 1.54 (s, 9H, 4-CO_2t-Bu), 3.00-3.15 (m, 2H, S-CH_2) 3.53 and 3.63 (AB, syst. J = 15 Hz, 2H, CH_2-CO_2), 4.10 (s, 3H, CH_3O), 5.40 (m, 1H, H-7), 6.70 (s, 1H, H-thiazole), 7.30 (bs, 15H, trityl), uv : (EtOH) 233 nm (sh) (ε = 28700) and 309 nm (ε = 15600)

tert-Butyl 7β-[2-(2-tritylaminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido]-3-[2-(tert-butoxycarbonylaminoethyl)thio]-1-dethia-2-thia-3-cephem-4-carboxylate (12j)

P_2I_4 : 2 molar equivalents, yield : 37 %, ^{1}H-nmr ($CDCl_3$, 250 MHz), δ : 1.43 (s, 9H, t-Bu of BOC), 1.54 (s, 9H, t-Bu of ester) 2.08-3.45 (m, 6H, CH_2N and 2 CH_2S), 4.05 (s, 3H, OCH_3), 5.47 (m, 2H, H7 and NH), 6.60 (s, 1H, H-thiazole), 7.30 (bs, 15H, trityl), ir : ($CHCl_3$) : 3450, 3410, 2830, 1772, 1705, 1695, 1595, 1565, 1525, 1510, 1495, 1370, 1156, 1048 cm^{-1}, uv : (EtOH) 230 nm (sh) (ε = 28800) and 304 nm (ε = 15500).

tert-Butyl 7β-[2-(2-aminothiazol-4 yl)-(Z)-2-methoxyiminoacetamido] -3-phenylthio-1-dethia-2-thia-3-cephem-4-carboxylate (14a)

A solution of 12a (200 mg, 0.25 mmol) in 66 % aqueous formic acid (5 ml) was stirred at room temp. *for 1 h. The precipitate was filtered off and the solution was evaporated under reduced pressure* below 30°C. The residue was recrystallized from ether to give 110 mg (82 %) of 14a : ^{1}H-Nmr (60 MHz) ($CDCl_3$), δ : 1.53 (s, 9H, t-Bu) 2.90-3.60 (m, 2H, S-CH_2), 3.91 (s, 3H, OCH_3), 4.16 (m, 1H, H-6), 5.72 (dd, J = 5Hz, 8Hz, 1H, H-7) 6.80 (s, 1H, H-thiazole), 8.40 (d, J = 8Hz, 1H, CONH), 7.30-7.70 (m, 5H, aromatics), ir ($CHCl_3$) 3487, 3400, 3310, 3200, 1767, 1710, 1677, 1621, 1605, 1580, 1545, 1530, 1472, 1370, 1155, 1050 cm^{-1}.

tert-Butyl 7β[2-(2-aminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido] -3-(4-methoxyphenylthio)-1-dethia-2-thia-3-cephem-4-carboxylate (14b)

12b (810 mg, 0.99 mmole) was dissolved in 66 % aqueous formic acid (10 ml) at room temp. A few drops of chloroform were added to facilitate solubilization, and the reaction mixture was stirred at room temp. for 1 h. The suspension formed was filtered and the solution was evaporated under reduced pressure to give a residue which was recrystallized from ether, yielding 516 mg (90 %) of 14b. ^{1}H-Nmr (90 MHz) ($CDCl_3$), δ : 1.46 (s, 9H, t-Bu), 3.76 and 3,81 (s, 2 x 3H, OCH_3), 5.60 (dd, J = 5Hz, 9Hz, 1H, H-7), 6.77 (s, 1H, H-thiazole), 6.91-7.00 and 7.40-7.48 (m, 4H, aromatics), 9.13 (d, J = 5Hz, 1H, NH); ir : (Nujol) 1753, 1678, 1652, 1590, 1580, 1530, 1507, 1495 cm^{-1}, uv (EtOH) 236 nm (ε = 28700) and 310nm (ε = 16900), FAB-MS m/z : 578 $(M+H)^+$.

7β-[2-(2-Aminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido] -3-phenylthio-1-dethia-2-thia-3-cephem-4-carboxylic acid (15a)

The ester 14 (168 mg, 0.31 mmol) was added to a solution of trifluoroacetic acid (0.8 ml) and dichloromethane (0.2 ml) at -20°C and stirred at -20°C for 1 h and at 0°C for another hour. A strong stream of dry nitrogen was passed through the flask to evaporate the solution, keeping the temperature at 0°C. The residue was stirred with diisopropyl ether, filtered and recrystallized from ethanol : ethyl acetate containing 3 drops of pyridine. The crystalline compound was further purified by column chromatography (CH_2Cl_2-methanol 7:3) and recrystallized from CH_2Cl_2-methanol to give 55 mg (36 %) of 15a. mp : 190-200°C (decomp.) ; ^{1}H-nmr (90 MHz)(DMSO-d_6), δ : *3.83 (s, 3H, OCH_3) 5.64 (dd, J = 5Hz, 10Hz, 1H, H-7), 6.81 (s, 1H, H-thiazole),* 7.40 (bs, 5H, aromatics), 9.20 (d, 1H, J = 10Hz, CONH), ir (Nujol) 1757, 1667, 1580, 1535 cm^{-1}, uv : (EtOH) 304 nm (ε = 15400), FAB-MS m/z : 492 $(M+H)^+$.

7β-[2-(2-Aminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido] -3-(4-methoxyphenylthio)-1-dethia-2-thia-3-cephem-4-carboxylic acid (15b)

14b (108 mg, 0.19 mmol) was dissolved in 66 % aqueous formic acid (2 ml) and heated at 50°C for 3 h. The solution was evaporated and the compound was recrystallized from ether to give 80 mg (82 %) of 15b mp 185-190°C (decomp). ^{1}H-Nmr (90 MHz) (DMSO-d_6), δ : 3.78 and 3.81 (s, 2 x 3H, OCH_3), 5.58 (dd, J = 5Hz, 9Hz, 1H, H-7), 6.78 (s, 1H, H-thiazole), 7.16 (bs, 2H, NH_2), 9.17 (d, J = 9Hz, 1H, NH), 6.92-7.02 and 7.41-7.50 (m, 4H, aromatics), ir (Nujol) 1767, 1658, 1635, 1592, 1590, 1570, 1247, 816 cm^{-1}, uv (EtOH, HCl N/10) 242 nm (ε = 23900) and 316 nm (ε = 14500), Anal. Calcd for $C_{20}H_{10}N_5O_6S_3$: C, 46.1 ; H, 3.7 ; N 13.5 ; S, 18.4 ; Found : C, 46.1 ; H, 3.8 ; N, 13.1 ; S, 18.1.

General method for one step deprotection of 12c-j

12 was dissolved in 10 volumes of 66 % aqueous formic acid, and heated at 60°C until the reaction was complete (followed by tlc, EtOAc-EtOH-H_2O, 7:2:1 ; 2-4 h). The triphenylcarbinol formed was filtered off and the solution was evaporated under reduced pressure to dryness. The residue was triturated with a mixture of dichloromethane-methanol followed by ether and isolated by filtration to give 15c-h.

7β-[2-(2-Aminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido] -3-(4-nitrophenylthio)-1-dethia-2-thia-3-cephem-4-carboxylic acid (15c)

Reaction time : 4 h, yield : 62 %, mp : 190-200°C (decomp), ^{1}H-nmr (90 MHz) (DMSO-d$_6$),δ : 3.86 (s, 3H, OCH$_3$), 4.22 (m, 1H, H-6), 5.74 (dd, J = 5Hz, 9Hz, 1H, H-7) 6.83 (s, 1H, H-thiazole), 7.22 (bs, 2H, NH$_2$), 7.51-7.61 and 8.16-8.26 (m, 4H, aromatics), 9.24 (d, J = 9Hz, 1H, NH), ir (Nujol) 1769, 1669, 1630, 1595, 1574, 1538, 1515, 1041, 852 cm^{-1}, uv (EtOH, HCl N/10) 222 nm (ε = 21800) and 290 nm (ε = 19700), FAB-MS m/z : 537 (M+H)$^+$.

7β-[2-(2-Aminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido] -3-[(1-methyltetrazol-5-yl)-thio]-1-dethia-2-thia-3-cephem-4-carboxylic acid (15d)

Reaction time : 7 h, yield : 83 %. ^{1}H-Nmr (90 MHz)(DMSO-d$_6$), δ : 3.83 (s, 3H , OCH$_3$), 4.10 (s, 3H, N-CH$_3$), 5.64 (dd, J = 5 and 8 Hz, 1H, H-thiazole), ir (Nujol) 1768, 1665, 1635, 1535, 1040 cm^{-1}, uv (EtOH) 231 nm (ε = 20100) and 305 nm (ε = 14400).

7β-[2-(2-Aminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido]-3-[(5-methyl-1,3,4-thiadiazol-2-yl)-thio]-1-dethia-2-thia-3-cephem-4-carboxylic acid (15e)

Reaction time : 3.5 h, yield : 77.4 %. ^{1}H-Nmr (90 MHz) (DMSO-d$_6$), δ : 2.72 (s, 3H, CH$_3$-O-C), 3.20 (m, 2H, CH$_2$-S), 3.84 (s, 3H, CH$_3$-O-N), 4.13 (m, 1H, H-6), 5.68 (dd, J = 5Hz, 9Hz 1H, H-7), 6.81 (s, 1H, H-thiazole), 7.22 (bs, 2H, NH$_2$), 9.23 (d, J = 9Hz 1H, NH), ir (Nujol), 1763, 1667, 1615, 1560, 1540, 1520 cm^{-1}, uv (EtOH, HCl N/10) 228 nm (ε = 17500), 262 nm (ε = 16000) 309 nm (sh) (ε = 12900), Anal. Calcd for : $C_{16}H_{15}N_7O_5S_4$: C, 37.4 ; H, 2.9 ; N, 19.0 S, 24.9. Found : C, 37.8 ; H, 3.0 ; N, 18.5 ; S, 23.5, FAB-MS m/z : 514 (M + H)$^+$.

7β-[2-(2-Aminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido] -3-(carboxymethylthio)-1-dethia-2-thia-3-cephem-4-carboxylic acid (15f)

Reaction time : 2.5 h, yield : 46 %. ^{1}H-Nmr (250 MHz)(DMSO-d$_6$), δ : 3.25 (m, 2H, S-CH$_2$), 3.70 (s, 2H, S-CH$_2$-COO), 3.85 (s, 3H, CH$_3$O), 4.00 (m, 1H, H-6), 5.61 (dd, J = 5Hz, 9Hz, 1H, H-7), 6.80 (s, 1H, H-thiazole), 7.20 (s, 2H, NH$_2$), 9.20 (d, J = 9Hz, 1H, NH), ir (Nujol), 1760, 1662, 1640, 1560, 1540, 1150, 1040 cm^{-1}, uv (EtOH, HCl N/10) 266 nm (ε = 14600), 283 nm (ε = 14600), 310 nm (sh) (ε = 10900), FAB-MS m/z : 474 (M + H)$^+$.

7β-[2-(2-Aminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido] -3-[2-(aminoethyl)thio]-1-dethia-2-thia-3-cephem-4-carboxylic acid (15g)

Reaction time : 5 h, yield : 71.6 %. ^{1}H-Nmr (90 MHz)(DMSO-d$_6$), δ : 2.50-3.39 (m, 6H, CH$_2$S and CH$_2$N), 3.85 (s, 3H, OCH$_3$), 5.51 (dd, J = 5 and 8Hz, 1H, H-7) 6.82 (s, 1H, H-thiazole), ir (Nujol) 1769, 1758, 1680, 1639, 1567, 1530 cm^{-1}, uv (EtOH) 298 nm (ε = 15800), FAB-MS m/z : 459 (M+H)$^+$, Anal. Calcd for : $C_{15}H_{15}N_5O_7S_2$: C, 38.0 ; H, 3.2 ; N, 14.8 ; S, 20.3. Found : C, 38.3 ; H, 3.3 ; N, 14.7 ; S, 19.3.

7β-[2-(2-Aminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido] -3-(4-nitrobenzylthio)-1-dethia-2-thia-3-cephem-4-carboxylic acid (15h)

Reaction time : 3 h, yield : 79.4 %. ^{1}H-Nmr (90 MHz)(DMSO-d$_6$),δ : 3.85 (s, 3H, CH$_3$O), 4.00 (m, 1H, H-6), 4.23 (s, 2H, S-CH$_2$-ϕ), 5.60 (dd, J = 5Hz, 9Hz, 1H, H-7), 6.82 (s, 1H, H-thiazole), 7.22 (s, 2H, NH$_2$), 9.21 (d, 9Hz, 1H, NH) 8.15-8.24 and 7.54-7.63 (d, J = 8Hz, 2 x 2H, aromatics), ir (Nujol) 1765, 1700, 1648, 1640, 1605, 1595, 1570, 1540, 1520, 1494, 1344, 1047 cm^{-1}, uv (EtOH, HCl N/10) 271 nm (ε = 26200) and 314 nm (sh) (ε = 14300), Anal. Calcd for : $C_{20}H_{18}N_6O_7S_3$: C, 43.6; H, 3.3; N, 15.3; S, 17.5. Found : C, 43.3; H, 3.2; N, 15.0; S, 17.1.

7β-[2-(2-Aminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido] -3-phenylthio-1-dethia-2-thia-3-cephem (16)

12a (400 mg, 0.50 mmol) was dissolved in trifluoroacetic acid (2 ml) and was left to stand at room temp. for 20 min. The acid was evaporated under reduced pressure. The residue was chromatographed (CH_2Cl_2 - MeOH 98:2) and the product was triturated with ether to give 60 mg (24 %) of 16. ^{1}H-Nmr (90 MHz) (DMSO-d_6), δ : 3.10 (m, 2H, S-CH_2), 3.87 (s, 3H, OCH_3), 5.59 (d, d, J = 5Hz, 9Hz, 1H, H-7), 6.82 (s, 1H, H-thiazole), 7.22 (s, 2H, NH_2), 7.37 (s, 1H, H-4), 7.20-7.40 (m, 5H, aromatics), 9.20 (d, J = 9Hz, 1H, NH), ir (Nujol) 3427, 3220, 1750, 1688, 1670, 1655, 1619, 1582, 1537, 1051, 1035 cm^{-1}, uv (EtOH) 236 nm (ε = 23700) and 295 nm (ε = 19600), FD-MS m/z : 447 (M^+), EI-MS (m/z, %) 447 (20), 240 (20), 218 (100), 209 (37), 208 (36), 110 (85), 109 (84).

(6S, 7S)-tert-Butyl 7β-phthalimido-3β-phenylthio-4α-hydroxy-1-dethia-2-thia-cepham-4-carboxylate (18a)

To a stirred solution of diphenyldisulfide (1.22 g, 5.6 mmol) in dichloromethane (12 ml) sulfuryl chloride (0.42 ml, 5.2 mmol) was added dropwise at 0-5°C and the stirring was maintained for 20 min. A solution of t-butyldiazopyruvate 9 (1.9 g, 11.2 mmol) in dichloromethane (5 ml) was added over a 5 min period and the stirring was continued at 5°C. When the nitrogen evolution ceased (∿ 10 min) mercaptomethylazetidinone 17 (2.1 g, 8 mmol) [6b] and triethylamine (1.46 ml, 10.4 mmol) were added and the solution stirred at 5°C for 30 min. The reaction mixture was washed successively with 0.1 N HCl, saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$ and evaporated. The crude product was purified by column chromatography (CH_2Cl_2 - EtOAc 9:1) to give 2.2 g (53.6 %) of 18a. ^{1}H-Nmr (400 MHz) ($CDCl_3$), δ : 1.60 (s, 9H, t-Bu) 2.43, (dd, J = 3.5 and 13 Hz, 1H, H-1α), 3.12 (dd, J = 13 and 12Hz, 1H, H-1β), 4.37 (ddd, J = 3.5, 5 and 12 Hz, 1H, H-6) 4.63, (s, 1H, OH), 4.76 (s, 1H, H-3) 5.30 (d, J = 5Hz, 1H, H-7), 7.45 and 7.56 (m, 5H, SPh), 7.76 and 7.87 (m, 4H, phthalimide), ir ($CHCl_3$) 3560, 3480, 1788, 1774, 1736, 1721, 1610, 1580, 1481, 1372 cm^{-1}, uv (EtOH) 220 nm (ε = 52000) and 300 nm (ε = 3100), Anal. Calcd for $C_{25}H_{24}N_2O_6S_2$: C, 58.6 ; H, 4.7 ; N, 5.5 ; S, 12.5. Found : C, 58.9 ; H, 4.7 ; N, 5.3 ; S, 12.3.

(6S, 7S)-tert-Butyl 7β-phtalimido-3-(4-nitrophenylthio)-4-hydroxy-1-dethia-2-thiacepham-4-carboxylate (18b)

The reaction yielded two isomers which were separated by column chromatography (CH_2Cl_2-EtOAc 8:2). Major isomer : yield : 56.9 % ; $[\alpha]_D$ = - 3.5 ± 0.5° (c = 1, CH_2Cl_2). ^{1}H-Nmr (250 MHz) ($CDCl_3$), δ : 1.52 (s, OH, t-Bu), 2.51 (dd, J = 4Hz, 13Hz, 1H, H-1α) and 3.26 (dd, J = 12Hz, 13Hz, 1H, H-1β), 4.40 (ddd, J = 4Hz, 5Hz, 12Hz, 1H, H-6), 4.64 (s, 1H, OH), 4.91 (s, 1H, H-3), 5.35 (d, J = 5Hz, 1H, H-7), 7.63 and 8.21 (m, 4H, aromatics), 7.79 and 7.90 (m, 4H, phthalimide), ir ($CHCl_3$) 3480, 1786, 1766, 1736, 1722, 1610, 1598, 1580, 1520, 1479, 1372, 1342, 1154, 853 cm^{-1}, uv (EtOH) 220 nm (ε = 50600) 323 nm (ε = 12000), Anal. Calcd for $C_{25}H_{23}N_3O_8S_2$: C, 53.8 ; H, 4.2 ; N, 7.5 ; S, 11.5. Found : C, 53.8 ; H, 4.1 ; N, 7.4 ; S, 11.4.

Minor isomer : yield : 9.7 %; $[\alpha]_D$ = - 65.5 ± 2.5° (c = 0.5, CH_2Cl_2). ^{1}H-Nmr (250 MHz) ($CDCl_3$), δ : 1.56 (s, 9H, t-Bu), 2.45 (dd, J = 4Hz, 12,5 Hz, 1H, H-1α), 3.32 (t, J = 12,5 Hz, 1H, H-1β), 4.46 (dt, J = 4.5 Hz, 12.5 Hz, 1H, H-6), 4.81 (s, 1H, H-3), 5.08 (s, 1H, OH), 5.56 (d, J = 5Hz, 1H, H-7), 7.71 (d) and 8.20 (d), 4H aromatics), 7.80 and 7.93 (m, 4H, phthalimide), ir ($CHCl_3$) 3568, 3480, 1786, 1766, 1736, 1722, 1650, 1598, 1520, 1480, 1479, 1372, 1342, 1154, 853 cm^{-1}, uv (EtOH) 240 nm (sh) (ε = 15200) and 332 nm (ε = 11700) ; Anal. Calcd for : $C_{25}H_{23}N_3O_8S_2$: C, 53.8 ; H, 4.1 ; N, 7.4 ; S, : 11.4. Found : C, 53.9 ; H, 4.1 ; N, 7.3 ; S, 11.3.

(6S, 7S)-tert-Butyl 7β-phthalimido-3-phenylthio-1-dethia-2-thia-3-cephem-4-carboxylate (19a)

P_2I_4 : 2 molar equivalents, yield : 49.7 % ; mp 170 °C and 190-195°C. ^{1}H-Nmr (300 MHz) ($CDCl_3$), δ : 1.55 (s, 9H, t-Bu), 2.80 (dd, J = 3Hz, 12Hz, 1H, H-1) 3.41 (dd, J = 10.5 Hz, 12Hz, 1H, H-1β), 4.15 (m, 1H, H-6), 5.79 (d, J = 5Hz, 1H, H-7), 7.35 and 7.52 (m, 5H, phenyl), 7.78 and 7.89 (m, 4H, phthalimide), ir ($CHCl_3$) 1792, 1781, 1773, 1727, 1610, 1582, 1475, 1370 cm^{-1}, uv (EtOH) 221 nm (ε = 56200), 243 nm (sh) (ε = 20300) and 308 nm (ε = 14900), Anal. Calcd for $C_{25}H_{22}N_2O_5S_2$ C, 60.7 ; H, 4.5 ; N, 5.61 ; S, 12.96. Found : C, 60.5 ; H, 4.4 ; N, 5.5 ; S, 12.8 ; FAB-MS m/z : 495 $(M+H)^+$.

(6S-7S)-tert-Butyl 7β-phthalimido-3-(4-nitrophenylthio)-1-dethia-2-thia-3-cephem-4-carboxylate (19b)

Using the major isomer of 18b ; P_2I_4 : 2 molar equivalents, yield 48.8 % ; $[\alpha]_D$ = 365± 5°, (c = 0.7, CH_2Cl_2). ^{1}H-Nmr (90 MHz)($CDCl_3$), δ : 1.48 (s, 9H, t-Bu), 2.91 (dd, J = 3Hz, 12Hz, 1H, H-1α), 3.48 (dd, J = 10Hz, 12Hz, 1H, H-1), 4.27 (m, 1H, H-6), 5.88 (d, J = 6Hz, 1H, H-7), 7.51 and 8.21 (m, 4H, ϕNO_2), 7.84 (m, 4H, phthalimide), ir ($CHCl_3$) 1795, 1784, 1727, 1610, 1596, 1576, 1519, 1475, 1370, 1340, 853 cm^{-1}, uv (EtOH) 221 nm (ε = 78500), 309 nm (ε = 28100) and 320 nm (sh) (ε = 27000), FAB-MS m/z : 540 $(M + H)^+$. Anal. Calcd for $C_{25}H_{21}N_3O_7S_2$: C, 55.6 ; H, 3.9 ; N, 7.8 ; S, 11.9. Found : C, 55.4 ; H, 3.9 ; N, 7.5 ; S, 11.7.

(6S, 7S)-7β-Phthalimido-3-phenylthio-1-dethia-2-thia-3-cephem (21a)

19a (100 mg, 0.20 mmol) was dissolved in trifluoroacetic acid (0.5 ml) and abandoned at room temp. for 1h. The solution was evaporated under reduced pressure, purified by chromatography (CH_2Cl_2 - EtOAc 9:1) and recrystallized from ether to give 50 mg (74 %) of 21a, mp 234°C. ^1H-Nmr (300 MHz) (DMSO-d_6), δ : 3.02 (dd, J = 10.5Hz, 12Hz, 1H, H-1β), 3.25 (dd, J = 3Hz, 12Hz, 1H, H-1α), 4.29 (ddd, J = 3Hz, 5Hz, 10,5Hz, 1H, H-6), 5.88 (d, J = 5Hz, 1H, H-7) 7.34 (m, 5H, ϕ-S), 7.54 (s, 1H, H-4), 7.90 (m, 4H, phthalimide), ir ($CHCl_3$) 1769, 1725, 1609, 1583, 1479 cm^{-1}, uv (EtOH) 220 nm (ε = 56800), 240 nm (sh), (ε = 20300) and 297 nm (ε = 18000), FD-MS m/z : 394 (M^+). Anal. Calcd for $C_{20}H_{14}N_2O_3$: C, 58.6 ; H, 4.7 ; N, 5.4 ; S, 12.5 ; Found : C, 58.9 ; H, 4.7 ; N, 5.3 ; S, 12.3

(6S-7S)-7β-Phthalimido-3-(4-nitrophenylthio)-1-dethia-2-thia-3-cephem (21b)

19b (50 mg, 0.09 mmole) was dissolved in trifluoroacetic acid (0.5 ml) and heated at 60°C for 2 h. The reaction mixture was evaporated under reduced pressure and the product was purified by column chromatography (CH_2Cl_2-EtOAc 9:1) to give 17 mg (42.5 %) of 21b. ^1H-Nmr (300 MHz) ($CDCl_3$),δ: 2.92 (dd, J = 3Hz, 12Hz, 1H, H-1α), 3.32 (dd, J= 10.5 Hz, 12Hz, 1H, H-1), 4.36 (ddd, J = 3Hz, 5Hz, 10.5Hz, 1H, H-6), 5.80 (d, J = 5Hz, 1H, H-7), 7.42 (d, J = 9Hz, 2H, H-2' and H-6' on phenyl) 8.19 (d, J = 9Hz, 2H, H-3' and H-5' on phenyl), 7.46 (s, 1H, H-4), 7.88 (m, 4H, phthalimido).

AKNOWLEDGEMENTS

Mrs N.Dupuy, Miss J. Fabian, Miss C. Lang, D. Jovanovic and R. Smolik are thanked for their participation in the struture determinations.

REFERENCES AND NOTES

1. K.G. Holden, "Chemistry and Biology of β-Lactam Antibiotics", vol. 2, ed. by R.B. Morin and M. Gorman, Academic Press, Inc., London, 1982, pp.99-164.
2. For a review of early methods, see F.A. Jung, W.R. Pilgrim, J. P. Poyser, and P.J. Siret, "Topics in Antibiotic Chemistry", Vol. 4, ed. by P.G. Sammes, Ellis Horwood Publishers, 1980, pp. 89-90.
3. a) D.M. Brunwin, and G. Lowe, J. Chem. Soc., Perkin Trans. I, 1973, 1521.
   b) J.E.T. Corrie, J.R. Hlubeck, and G. Lowe, J. Chem. Soc., Perkin Trans. I, 1977, 1421.
   c) D.B. Bryan, R.F. Hall, K.G. Holden, W.F. Huffmann, and J.G. Gleason, J. Am Chem. Soc, 1977, 99, 2353.
   d) T.W. Doyle, J.L. Douglas, B. Belleau, J. Meunier, and B.Y. Luh, Can. J. Chem., 1977, 55, 2873.
   e) J.L. Douglas, D.E. Horning, and T.T. Conway, Can. J. Chem., 1978, 56, 2879.
   f) T.W. Doyle, J.L. Douglas, B. Belleau, T.T. Conway, C.F. Ferrari, D.E. Horning, G. Lim, B.Y. Luh, A. Martel, M. Menard, and L.R. Morris, Can. J. Chem., 1980, 58, 2508.

g) S.W. Mc Combie, W.A. Metz, and A. Alfonso, Tetr. Lett., 1986, 27, 305.

h) H. Nitta, H. Hatanaka, and T. Ishimaru, J. Chem Soc., Chem. Com., 1987, 51.

4. Sumitomo Chemical Co., Japan Kokai Tokkyo Koho, JP 57,116,091.

5. a) Roussel-Uclaf UK Patent Application, GB 2098 217A.

b) ibid., French Patent FR 2552089.

6. a) Roussel-Uclaf, Belgian patent 894785.

b) Roussel-Uclaf, French patent FR 2538389.

7. All β-lactams are racemic (exept compouds 17 through 21 but only one enantiomer is depicted on the schemes.

8. a) F. Weygand, and H.J. Bestmann, Z. Naturforsch. Teil B, 1955, 10, 296.

b) ibid., Chem. Ber., 1955, 88, 1988.

c) ibid., 1956, 89, 1912. 9. L.G. Mueller, and R.G. Lawton, J. Org. Chem., 1979, 44, 4741.

10. D.N. Harpp, and P. Mathiaparanam, J. Org. Chem., 1972, 37, 1367.

11. E. Kühle, Synthesis, 1970, 56.

12. a) J.N. Denis, S. Desauvage, L. Hevesi, and A. Krief, Tetr. Lett., 1981, 22., 4009.

b) J.N. Denis, W. Dumont, and A. Krief, Tetr. Lett., 1979, 4111.

13. D.A. Konen, P.E. Pfeffer, and L.S. Silbert, Tetrahedron, 1976, 32, 2507.

14. a) T. Endo, H. Fukuda, and H. Hirota, J. Am. Chem. Soc., 1984, 106, 4035.

b) A. Thuillier, and J. Vialle, Bull. Soc. Chim. Fr., 1962, 2182.

15. a) H.H. Huang, and F.A. Long, J. Am. Chem. Soc., 1969, 91, 2872.

b) J.L. Longridge , and F.A. Long, J. Am. Chem. Soc., 1968, 90, 3092.

16. F. Montanari Gazz. Chim. Ital., 1956, 86, 406.

17. H.R. Kriecheldorf, and J. Kaschig, Liebigs Ann. Chem., 1976, 882.

18. The reaction with the ethyl ester was reported by H. Seliger, and H. H. Görtz, Synth. Comm., 1980, 10, 175.

Received, 24th September, 1988