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ENANTIOSELECTIVE SYNTHESIS OF A VERSATILE 2-ISOCEPHEM SYNTHON#

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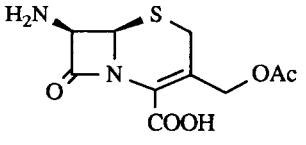
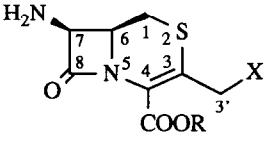
Abstract Enantioselective synthesis of the isocephem synthon 2 has been carried out by assembling 3 building blocks Cycloaddition of phthalimido acetyl chloride with a chiral imine gave the ß-lactam nucleus in 80% diastereoisomeric excess (d e) The elaboration of the thiazine ring was carried out using a highly functionalised epoxy ester 12 and P_2I_4 mediated water elimination

In the course of our ongoing investigations on the chemistry and biological activity of 2-isocephems we needed a stereocontrolled, straightforward approach towards a basic synthon which could give rise to a variety of molecules with different side chains in the 3' and 7 positions As we have shown recently, molecules having a 3-S-alkyl or S-aryl type of substituent display only moderate antibacterial activity[1] Thus we decided to synthesize compounds with 3-CH_2X substituents of the type found in most commercial cephalosporins, especially the so-called third generation products 7-Amino-cephalosporanic acid, (7-ACA) (1), a compound of natural origin is a common precursor for most of these cephems obtained by hemisynthesis[2] From this molecule highly elaborated compounds can be obtained in a few steps Consequently it was desirable to synthesize its 1-carba-2-thia equivalent 2 (X=OAc or OH)

Scheme 1



1 7-ACA

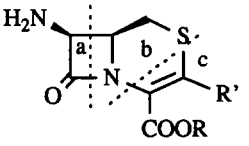


2 X = OH, R = t-Bu

The isocephem nucleus can be decomposed into 3 simple fragments a,b,c (Scheme 2), where the azetidinone is made by cycloaddition and the second ring is built up in two steps according to a method developed earlier for the 3-unsubstituted and 3 methyl compound[3d]

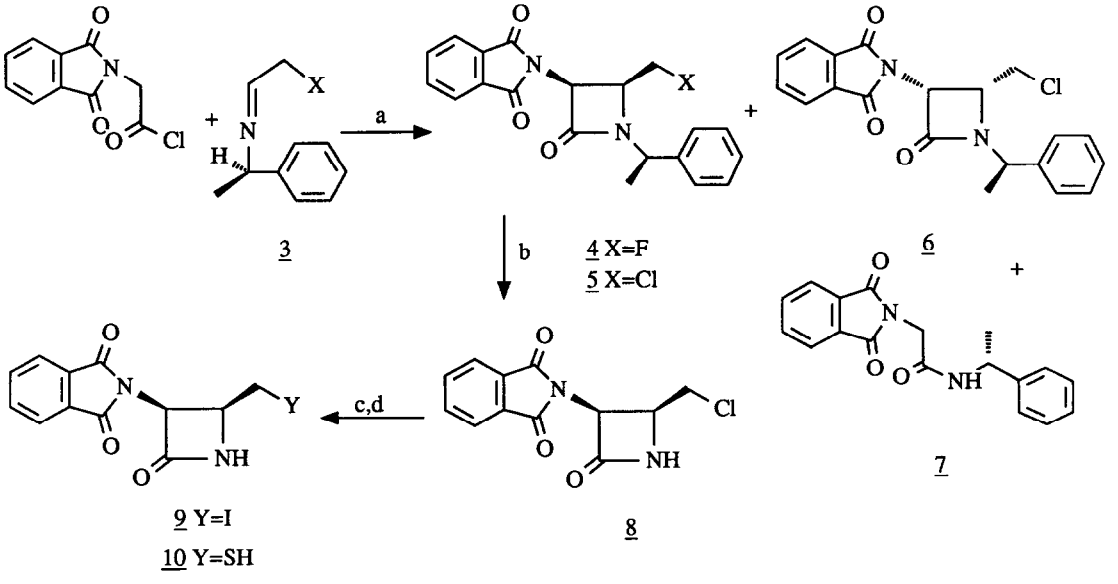
Dedicated to Professor Dr Wolfgang Hilger on the occasion of his 60th birthday

Scheme 2



The ß-lactam nucleus was prepared in an enantioselective manner by cycloaddition Our previous experience had shown that a Schiff base formed from fluoroacetaldehyde and R(+)-phenylethylamine reacts with phthalimidoacetyl chloride[4] to give the ß-lactam 4 in 63% d e [5] In a similar way, reaction of an aqueous solution of chloroacetaldehyde with R(+) phenylethylamine gave an aminal as an oily precipitate which slowly lost water and was transformed into the unstable imine (3, X=Cl) which could be extracted by alcohol-free chloroform (Scheme 3) The cycloaddition was carried out at low temperature by simultaneous addition of phthalimidoacetyl chloride and triethylamine to give 74% of a mixture of the cycloadducts 5 and 6, accompanied by some amide 7 The amount of 7 can be kept below 10% by careful drying of the Schiff base (3) solution The optical outcome of the reaction was slightly solvent dependent, chloroform giving the best results (80% d e)(Table 1) Dichloromethane or toluene gave lower diastereoselection

Scheme 3



a, Et_3N, b, $K_2S_2O_8$, c, NaI, d, H_2S, DIEA

Table 1

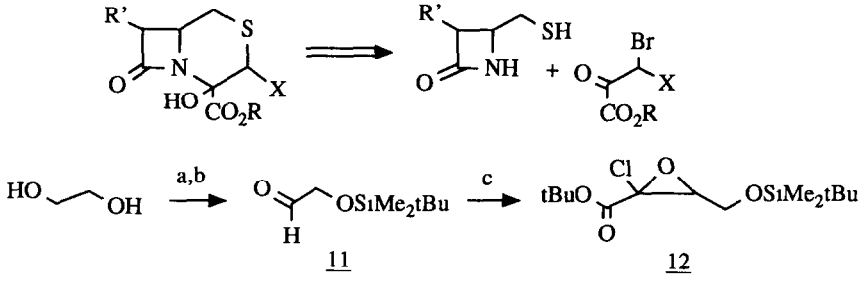
Solvent	Ratio 5/6[a]	Yield (%)[b]
$CHCl_3$	90/10	74
CCl_4	80/20	53
CCl_2=CHCl	75/25	58
$PhCH_3$	70/30	53
CH_2Cl_2	65/35	64

a The ratio of the two diastereoisomers was determined by ^{1}H-NMR
b Yield of the mixture of 5 and 6 before separation

The two isomers were readily separated by column chromatography Oxidative cleavage of the phenylethyl protecting group was achieved with potassium persulfate in acetic acid to give 51 5 % of optically pure 8 The transformation of 8 to the iodo compound 9 and the introduction of the sulfhydryl group were performed in one pot heating of 8 with NaI in dry DMF followed by treatement with H_2S in the presence of diisopropylethylamine (DIEA) gave 10 in 66% yield

The reaction of 4-mercaptomethyl azetidinones with bromopyruvates affords the thiazine ring of isocephems as was shown earlier by SKF scientists on simple molecules (Scheme 4, X=H or CH_3)[3d] However functionalization of the 3' position does not proceed well For this reason we looked for a more convergent route using a precursor (12) possessing the desired potential 3' leaving group In fact epoxide 12 can be transformed to a bromopyruvate derivative by simple treating with LiBr in THF, but this transformation was found to be redundant 12 Was obtained via Darzens reaction[6] between t-butyl dichloroacetate and the adequately substituted acetaldehyde 11, in presence of KOtBu (Scheme 4) The aldehyde was conveniently prepared via monoprotection of ethyleneglycol[7] followed by Swern oxidation (When the reaction was attempted with acetoxy acetaldehyde, no corresponding epoxide could be isolated) The relative configuration of C_2-C_3 has not been determined, however no doubling of proton signals could be observed in the NMR spectrum indicating that possibly only one isomer was formed in the reaction

Scheme 4



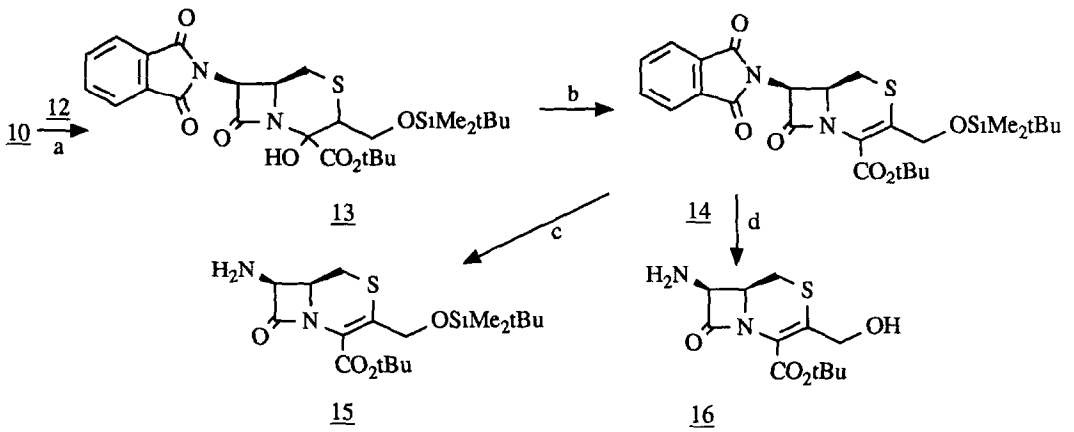
11 12

a, $tBuMe_2SiCl$, imidazole, b, Swern oxidation, c, $tBuO_2C$-$CHCl_2$/KOtBu

As we mentioned earlier the transformation of the epoxide to halopyruvate was not necessary as it could be reacted directly with the SH of 10 to develop a carbonyl group by the expulsion of a chloride ion, ready to cyclise to form 13 (Scheme 5) This reaction is surprisingly sluggish when using tertiary amine bases but can be promoted with Li^+ ions Thus reaction of the epoxide (12) with (10) in DMF in the presence of Li_2CO_3 provided the cyclised compound 13 as a roughly 1 1 mixture of diastereoisomers (Scheme 5) These isomers were not separated but submitted directly to dehydration Water elimination on this kind of structure is known to be difficult[3d,j] Diphosphorous tetraiodide in pyridine was found to be the best reagent giving 59% of 14 Contrary to the expectations[3d] both isomers have participated in the reaction In fact under the elimination conditions the hemiacetal can be opened permitting the epimerisation of both the 3 and 4 carbons[1a] In the last step the phthalimido protecting group was removed to give the free amines 15 or 16 depending on the reaction conditions

The use of 16 to produce highly active antibiotics will be reported elsewhere

Scheme 5



a, Li_2CO_3/DMF, b, P_2I_4/pyridine, c,hydrazine,CH_3CO_2H, d, hydrazine, HCl

EXPERIMENTAL

Melting points were determined on a Kofler hot plate Spectral data were recorded on the following spectrometers IR, Perkin-Elmer 580, NMR, Brucker 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 3Å molecular sieves respectively Commercially available (Aldrich Sure/Seal packed) anhydrous DMF and THF were used without further purification All non aqueous reactions were carried out under dry nitrogen atmosphere

(3S,4S)-4-Chloromethyl-1-[1(R)-phenylethyl]-3-phthalimido-azetidin-2-one (5)

For this reaction alcohol free chloroform was used, stabilized with 2-methyl-2-butene and dried over 4Å molecular sieves A solution of aqueous chloroacetaldehyde (50-55%)(31 2 mL, 0 25-0 27 mole) in 625 mL of water was cooled down in a methanol-ice bath to 0-5°C and R(+) 1-phenylethylamine (31 8 mL, 0 25 mole) was added in one portion After 10 minutes at the same temperature the precipitate formed was rapidly filtered, washed with cold water and dissolved in chloroform (450 mL) The solution was heated up to 30°C and the water formed was separated The organic phase was dried rapidly over $MgSO_4$ and then over freshly activated Drierite powder (150 g 10-20 MESH, heated to 220°C under vacuum and cooled down under dry nitrogen before use) during 1 hour The solution was filtered through a celite pad, washed with dry chloroform and cooled down to -50°C under nitrogen A solution of freshly prepared crude phthalimido acetyl chloride (containing 87% of acid chloride by titration) (41 7g, 0 16 mole) in chloroform (180 mL) and triethylamine (26 mL, 0 19 mole) were added dropwise and simultaneously As soon as the addition was finished the reaction mixture was rapidly brought to room temperature and stirred for 1 hour It was washed with 5% aqueous $NaHCO_3$ (220 mL) and the aqueous phase was reextracted twice with chloroform The combined organic extracts were dried over $MgSO_4$, filtered and evaporated The residue was taken up in ethanol (250 mL), thoroughly stirred and the insoluble material was removed by filtration, washed with ethanol and dried to give 4 8g of 7 (9 6%) The filtrate was again stirred for 2 hours and the material which crystallized out was isolated by filtration, washed with ethanol and dried to give 8 5g (14%) of a 1 1 mixture of the two diastereoisomers 5 and 6 The resulting filtrate was stirred with charcoal for 30 min , filtered through a celite pad and evaporated Chromatography on silica gel(250 g), eluting with dichloromethane/ether (9 1) gave 35 9 g (60%) of 5 as a foam α_D ($CHCl_3$,c=1%) -51°±1 5° IR ($CHCl_3$) 1785, 1720, 1612, 1603, 1595, 1589 cm^{-1} ^{1}H-NMR ($CDCl_3$) δ 1 78(3H,d,J=7Hz,CH_3), 3 49(2H,m, CH_2Cl), 3 94(1H,m,H-4), 4 96(1H,q,J=7Hz,Ph-CH), 5 43(1H,d,J=5Hz,H-3), 7 40(5H,bs,phenyl), 7 78(4H,m,phthalimido) Anal Calcd for $C_{20}H_{17}ClN_2O_3$ C, 65 13, H, 4 64, Cl, 9 61, N, 7 59 Found C,65 1, H, 4 6, Cl, 9 4, N, 7 5

(3S,4S)-4-Chloromethyl-3-phthalimido-azetidin-2-one (8)

5 (35 9g, 97 3 mmole) was dissolved in a mixture of acetic acid (310 mL) and water (210 mL) by stirring and heating rapidly to 86-88° Maintaining this inner temperature potassium persulfate (68 3g, 0 25 mole) was added over 1 hour The heating was maintained for 10 minutes followed by cooling down to 50°C by means of an ice bath K_2HPO_4 (97g) was added and the solvent was removed under reduced pressure The dry residue was taken up in water (480 mL) and ethyl acetate (290 mL), and under vigorous stirring solid $NaHCO_3$ was added until the foaming ceased and the color turned to dark The suspension was filtered through a celite pad and rinsed with ethyl acetate After recovery of the organic phase, the aqueous phase was extracted with ethyl acetate and the combined organic extracts were dried over $MgSO_4$ and evaporated Double chromatography on silica gel (CH_2Cl_2/EtOAc=75 25), and crystallisation with ether yielded 13 2g (51 5%) of 8 Mp 186°C α_D (DMF, c=1%) -40° ±1° IR ($CHCl_3$) 3420, 1787, 1770, 1728, 1613, 1515 cm^{-1} ^{1}H-NMR ($CDCl_3$) δ 3 65 and 3 82(2x1H,dd,J=11 and 7 Hz ,CH_2Cl), 4 26(1H,dt, J=5 and 7 Hz,H-4), 5 53(1H,dd,J=5 and 1 Hz(d after D_2O, J=5 Hz), H-3), 6 65(1H,bs,NH), 7 80 and 7 90(4H,m,phthalimido) Anal calcd for $C_{12}H_9O_3N_2Cl$ C, 54 46, H, 3 43, N, 10 58, Cl, 13 4, Found C, 54 7, H, 3 5, N, 10 5, Cl, 13 2

(3S,4S)-4-Mercaptomethyl-3-phthalimido-azetidin-2-one (10)

A mixture of 8 (24.7g, 93 mmole), sodium iodide (28g, 186 mmole) and DMF (80 mL) was heated to 120°C for 3 hours. 70 mL more DMF was added to prevent crystallisation and the solution was cooled down to 30°C. Hydrogen sulfide was bubbled through for 20 min. During this time 6.5g (0.19 mole) of H_2S was dissolved. Diisopropylethylamine (18.7 mL, 0.11 mole) was added to the solution and the bubbling was maintained for another 2 hours. At the beginning the temperature reached 46°C and later decreased to room temperature. The solution was poured into a stirred mixture of water (1.5 l), 1N hydrochloric acid (187 mL) and ethyl acetate (250 mL). After separation the aqueous phase was twice extracted with ethyl acetate. The combined organic extracts were washed with water, brine, dried over $MgSO_4$ and concentrated under vacuum to a volume of about 40 mL. The concentrated solution was abandoned for 10 min, during which time crystallisation occurred. The suspension was filtered, washed with ethyl acetate and ether and dried to give 14,3 g of 10. The mother liquors were concentrated and abandoned during the night to give after filtration, another 1.7 g of the product. (Combined yield: 66%) Mp: 197°C. α_D ($CHCl_3$,c=0.8%) +30.5°±1°. IR ($CHCl_3$) 3420, 2580, 1780, 1770, 1737, 1612, 1515, cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 2.66(2H,m,CH_2S); 3.73-4.04(1H,m,J= 5.5Hz,H-4); 5.41(1H,d,J=7Hz,H-3); 8.01(4H,m,phthalimido); 8.83(1H,bs, NH). Anal. calcd. for $C_{12}H_{10}O_3N_2S$: C, 54.95; H, 3.84; N, 10.68; S, 12.22; Found: C, 54.5; H, 3.8; N, 10.3; S, 11.0.

2-*tert*-Butyldimethylsilyloxy)-acetaldehyde (11)

To a solution of oxalyl chloride (4.7 mL, 55 mmole) in dichloromethane (120 mL) was added dropwise under nitrogen at -70°C a solution of DMSO (8.6 mL, 0.12 mole) in dichloromethane (26mL) over 12 min. During the addition the temperature was maintained at -65°C. The reaction mixture was stirred for 10 min. and a solution of 2-*tert*-butyldimethylsilyloxy-ethanol (8.81g, 50 mmole) and pyridine (8.8 mL, 0.1 mole) in dichloromethane (50 mL) was added over 12 min. at the same temperature. The stirring was maintained for 15 min and triethylamine (35 mL,0.25 mole) was added over 8 min. at -65°C. After the addition the mixture was warmed up to 10°C over 5 min. and maintained at this temperature for an additional 20 min.. 1N HCl was added to adjust the pH to 4, the phases were separated, the aqueous phase was extracted with CH_2Cl_2 and the combined organic extracts were dried over $MgSO_4$, filtered and evaporated. The residue was chromatographed on silica gel (CH_2Cl_2) to give 7.95g (91%) of 11. IR ($CHCl_3$) 2820, 2713, 1735, 1259, 840cm^{-1}. ^{1}H-NMR($CDCl_3$) δ 0.10(6H,s,Si(CH_3)$_2$); 0.83(9H,s,tBu); 4.17(2H,d,J=1Hz,CH_2), 9.75(1H,t,J=1Hz,CHO). Anal. calcd. for $C_8H_{18}O_2Si$: C, 55.12; H, 10.41; Found: C, 54.5; H, 10.4.

tert-Butyl-2-chloro-2,3-epoxy-4-*tert*-butyldimethylsilyloxy-butanoate (12)

A solution of *tert*-butyl dichloroacetate (8.46g, 46 mmole) in dry THF was cooled to -20°C under nitrogen. 11 (7.95g, 46 mmole) in 40 mL of THF was added simultaneously with 46 mL of a one molar KOtBu solution in THF over 20 min. The mixture was warmed up slowly to room temperature over 35 min. Water (40 mL) and ether (40 mL) were added, stirred thoroughly and separated. The aqueous phase was extracted once with ether, the combined organic phases were washed twice with brine, dried over $MgSO_4$ and evaporated. Silica gel chromatography (hexane/CH_2Cl_2=6:4) yielded 9.4g (64%) of 12. IR ($CHCl_3$) 1743, 1372, 1158, 840 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 0.10(6H,s,(CH_3)$_2$); 0.82(9H,s, SitBu); 1.42(9H,s,CO_2tBu); 3.33-4.08(3H,m,H-3,H-4).

tert-Butyl(6S,7S)-7-phtalimido-3-*tert*-butyldimethylsilyloxymethyl-2-hydroxy-8-oxo-4-thia-1-azabicyclo[4 2 0]octane-2-carboxylate (13)

12 (39 7g, 0 12 mole) and 10 (26 9g, 0 1 mole) were dissolved in DMF (300 mL) Li_2CO_3 (9 8g, 0 13 mole) was added and the mixture was stirred for 3 hours and poured into water (3 L) containing 186 mL of 1N hydrochloric acid The product was extracted with ethyl acetate, washed with water, brine, dried over $MgSO_4$, filtered and evaporated The residue was purified by column chromatography on silica gel (CH_2Cl_2/EtOAc=9 1) to give 42 3g (76%) of 13 as a 45/55 mixture of diastereoisomers ^{1}H-NMR ($CDCl_3$) δ 0 08 (0 55H,s,MeSi) and 0 23 and 0 25(0 45H,2s,MeSi), 0 92 and 0 98(9H,2s,SitBu), 1 57 and 1 65(9H,2s,OtBu), 5 29 and 5 50 (1H,d,J=4 5Hz and 3 5 Hz,H-7), 7 86(4H,m,phthalimido)

tert-Butyl(6S,7S)-7-phthalimido-3-*tert*-butyldimethylsilyloxymethyl-8-oxo-4-thia-1-azabicyclo[4 2 0]oct-2-ene-2-carboxylate (14)

A solution of 13 (42.2g,0 077 mole) in pyridine (560 ml) was cooled to 13°C under nitrogen Diphosphorus tetraiodide (87 8g, 0 154 mole) was added in one portion The inner temperature was kept below 32°C by means of a water bath The stirring was maintained at room temperature for 1 hour The reaction mixture was poured onto a well stirred mixture of ethyl acetate (650 ml) and water (3 5 l) and concentrated HCl (530 ml) was added dropwise to reach a pH of 1 4 while the inner temperature was kept below 32°C with an ice bath The insoluble material was filtered off through a celite pad and washed with ethyl acetate The organic phase was separated and the aqueous solution extracted three times with ethyl acetate The combined organic extracts were washed successively with saturated $NaHCO_3$, brine, dried over $MgSO_4$, and evaporated The residue was purified by column chromatography (CH_2Cl_2-ether=95 5) and crystallized with pentane to give 22 81g (53%) of 14 Mp 172°C, α_D ($CHCl_3$,c=0 8%) +30°±2°, IR ($CHCl_3$) 1784, 1772, 1726, 1700, 1610, 1573, 1470, 1309, 1250, 1150, 839 cm^{-1} ^{1}H- NMR ($CDCl_3$) δ 0 11(6H,s,MeSi), 0 91(9H,s,tBuSi), 1 53(9H,s,tBuO), 2 77-3 44 (2H,m,CH_2S), 3 95(1H,m,H-6), 4 62 and 4 95 (2H,ABq,J=15 Hz,CH_2O), 5 77(1H,d,J=5 5Hz,H-7), 7 81(4H,m,phthalimido) Anal Calcd for $C_{26}H_{34}O_6N_2SSi$ C, 60 3, H,7 1, N, 4 9, S, 5 7 Found C, 60 1, H, 7 0, N, 5 0, S, 5 9

tert-Butyl(6S,7S)-7-amino-3-*tert*-butyldimethylsilyloxymethyl-8-oxo 4-thia -1-azabicyclo[4 2 0]oct-2-ene-2-carboxylate (15)

14 (5 31g, 10 mmole) was dissolved in DMF (10 mL) and a solution of hydrazine hydrate (0 535 mL, 11 mmole) in DMF (3 mL) was added dropwise over 45 min (Faster addition led to partial opening of the ß lactam ring) 0 63 mL (11 mmole) of acetic acid was added and the reaction mixture was stirred at room temperature for 2 hours and at 50°C for 15 min Most of the solvent was evaporated under reduced pressure at 40°C The residue was taken up in CH_2Cl_2 and filtered The filtrate was washed with saturated $NaHCO_3$ solution and water, dried, evaporated and the remaining solid was crystallized with ether to give 1 85g (46 2%) of 15 Mp 180-182°C IR ($CHCl_3$) 3395, 3350, 1764, 1697, 1621, 1574, 1369, 1246 cm^{-1} ^{1}H-NMR ($CDCl_3$) δ 0 10(6H,S,$SiMe_2$), 0 92(9H,s,SitBu), 1 53(9H,s,OtBu), 2 73-3 15(2H, m,CH_2S), 3 83(1H,m,H-6), 4 58-4 64(1H,m,H-7), 4 62 and 4 95 (2H,ABq ,J=15 Hz,CH_2O) Anal Calcd for $C_{18}H_{32}N_2O_4SSi$ C, 54 0, H, 8 1, N, 7 0, S, 8 0, Found C, 54 1, H, 8 3, N, 7 0, S, 7 7

tert-Butyl(6S,7S)-7-amino-3-hydroxymethyl-8-oxo-4-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (16).

To a solution of 14 (1.59g, 3 mmole) in DMF (4 mL) was added dropwise a solution of hydrazine hydrate (3.3 mL of a one molar solution in DMF) at room temperature over 12 min. Most of the solvent was distilled off at reduced pressure (below 45°) and the residue was taken up in 10 mL of water. 1N hydrochloric acid (3.3 mL) and ethanol (8 mL) was added and the solution was stirred for 2 hours. The precipitated phthalyl hydrazide was filtered off, washed with water and ether. The filtrate was concentrated to remove most of the ethanol and the residue was extracted once with ethyl acetate. The organic solution was discarded. The pH of the remaining aqueous phase was adjusted to 7.5 by $NaHCO_3$ and the deprotected material was extracted with ethyl acetate dried and evaporated. The residue was crystallized with ether to give 604 mg (71%) of 16. Mp: 112°C. IR ($CHCl_3$) 3500, 3410, 3350, 1765, 1688, 1622, 1580, 1368, 1154 cm^{-1}. ^1H-NMR ($CDCl_3$) δ 3.0-3.08(2H,m,CH_2S); 3.83(1H,m,H-6); 3.92 and 4.59(2H,2d,J=14 Hz, CH_2O); 4.71(1H,d,J=6 Hz,H-7). Anal. Calcd. for $C_{12}H_{18}O_4N_2S$ C, 50.3; H, 6.3; N, 9.8; S, 11.2. Found C, 50.4; H,6.3; N, 9.7; S, 11.0.

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REFERENCES

1a. Aszodi, J.; Chantot, J.-F.; Collard, J.; Teutsch, G. *Heterocycles* **1989**, *28*, 1061-1076.
b. Costerousse, G.; Cagniant, A.; Didierlaurent, S.; Proust, D.; Teutsch, G. *Bull. Soc. Chim. Fr.* in press.
2a. Dürckheimer, W.; Blumbach, J.; Lattrell, R.; Scheunemann, K.H. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 180-202.
b. Dürckheimer, W.; Adam, F.; Fischer, G.; Kirrstetter, R. "Frontiers of Antibiotic Research", ed. by H. Umezawa, Academic Press, Inc., Tokyo, **1987**, pp.161-192.
3. For different methods of Isocephem synthesis see
a. Jung, F.A.; Pilgrim, W.R.; Poyser, J.P.; Siret, P.J. "Topics in Antibiotic Chemistry", Vol. 4, ed. by P.G. Sammes, Ellis Horwood Publishers, **1980**, pp. 89-90.
b. Brunwin, D.M.; Lowe, G. *J. Chem, Soc., Perkin I.* **1973**, 1321-1328.
c. Corrie, J.E.T.; Hlubeck, J.R.; Lowe, G. *J. Chem. Soc., Perkin Trans. I* **1977**, 1421-1425.
d. Bryan, D.B.; Hall, R.F.; Holden, K.G.; Huffmann, W.F.; Gleason, J.G. *J. Am. Chem. Soc.* **1977**, *99*, 2353-2355.
e. Doyle, T.W.; Douglas, J.L.; Belleau, B.; Meunier, J.; Luh, B.Y. *Can. J. Chem.* **1977**, *55*, 2873-2884.
f. Douglas, J.L.; Horning, D.E.; Conway, T.T. *Can. J. Chem.* **1978**, *56*, 2879-2883.
g. Doyle, T.W.; Douglas, J.L.; Belleau, B.; Conway, T.T.; Ferrari, C.F.; Horning, D.E.; Lim, G.; Luh, B.Y.; Martel, A.; Menard, M.; Morris, L.R. *Can. J. Chem.* **1980**, *58*, 2508-2523.
h. Mc Combie, S.W.; Metz, W.A.; Alfonso, A. *Tetr. Lett.* **1986**, *27*, 305-308.
i. Nitta, H.; Hatanaka, H.; Ishimaru, T. *J. Chem. Soc., Chem. Com.* **1987**, 51-52.
j. Aszodi, J.; Bonnet, A.; Chantot, J.-F.; Costerousse, G.; Teutsch, G. "Recent Advances in the Chemistry of ß-Lactam Antibiotics", The Royal Society of Chemistry, London, Special Publications No. 70, **1989**, pp. 350-364.
4. Sheehan, J.C.; Ryan, J.J. *J. Am. Chem. Soc.* **1951**, *73*, 1204-1206.
5. Teutsch, G.; Bonnet, A. *Tetr. Lett.* **1984**, *25*, 1561-1562.
6a. Tsuboi, S.; Furutani, H.; Takeda, A. *Synthesis* **1987**, 292-293.
b. Villieras, J.; Coutrot, P.; Combret, J.-C. *C. R. Acad. Sc. Paris, ser. C* **1970**, 1250-1252.
c. Villieras, J.; Castro, B.; Ferracutti, N.N. *Bull. Soc. Chim. Fr.* **1970**, 1450-1455.
7. McDougal, P.G.; Rico, J.G.; Oh, Y.I.; Condon, B.D. *J. Org. Chem.* **1986**, *51*, 3388-3390.