Tetrahedron Vol. 45, No. 3, pp. 687 to 694, 1989
Printed in Great Britain.

0040-4020/89 $3.00+.00
Pergamon Press plc

STUDIES TOWARD THE TOTAL SYNTHESIS OF 1-OXACEPHALOSPORINS 1: 3-AMINO-4-THIO-2-AZETIDINONES WITH PROTECTED γ,γ'-DIHYDROXYALKENOATE SIDE CHAIN [1,2]

DIETER HOPPE*[a)], HANS SCHMINCKE[a)], and HEINZ-WERNER KLEEMANN[b)]

a) Institut für Organische Chemie, Universität Kiel, Olshausenstr. 40, D-2300 Kiel 1, FRG

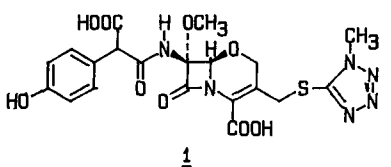
b) Institut für Organische Chemie, Universität Göttingen, Tammannstr. 2, D-3400 Göttingen, FRG

(*Received in Germany* 21 *October* 1988)

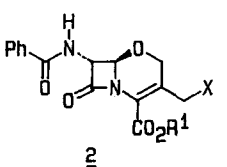
Abstract. Racemic trans-3-benzoylamino-4-methylthio-2-azetidinones **16**, bearing an acetonide-protected β,β'-bis(hydroxymethyl)acrylate moiety and being potential candidates for the total synthesis of 1-oxacephems, were obtained from 2,2-dimethyl-1,3-dioxan-5-one (**4**), alkyl isocyanoacetates **3** and azidoacetyl chloride (**5**) with 5 steps in overall yields of 13-33%. 2-Formylaminoacrylates **6**, 1,3-thiazoline-4-carboxylates **9**, produced by direct thiation of **6**, and S-methyl thioformimidates **14** are the intermediates.

1-Oxacephalosporins,[3,4,5] e.g. Latamocef® (**1**), in which the sulfur atom of the naturally occurring cephem antibiotics is replaced by oxygen are of interest because of their high antibacterial potency.[3,6,7] Since the first members became known[8,9] in 1974, various multi-step partial syntheses starting from penicillins or cephalosporins have been worked out.[3] In several approaches trans-1-oxacephems of type **2** are the key intermediates. The configuration at C-7 later is inverted to cis, essential for biological activity, with the methoxylation step.[3] One of the main problems in partial and total synthesis, as well, consists in the introduction of a polar hetero substituent to the 3'-position.

Scheme 1

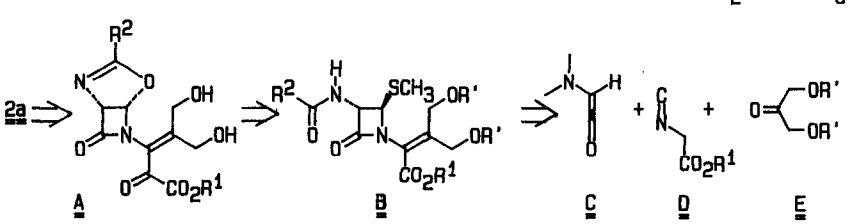


1



2

a X = OH, R^1 = alkyl
b X = OCON(iPr)$_2$, R^1 = CH_3



A **B** **C** **D** **E**

When we started our studies in 1978, cyclo-acetalization of an oxazolinoazetidinone **A**, bearing two hydroxymethyl groups in the alkenoate side chain,[10,11] was anticipated to be an attractive

route[5] for the rapid total synthesis of racemic[12] 1-oxacephems **2a** (Scheme 1). Here, less restricted to the availability of starting materials, the highly functionalized carbon framework of **2** can be constructed with the correct pattern by proper selection of the building blocks. Although it was not clear whether the imminent lactonization of the stage of **A** could be prevented we undertook the synthesis of the precursors **B** from a protected 1,3-dihydroxyacetone **E**, an isocyanoacetate **D**, and an aminoketene equivalent **C** by a general method developed recently by us (Scheme 1).[13] The subsequent contributions deal with the synthesis and reactions[14] of oxazolinoazetidinones **A** and with the total synthesis of the 3'-carbamoyloxy-1-oxacephem[15] **2b**.

Synthesis of the Azetidinones 16

For building block **E**, 2,2-dimethyl-1,3-dioxan-5-one[16] (**4**) was selected because deprotection of the hydroxyl groups should occur under slightly acidic conditions suitable for the cyclo-acetalization of **A** (Scheme 2). After assemblage of the units **D** and **E** by the Schöllkopf formylamino-methylenation,[17] **6** was scheduled to be transformed via the 2-isocyanoacrylate[18] **7**, addition of hydrogene sulfide to give the thiazolinecarboxylate[19] **9** and its base-induced ring-opening[13] into the methyl thioformimidate **14**, prior cycloaddition[13,20] of azidoacetyl chloride[21] (**5**) to afford the trans-ß-lactam **15**.

The condensation of ketone **4** with methyl-, benzyl-, or (diphenylmethyl) 2-isocyanoacetate[17] **3a-c** by means of potassium tert.-butoxide gave smoothly the 2-formylamino-acrylates **6a**, **6b**, or **6c** with 93%, 69%, or 67% yield after recrystallization (Scheme 2). In the ^{1}H NMR spectra of **6** in $CDCl_3$ solution (Table 1) both E- and Z-amides are recognized.[22] On dehydration of **6** by the usual methods[18] ($COCl_2$, Ph_3P/CCl_4, or $POCl_3$[23]) in the presence of tertiary amines as bases not the expected isocyanoacrylates **7** but the sensitive 5,6-dehydro-1,3-dioxanes **8** were isolated,[24] e.g. 51% of **8b**. Clearly, the double bond migration with formation of the more stable isomers **8** is initiated by the γ-deprotonation of **7** even by weak bases. After several unsuccessful attempts, finally, thiation of the formamides **6** by the Lawesson reagent[25] (**18**) led directly to the thiazolines **9a**, **9b**, or **9c** (65%, 84%, or 85% yield). Careful observation of the experimental details (1,2-dimethoxyethane/triethyl amine, 20 °C) is essential for obtaining reproducible results; otherwise N-formylcysteines **12** are formed in substantial amounts.[19,16]

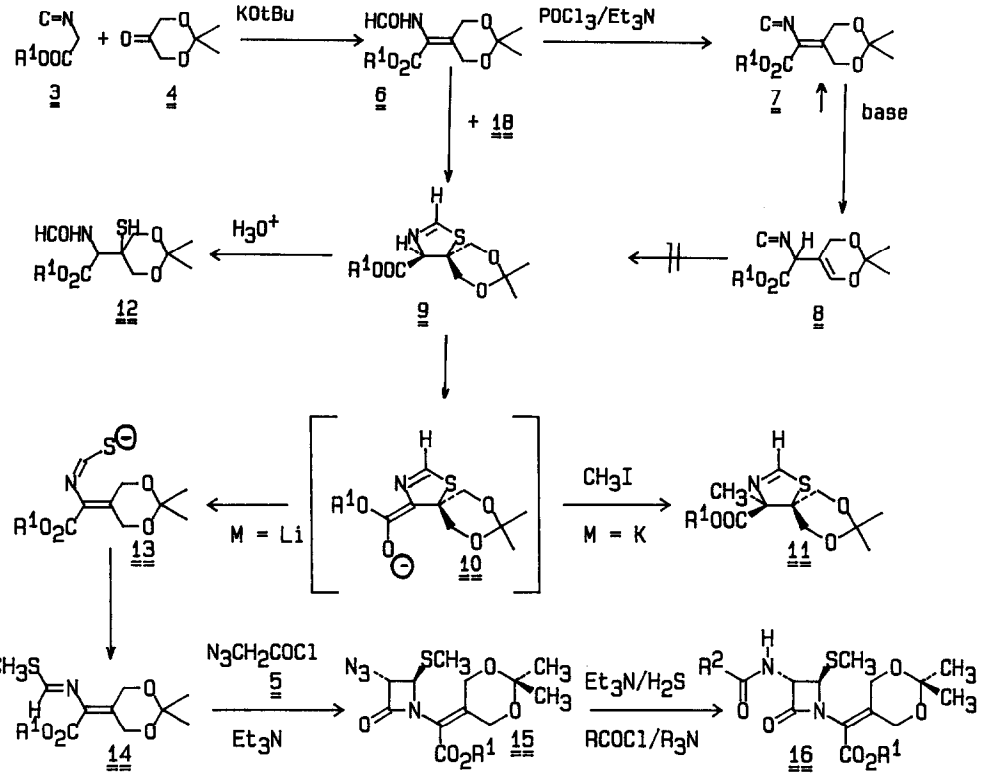
When the thiazoline **9c** was treated as usual[13] with a slight excess of potassium tert.-butoxide in THF below -30 °C and the reaction mixture quenched with methyl iodide, instead of the expected methyl thioformimidate **14c**, the 4-methylated thiazoline **11c** was isolated with 70% yield, indicating that the electrocyclic ring-opening[13] of the enolate **10c** to form the thioformate anion **13c**, surprisingly, here is not a facile process. Neither the methyl or benzyl esters **13a** or **13b** nor the application of different bases and solvents (e.g. LDA or n-butyllithium/THF, sodium methylsulfinylmethanide/DMSO/THF and others) below -20 °C gave rise to clean formation of the thioimidates **14** after methylation. The reluctance of the enolates **10** to undergoe the ring-opening is in contrast to the behaviour of similar thiazolines bearing a spiro-annulated carbocyclic ring.[13] Therefore we assumed that a high barrier is caused by an infavourable antibonding interaction between the developing negative charge at the sulfur atom and the lone electron pairs at both the oxygen atoms in the transition state **F**.

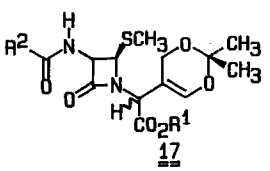
Guided by the idea to decrease the effective negative charge on sulfur by a hydrogen bridge and to lower the donating power of the oxygens by complexation to a Lewis acid, and in addition, to surpress the thermal decomposition of the enolates **10**, a sophisticated but reliable procedure was found: To a solution of **9** and methyl iodide (10 eq) in THF, kept at 20 °C, a solution of lithium 2-propoxide/2-propanol in THF/hexane, chilled to -70 °C, was added. After aqueous work-up, the crude methyl thioimidates **14a-c** were obtained with 97%, 73%, and 92% yield, respectively.

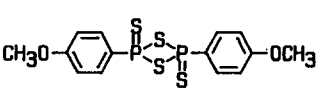
The solutions of crude **14** in dichloromethane/triethyl amine[13] immediately were converted by azidoacetyl chloride[21,27] (**5**) to afford the trans-3-azido-4-methylthio-2-azetidinones **15a-c**, yield 65%, 84%, and 85% after LC purification. As deduced from the coupling constant $J_{3,4}$ of 2 Hz[13] in the ^{1}H NMR spectra (Table 2), only the trans-isomers **15** are present. Reduction of **15** (hydrogen sulfide/triethyl amine[28]), followed by acylation (benzoyl chloride/pyridine), both at -20 °C, gave

the benzamides **16a-c** with 43%, 80%, and 31%;[29] similarly the phenylacetyl derivative **16d** (62%) was obtained. Again, under the influence of higher temperatures and prolonged reaction times, partial double bond migration into the six-membered ring with formation of the isomers **17** occurs. Altogether, starting from the ketone **4**, with only 5 steps, the highly functionalized 2-azetidinones **16** are accessible with overall yields between 13% and 33%. Further transformations[14] of **16** and related compounds[15] are reported in subsequent papers.

Scheme 2







3, 6–15	a	b	c	d
R^1	CH_3	CH_2Ph	$CHPh_2$	
16, R^1	CH_3	CH_2Ph	$CHPh_2$	CH_3
R^2	Ph	Ph	Ph	CH_2Ph

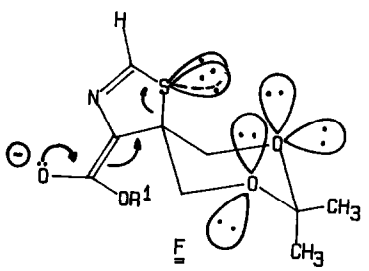
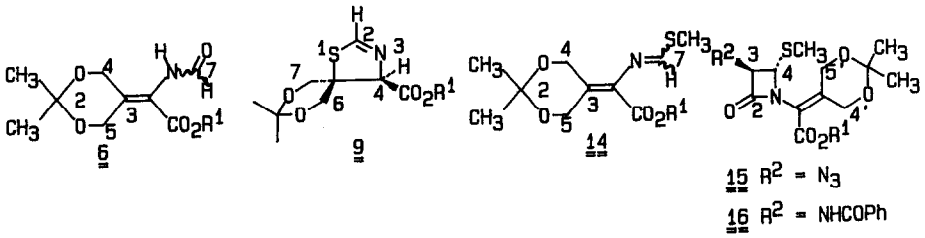


Table 1: ^{1}H-NMR data of the formamides **6**, thiazolines **9**, thioformimidates **14** and azetidinones **15** and **16** (δ ; in $CDCl_3$; 300 MHz):



15 R^2 = N_3

16 R^2 = NHCOPh

a) Thiazolines **9**

	2-H	4-H	6-H	7-H	$(CH_3)_2C$	R^1
9a	8.08 d;2Hz	4.85 d;2Hz	3.7 - 4.3 m	(2xAB)	1.45+1.45	3.83
9b	8.07 d;1.8Hz	4.73 d;1.8Hz	3.78 - 4.08 m	(2xAB)	1.27+1.38	5.24; 7.37
9c	8.12 d;2Hz	4.81 d;2Hz	4.13+3.90 ABX;11Hz; 2Hz	3.82+3.64 ABX;11Hz; 2Hz	1.18+1.38	7.01; 7.2

b) Thioformimidates **14** and the formamides **6**

	N-E-Isomer					N-Z-Isomer				
	R^1	4-H	5-H	7-H	SCH_3	R^1	4-H	5-H	7-H	SCH_3
14a	3.26	4.57	4.48	8.94	2.38	3.24	4.78	4.16	8.32	2.47
14b	5.2; 7.3	4.70	4.53	8.53	2.31	5.2; 7.3	4.81	4.19	8.32	2.32
14c	6.84; 7.22	4.60	4.41	8.38	2.28	6.79;7.2	4.67	4.08	8.16	2.24
					N-H					N-H
6a	3.74	4.17	4.72	-	7.84	3.74	4.36	4.72	8.16	7 98
6b	5.1; 7.2	4.16	4.38	-	-	5.1; 7.2	4.23	4.38	8.0	7.60
6c	6.97;7.36	4.23	4.38	7.93	-	6.97;7.32	4.40	4.86	8.25	7.0

c) Azetidinones **15** and **16** ($CDCl_3$; 100 MHz):

	R^1	R^2	4-H	3-H	4'-H	5'-H	SCH_3	$(CH_3)_2C$
15a	3.84	N_3	5.07 d; 2 Hz	4.52	4.88+4.63 AB; 17 Hz	4.49+4.18 AB; 18 Hz	2.12	1.41+1.41
15b	5.12+5.36;7.2 AB; 11.8 Hz	N_3	4.98 d; 2.3 Hz	4.42	4.85+4.65 AB;1.7 Hz	4.48+4.12 AB; 16 Hz	1.98	1.40+1.40
15c	6.99; 7.36	N_3	4.99 d; 2 Hz	4.48	4.82+4.71 AB	4.52+4.17 AB; 16 Hz	1.87	1.39+1.39
16a	3.80	PhCONH	5.12 dd; 2 Hz	5.20	4.74 m	4.43+4.34 AB;6.4 Hz	2.08	1.37+1.37
16b	5.02+5.23;7.2 AB: 11.8 Hz	PhCONH	5.15 dd; 2.5 Hz	5.24	4.90+4.66 AB;17.5Hz	4.55+4.26 AB;16.5Hz	2.07	1.42+1.42
16c	6.95; 7.2	PhCONH	5.02 dd; 2.4 Hz	5.16	4.80 m	4.56+4.28 AB; 16 Hz	2.01	1.37+1.54

EXPERIMENTAL

All carbanion reactions and thiations were performed under N_2 or Ar with exclusion of air and water. Diethyl ether, THF, and 1,2-dimethoxyethane (DME) were distilled from $LiAlH_4$; triethyl amine, pyridine, and dimethylformamide from CaH_2; dichloromethane from P_4O_{10} prior use. - LC separations for more than 1 g were carried out with "Kieselgel 60", 0.05 - 0.2 mm, (Merck, Darmstadt, or Macherey-Nagel GmbH & Co KG, Düren), or, for less than 1 g, on "Silicagel 32-63", 0.032 - 0.063 mm, (ICN Biochemicals, Eschwege) at 1 - 3 bar. - 0.1 M Phosphate buffer was used.

2,2-Dimethyl-1,3-dioxan-5-one[16] (**4**): 2-Amino-2-(hydroxymethyl)-1,3-propandiol hydrochloride (69.3 g, 0.44 mol), 2,2-dimethoxypropane (52.1 g, 0.50 mol), p-toluenesulfonic acid monohydrate (3.5 g, 22 mmol) in dry dimethylformamide (140 mL) were stirred (12 h, 20 °C). After addition of triethyl amine (3.5 mL, 25 mmol) the solvent was removed i. vac., the residue diluted with triethyl amine (56 mL, 0.40 mol) and ethyl acetate (1 L). The ammonium salts were filtered off, the solvent evaporated i. vac. Distillation afforded 5-amino-(2,2-dimethyl-1,3-dioxan-5-yl)methanol (**20**) (52.6 g, 74%), bp 110 °C/0.3 torr. - To a soln of **20** (25.1 g, 0.157 mol) and KH_2PO_4 (21.3 g, 0.157 mol) in water (160 mL) a 0.5 M aqueous soln (314 mL) of $NaIO_4$ at 10 °C was added dropwise during 3 h and the reaction mixture further stirred (1 h at 10 °C and 5 h at 20 °C). Extraction with CH_2Cl_2 (10 x 30 mL), drying over $MgSO_4$ and distillation gave **4** (18.8 g, 92%), bp 67 °C/20 torr. ^1H NMR (CCl_4): δ = 1.37 (s, 6 H, CH_3) and 4.01 (s, 4 H, CH_2).

Methyl isocyanoacetate (**3a**) is commercially available. - Benzyl isocyanoacetate (**3b**) was prepared according to ref.[30]

Diphenylmethyl isocyanoacetate (**3c**): A slurry of potassium isocyanoacetate[31] (22.3 g, 0.18 mol) and diphenylmethyl bromide (44.7 g, 0.18 mol) in dry HMPTA (35 mL) were stirred (8 d at 40 °C). The reaction mixture was diluted with ether (180 mL) and extracted with water (3 x 100 mL). The ether soln was dried over Na_2SO_4, the solvent evaporated and the residue purified by LC on silica gel (200 g) with cyclohexane/ethyl acetate (2 : 1), yield 40.5 g (89%), yellow crystals, mp 57 °C from ether/pentane (1 : 1). - IR (KBr): 2140 (N=C), 1740 cm^{-1} (C=O). - ^1H NMR ($CDCl_3$): = 4.21 (s, CH_2), 6.89 (s, CH), 7.31 (m, 10 H, C_6H_5).
$C_{16}H_{13}NO_2$ (251.29). Calc. C 76.46 H 5.21. Found C 76.33 H 5.28.

Azidoacetyl chloride[21] (**5**) was prepared according ref.[13]. CAUTION![27]

Formamides **6**. General procedure[15]: To freshly sublimed[32] potassium tert.-butoxide (9.00 g, 80 mmol) in dry THF (60 mL) below -60 °C the isocyanoacetate **3** (80 mmol) is added dropwise and after 15 min stirring ketone **4** (80 mmol) in THF (50 mL) is slowly added, stirring is continued (30 min), the reaction mixture allowed to warm to 0 °C and kept at this temp. (30 min). Acetic acid (4.86 g, 80 mmol) in dichloromethane (200 mL) is added, the suspension extracted with water (3 x 50 mL), dried over Na_2SO_4, and the solvent is removed i. vac.. Crude **6** is purified by crystallization or by LC on silica gel (ether/pentane 1 : 1).

Methyl 2-(2,2-dimethyl-1,3-dioxan-5-ylidene)-2-formylamino-acetate (**6a**): Yield 93% after crystallization from few ether, mp 89 °C. - IR (KBr): 3460 (NH), 1720 (OC=O), 1685 cm^{-1} (NHC=O).
$C_{10}H_{15}NO_5$ (229.23). Calc. C 52.40 H 6.60. Found C 52.49 H 6.68.

Benzyl ester **6b**: Yield 69% after recrystallization from ether/pentane, mp 90 °C. - IR (CCl_4): 3550 - 3300 (NH), 1720 (OC=O), 1670 cm^{-1} (NHC=O).
$C_{16}H_{19}NO_5$ (305.33). Calc. C 62.94 H 6.27. Found C 62.65 H 6.37.

Diphenylmethyl ester **6c**: Yield 67% after recrystallization from ether/pentane, mp 125 °C. - IR (KBr): 3150 (NH), 1720 (OC=O), 1670 cm^{-1} (NHC=O).
$C_{22}H_{23}NO_5$ (381.43). Calc. C 69.28 H 6.08. Found C 69.35 H 6.06.

Thiazolines **9**; general procedure: To a soln of formamide **6** (60 mmol) and triethyl amine (0.8 mL) in anhydrous 1,2-dimethoxyethane (DME; 180 mL) in argon atmosphere the Lawesson reagent **18** (13.3 g, 33 mmol), washed with ice-cold DME (50 mL) prior use, is added and the mixture is stirred vigorously at 20 °C for 20 min. Triethyl amine (42 mL, 0.30 mol) and ether (1.8 L) are added to the clear reaction mixture and stirring is continued until a viscous yellow oil deposites completely at the flask wall. The ether soln is decanted, washed with phosphate buffer soln (pH 7, 500 mL) and dried over $Na_2SO_4/NaHCO_3$. The solvent is evaporated; yield 95% crude **9** (approx. 90 proz.; ^1H NMR). For further purification the residue can be filtered rapidly over a silica gel column (500 g) with tert.-butyl methyl ether/hexane (1 : 1), accompanied by some hydrolysis to form **12**. - When the reaction was carried out in absence of triethyl amine and work-up was accomplished with $NaHCO_3$ soln, the cysteines **12** were isolated.

Methyl 2,2-dimethyl-spiro[1,3-dioxane-5,5'-1',3'-thiazoline]-4'-carboxylate (**9a**): Yield 60%, oil. - IR (KBr): 1745 (C=O), 1590 cm^{-1} (C=N). - ^1H NMR ($CDCl_3$): δ = 1.45 (s, 2 x 2-CH_3); 3.7 - 4.3 (2 x AB, 4- and 6-H_2); 4.85 (d, J = 2 Hz, 4'-H); 3.83 (s, OCH_3); 8.08 (d, J = 2 Hz, 2'-H).

Benzyl ester **9b**: Yield 64%, oil. - IR (KBr): 1743 (C=O), 1580 cm^{-1} (C=N). - ^1H NMR ($CDCl_3$): δ = 1.27 and 1.38 (s, 2 x 2-CH_3); 3.78, 3.87, 3.95 and 4.08 (each AB, 4- and 6-H_2); 4.73 (d, J = 1.8 Hz, 4'-H); 5.24 (s, CH_2Ph); 7.37 (m, C_6H_5); 8.07 (d, 2'-H).

Diphenylmethyl ester **9c**: Yield 71%, oil. - IR (KBr): 1720 (C=O), 1575 cm^{-1} (C=N). - ^1H NMR ($CDCl_3$): δ = 1.18 and 1.38 (s, 2 x 2-CH_3); 3.64, 3.84 and 3.90, 4.13 (each ABX, J = 11 and 2 Hz, E- and Z-4-H_2); 4.81 (d, J = 2 Hz, 4'-H); 7.01 (s, $CHPh_2$); 7.2 - 7.5 (m, 2 x C_6H_5); 8.12 (d, 2'-H).

Methyl 2-(2,2-dimethyl-5-thio-1,3-dioxan-5-yl)acetate (**12a**): Yield 42%, mp 108 °C (ether). - IR (KBr): 3200 (NH), 2570 (SH), 1730 (OC=O), 1650 cm^{-1} (NHC=O). - ^1H NMR ($CDCl_3$): δ = 1.42 (s, 2 x

2'-CH_3); 2.06 (s, SH); 3.4 - 4.2 (m, 4'- and 6'-H_2); 3.75 (s, OCH_3); 4.96 and 5.23 (each d, J = 10 Hz, Z- and E-2-H); 6.4 - 6.8 (m, NH); 8.03 (d, J = 13 Hz, E-HC=O), 8.19 (bs, Z-CH=O).
$C_{10}H_{17}NO_5S$ (263.31). Calc. C 45.61 H 6.51. Found C 45.79 H 6.45.

Benzyl ester **12b**: Yield 38%, mp 73 °C (ether). - IR (KBr): 3320 (NH), 2520 (SH), 1740 (OC=O), 1690 cm^{-1} (NHC=O). - ^1H NMR ($CDCl_3$): δ = 1.38 (s, 2'-CH_3); 1.40 (s, 2'-CH_3); 2.05 (s, SH); 3.53 - 4.17 (m, 4'- and 6'-H_2); 5.19 (s, CH_2Ph); 5.28 (d, J = 10 Hz, 2-H); 6.79 (d, J = 10 Hz, NH); 7.37 (m, C_6H_5); 8.26 (s, HC=O).

Diphenylmethyl ester **12c**: Yield 65%, mp 128 °C (ether/pentane, 1 : 1). - IR (KBr): 3385 (NH), 2540 (SH), 1730 (OC=O), 1675 cm^{-1} (NHC=O). - ^1H NMR ($CDCl_3$): δ = 1.43 (s, 2 x 2'-CH_3); 1.91 (s, SH); 3.5 - 4.2 (m, 4'- and 6'-H_2); 5.19 and 5.39 (each d, J = 10 Hz, E- and Z-2-H); 6.55 (d, NH); 6.88 (s, $CHPh_2$); 7.2 - 7.4 (m, 2 x C_6H_5); 8.21 (bs, HC=O).
$C_{22}H_{25}NO_5$ (415.51). Calc. C 63.59 H 6.06. Found C 63.43 H 6.16.

Methylation of thiazolines **9**; diphenylmethyl 2,2,4'-trimethyl-spiro[1,3-dioxane-5,5'-1',3'-1,3-thiazoline]-4-carboxylate (**11c**): **9c** (130 mg, 0.327 mmol) in THF (1 mL) was added to a soln of potassium tert.-butoxide (48 mg, 0.37 mmol) in THF (2 mL) below -70 °C and the reaction mixture stirred for 1 h at -30 °C. Methyl iodide (0.10 mL, 1.6 mmol) was added and stirring was continued at this temp. (20 min) and at 20 °C (20 min). The mixture was filtered over silica gel and the solvent evaporated. Crystallization from ether/pentane (1 : 1) gave **11c** (167 mg, 70%), mp 132 °C. - IR (KBr): 1750 (C=O), 1580 cm^{-1} (C=N). - ^1H NMR ($CDCl_3$): δ = 1.03 and 1.32 (each s, 2 x 2-CH_3); 1.42 (s, 4'-CH_3); 3.43 and 3.62, 3.93 and 4.33 (each ABX, J = 12 and 2 Hz, E-4- and Z-6-H_2); 7.03 (s, $CHPh_2$); 7.2 - 7.5 (m, 2 x C_6H_5); 7.98 (2'-H). Calc. C 67.13 H 6.12. Found C 66.96 H 6.24.

S-Methyl thioformimidates **14**; general procedure: To a soln of **9** (20 mmol) and methyl iodide (10 mL, 0.16 mol) in anhydrous THF (500 mL), vigorously stirred at 20 °C, a chilled (-70 °C) soln of lithium 2-propoxide (20 mmol, prepared from 40 mmol 2-propanol in 20 mL THF and 12.5 mL (20 mmol) 1.60 N n-butyllithium in hexane) is introduced during 45 min. Stirring is continued (1 h), phosphate buffer soln (pH 7, 200 mL) and ether (200 mL) added and the aqueous layer extracted with ether (2 x 200 mL), the combined organic solns washed with brine (2 x 200 mL), and dried over Na_2SO_4. Evaporation of the solvents yields crude thioimidates **14**, which immediately were carried to the next step. Samples of **14** were purified by rapid LC on silica gel with ether/pentane (1 : 3).

Methyl 2-(2,2-dimethyl-1,3-dioxan-5-ylidene)-2-[(N-methylthiomethylene)amino]acetate (**14a**): Yield 97%, oil. - IR (KBr): 1715 (C=O), 1680 cm^{-1} (C=N).

Benzyl ester **14b**: Yield 73%, oil. - IR (KBr): 1713 (C=O), 1588 cm^{-1} (C=N). - ^{13}C NMR ($CDCl_3$): δ = 11.3 (SCH_3), 24.2 (2 x 2'-CH_3), 60.3 and 61.2 (C-4' and C-6'), 67.2 (CH_2Ph), 100.2 (C-2'), 128.9, 129.0, 129.2, 130.8, 135.8 and 142,0 (C_6H_5, C-2 and C-5'), 161.0 (C=N), 163.5 (C=O).

Diphenylmethyl ester **14c**: Yield 92%, viscous oil. - IR (KBr): 1700 (C=O), 1575 cm^{-1} (C=N).

Azido-ß-lactams **15**; general procedure: To a vigorously stirred solution of crude methyl thioimidate **14**, obtained from the thiazoline **9** (20 mmol), and triethyl amine (4.18 mL, 30 mmol) in anhydrous dichloromethane (500 mL) at 20 °C azidoacetyl chloride[27] (**5**) (3.58 g, 30 mmol) in dichloromethane (15 mL) was added dropwise (within 2 h). Stirring was continued for 2 - 12 h before the solvent was evaporated i. vac. at rt. The residue was dissolved in dichloromethane (30 mL) and purified by LC on silica gel (1 kg) with ether/hexane (1 : 1).

Methyl (3R*,4S*)-2-(3-azido-4-methylthio-2-oxo-azetidin-1-yl)-2-(2,2-dimethyl-1,3-dioxan-5-ylidene)-acetate (**15a**): 12 h; yield 65% (based on **9**); mp 65 °C (ether/cyclohexane). - IR (KBr): 2115 (N_3), 1775 (NC=O), 1722 cm^{-1} (OC=O). - ^{13}C NMR ($CDCl_3$): δ = 13.2 (SCH_3), 23.8 and 23.9 (2 x 2'-CH_3), 52.1 (OCH_3), 60.2 and 60.6 (C-4' and C-6'), 66.8 (C-4), 69.0 (C-3), 100.1 (C-2'), 114.1 and 155.7 (C=C), 160.8 (OC=O), 161.8 (NC=O).
$C_{13}H_{18}N_4O_5S$ (342.38). Calc. C 45.81 H 5.36. Found C 45.79 H 5.32.

Benzyl ester **15b**: 12 h; yield 84%; mp 74 °C (ether/hexane). - IR (KBr): 2100 (N_3), 1775 (NC=O), 1718 cm^{-1} (OC=O).

Diphenylmethyl ester **15c**: 2 h (prolonged stirring caused double bond migration); yield 85%; oil. - IR (KBr): 2115 (N_3), 1775 (NC=O), 1720 cm^{-1} (OC=O). - ^{13}C NMR ($CDCl_3$): δ = 13.15 (SCH_3), 23.52 and 23.64 (2 x 2'-CH_3), 60.69 and 60.93 (C-4' and C-6'), 67.32 (C-4), 69.46 (C-3), 78.81 ($CHPh_2$), 100.51 (C-2'), 100.51 and 114.78 (C=C), 126.19, 129.19, 138.71, and 139.10 (2 x C_6H_5), 156.01 (C=C), 160.93 (OC=O), 161.23 (NC=O).

Acylamino azetidinones **17**; general procedure: To a soln of azide **15** (10.0 mmol) and of triethyl amine (2.09 mL, 15 mmol) in dichloromethane at 0 °C a stream of hydrogen sulfide is passed until **15** has disappeared (1 - 4 h; IR). Excess H_2S and the solvent is evaporated at rt, chilled anhydrous dichloromethane (100 mL) and at -20 °C triethyl amine or pyridine (15 mmol) and acyl chloride (15 mmol) added. Stirring is continued for 8 h, the reaction mixture washed with water and phosphate buffer soln (pH 7), dried over Na_2SO_4, the solvent removed and the residue purified by LC on silica gel.

Methyl (3*R,4*S)-2-(3-benzoylamino-4-methylthio-2-oxo-azetidin-1-yl)-2-(2,2-dimethyl-1,3-dioxan-5-ylidene)acetate (**16a**): With benzoyl chloride and pyridine; ether/hexane (1 : 1); yield 43%, mp 169 °C (ether). - IR (KBr): 3350 (NH), 1770 (ß-lactam C=O), 1725 (OC=O), 1640 cm^{-1} (NC=O). ^{13}C NMR ($CDCl_3$): δ = 10.65 (SCH_3), 26.98 (2'-CH_3), 52.89 (OCH_3), 55.39 and 59.94 (C-4' and C-6'), 62.93 (C-3), 64.81

(C-4), 99.59 (C-2'), 104.29 and 143.02 (C=C), 127.18 - 132.76 (C_6H_5), 166.89, 167.68 and 168.69 (3 C=O).
$C_{20}H_{25}N_2O_6S$ (412.49). Calc. C 56.99 H 5.98. Found C 56.86 H 5.90.

Benzyl ester **16b**: With benzoyl chloride and pyridine; tert.-butyl methyl ether (1 : 1); yield 90%, mp 138 °C. - IR (KBr): 3360 (NH), 1773 (ß-lactam C=O), 1720 (OC=O), 1668 (NC=O). - ^{13}C NMR ($CDCl_3$): δ = 12.4 (SCH_3), 23.7 and 23.9 (2'-CH_3), 61.0 and 61.3 (C-4' and C-6'), 62.4 (C-3), 68.0 (CH_2Ph), 68.2 (C-4), 100.8 (C-2'), 115.7 and 155.2 (C=C), 123.7, 128.8, 129.0, 132.3, 133.1, and 135.5 (2 x C_6H_5); 162.6, 163.8, and 167.7 (3 C=O). Calc. C 62.89 H 5.68. Found C 62.65 H 5.75.

Diphenylmethyl ester **16c**: With benzoyl chloride, triethyl amine; tert.-butyl methyl ether/hexane (1 : 1), partial crystallization from the solvent; yield 31%, mp >200 °C (decomp.). - IR (KBr): 3360 (NH), 1768 (ß-lactam C=O), 1720 (OC=O), 1665 cm^{-1} (NC=O).
$C_{32}H_{32}N_2O_6S$ (572.68). Calc. C 67.11 H 5.63. Found C 67.20 H 5.82.

Methyl (3R*,4S*)-2-(4-methylthio-2-oxo-3-phenylacetylamino-azetidin-1-yl)-2-(2,2-dimethyl-1,3-dioxan-5-ylidene)acetate (**16d**): With phenylacetyl chloride and pyridine; cyclohexane/ethyl acetate (1 : 1), yield 62%, mp 168 °C (ether). - IR (KBr): 3295 (NH), 1768 (ß-lactam C=O), 1723 (OC=O), 1653 (NC=O). - ^{13}C NMR ($CDCl_3$): δ = 12.22 (SCH_3), 23.54 and 23.68 (2 x 2'-CH_3), 42.98 (CH_2Ph), 52.90 (OCH_3), 60.41 and 60.60 (C-4' and C-6'), 61.50 (C-3), 67.13 (C-4), 100.22 (C-2'), 114.95 and 154.39 (C=C), 126.9 - 133.94 (C_6H_5), 162.78, and 171.30 (3 C=O).

Acknowledgement - Generous support by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged.

REFERENCES AND FOOTNOTES

1. In part from: H. Schmincke, Dissertation, University of Göttingen (1987).
2. In part from: H.-W. Kleemann, Dissertation, University of Göttingen (1982).
3. Review: W. Nagata, M. Narisada, T. Yoshida in R. B. Morin and M. Gorman (Ed.), Chemistry and Biology of ß-Lactam Antibiotics, Vol. 2, p. 1 - 98, Academic Press, New York 1982.
4. Review: W. Dürckheimer, J. Blumbach, R. Lattrell, K. H. Scheunemann, Angew. Chem. **97** (1985) 183; Angew. Chem., Int. Ed. Engl. **24** (1985) 180.
5. R. Bucourt in G. I. Gregory (Ed.), Recent Advances in the Chemistry of ß-Lactam Antibiotics, Chem. Soc. Spec. Publ. No 38, p. 1 - 25, London 1981.
6. Review: M. Narisada, Pure Appl. Chem. **59** (1987) 459.
7. W. Hartwig, D. Häbich, P. Naab, K. Metzger in A. G. Brown and S. M. Roberts (Ed.), Recent Advances in the Chemistry of ß-Lactam Antibiotics, Chem. Soc. Spec. Publ. No 52, p. 350 - 356, London 1985.
8. S. Wolfe, J.-B. Ducep, K. C. Tin, S.-L. Lee, Can. J. Chem. **52** (1974) 3996.
9. L. D. Cama, B. G. Christensen, J. Am. Chem. Soc. **96** (1974) 7582.
10. Attempts to prepare derivatives of type A from penicillins are reported. a) M. M. Campbell, D. I. Rawson, A. F. Cameron, Tetrahedron Lett. **1979**, 1257. b) S. Wolfe in H. Nozaki (ed.) in Current Trends in Organic Synthesis, p. 101 - 114, Pergamon Press, Oxford 1983.
11. All compounds reported in this paper are racemates.
12. D. Hoppe, M. Kloft, Liebigs Ann. Chem. **1980**, 1527.
13. a) D. Hoppe, M. Kloft, Liebigs Ann. Chem. **1980**, 1512. b) M. Kloft, D. Hoppe, Tetrahedron Lett. **1977**, 2141.
14. D. Hoppe, H. Schmincke, H.-W. Kleemann, Tetrahedron **45** (1989), preceding paper.
15. H. Schmincke, D. Hoppe, Tetrahedron **45** (1989), next paper but one.
16. R. B. Woodward, H. Vorbrüggen, unpublished results.
17. U. Schöllkopf, F. Gerhart, R. Schröder, D. Hoppe, Liebigs Ann. Chem. **766** (1972) 116. - Review: D. Hoppe, Angew. Chem. **86** (1974) 878; Angew. Chem., Int. Ed. Engl. **13** (1974) 789.
18. U. Schöllkopf, R. Harms, D. Hoppe, Liebigs Ann. Chem. **1973**, 611.
19. U. Schöllkopf, D. Hoppe, Angew. Chem. **85** (1973) 1102; Angew. Chem., Int. Ed. Engl. **12** (1973) 1006.
20. A. K. Bose, B. Anjaneyulu, S. K. Bhattacharya, M. S. Manhas, Tetrahedron **23** (1967) 4769.
21. Review: K. G. Holden in ref. c, p. 99 - 164 (1982).
22. R. Glaser, S. Gheresh, U. Schöllkopf, R. Meyer, J. Chem. Soc., Perkin 1 **1979**, 1746.
23. K. Mumami, M. Suzuki, N. Yoneda, Synthesis **1978**, 840.
24. M. Kloft, unpublished results, 1978.
25. a) B. S. Pedersen, S. Scheibye, K. Clausen, S.-O. Lawesson, Bull. Soc. Chim. Belg. **87** (1978) 229. b) T. B. Rauchfuss, G. A. Zank, Tetrahedron Lett. **27** (1986) 3445. c) G. Lajoie, F. Lêpine, L. Maziak, B. Belleau, Tetrahedron Lett. **24** (1983) 3815.

26. See also: C. F. Stanfield, W. L. Cody, V. J. Hruby, J. Org. Chem. **51** (1986) 5153.

27. CAUTION! Azidoacetyl chloride is a potential explosive! Although in our laboratory within several dozens preparations no incident happened, careful following the procedure given in ref. 13 is strongly recommended. Special attention is advised in the use of chloroacetic acid, free of higher chlorinated products.

28. B. G. Christensen, K. Hoogsten, F. Plavac, R. W. Ratcliffe, in J. Elks (Ed.) Recent Advances in the Chemistry of ß-Lactam Antibiotics, Chem. Soc. Spec. Publ. No 28, p. 260 - 268, London 1977.

29. The losses are caused during LC by the unexpectedly low solubility of **17c**.

30. R. Meyer, U. Schöllkopf, K. Madawinata, D. Staffhorst, Liebigs Ann. Chem. **1978**, 1982. - We used HMPTA (180 mL/mol) instead of acetonitrile; 2 h stirring at 40 °C; yield 79%.

31. I. Hoppe, U. Schöllkopf, Chem. Ber. **109** (1976) 482.

32. D. E. Pearson, C. A. Buehler, Chem. Rev. **74** (1974) 45.