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STUDIES TOWARD THE TOTAL SYNTHESIS OF 1-OXACEPHALOSPORINS 2: SYNTHESIS AND REACTIONS OF OXAZOLINOAZETIDINONES BEARING A γ,γ'-BIS-OXYGEN-FUNCTIONALIZED ß-METHYLBUTENOATE SIDE CHAIN[1,2]

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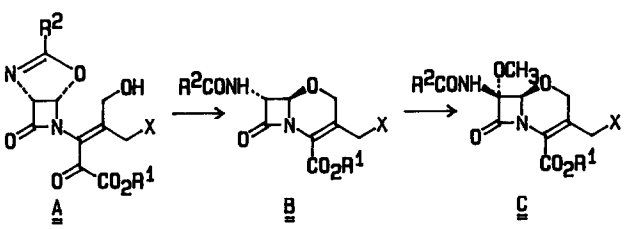
Abstract. The racemic title compounds **3** were prepared by chlorolysis of the appropriate 3-acylamino-4-methylthio-2-azetidinones **1**. The cleavage of the 1,3-dioxane ring was accomplished by proton and Lewis acids to form the intermediate diols **8**, which rapidly undergo lactonization with formation of hydroxymethyl substituted butenolides **10**. Neither **8** nor **10** cyclizes to give the 1-oxacephems **9** or **12**. A convenient one-pot procedure for the synthesis of the oxazolino-azetidinone hydroxymethyl butenolide **10b** from **1b** is given.

1-Oxacephalosporins C are artificial ß-lactam antibiotics of high antibacterial potential[3]. They are usually prepared semisynthetically in multi-step sequences from penicillins or cephalosporins[4]. One of the most appealing approaches consists in the cyclo-acetalization of oxazolino-azetidinones[5] of type **A** which bear a free (Z)-hydroxy group in the side chain (Scheme 1). Under the influence of proton or Lewis acids, from **A** the trans-oxacephem **B** is formed with inversion of configuration at C-6. Later, during the introduction of the 7-methoxy group to give **C**, the configuration at C-7 is inverted, which is essential for biological activity.

Scheme 1



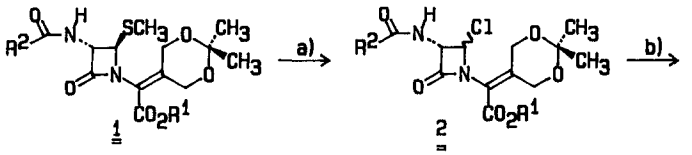
The reactions mentioned above were successfully applied to the methyl (**A**, X = H)[6] or heteroarylthiomethyl (**A**, X = SAr)[7] derivatives, but failed with monoacetates **A** (X = OAc)[6b,7]. An attempt to prepare a diol **A** (X = OH, R^1 = R^2 = tBu) by alkaline hydrolysis of the diformate was reported[8] to lead to complete destruction of the azetidinone ring with formation of a 1,5-oxacine derivative. In this paper we report the synthesis of racemic acetonide-protected oxazolinoazetidinones from appropriate 3-acylamino-4-methylthio-2-azetidinones **1**, prepared by total synthesis[9], and the reactions of the diols **8** liberated under acidic conditions.

Synthesis of Oxazolinoazetidinones

For the oxidative removal of the 4-methylthio group in the azetidinones **1** we applied the chlorolysis, introduced by Kukolja[10] and Wolfe[5c], which was also applied by us[11] to simpler analogous

of **1**. The reaction of **1** with 2 equiv. of chlorine in dichloromethane at -22 °C led to cis/trans mixtures of the 4-chlorides **2a - c** with essential quantitative yield (Scheme 2). In order to prevent side reactions of methylsulfenyl chloride and excess chlorine with the reactive double bond, the reaction mixture was evaporated to dryness at low temperature (-22 °C, 10^{-5} Torr). The crude chlorides **2** on treatment with aqueous phosphate buffer (pH 7) and LC on silica gel afforded the oxazolinoazetidinones **3a** and **3b** with 82% and 78% yield, respectively. Under these conditions, the benzhydryl ester **3c** was accompanied by approx. 35% of its deconjugated isomer **4c** (combined yield 34%). The base catalysed double-bond migration into the 1,3-dioxane ring, which threatens all reaction steps[2,12], could be avoided by using pyridine at -22 °C as a base; yield 79% of **3c**.

Scheme 2



1, **2**, **3**, **4**

1-4	a	b	c
R^1	CH_3	$PhCH_2$	Ph_2CH
R^2	CH_2Ph	Ph	Ph

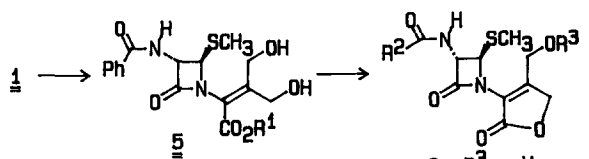
a) Cl_2, CH_2Cl_2, -40 to -15 °C. b) Aqueous phosphate buffer pH7.

The sensitive compounds **3** - although crystalline - could not be obtained analytically pure. Its constitution is well documented by the IR (1780 and 1720 cm^{-1}, C=O; 1630 cm^{-1}, C=N and C=C) and ^1H NMR data (H-1: δ = 5.27 - 5.28; H-5: δ = 6.10 - 6.20 ppm)[5c,11].

Deprotection of Acetonides 1 and 3

The liberation of the hydroxy groups and the formation of the oxacephem nucleus both require acidic catalysts. Initial studies for the first step were performed with 4-methylthio-2-azetidinones **1**. When the methyl ester **1a** was kept in formic acid (70%, 2 min at 25 °C), the hydroxymethylbutenolide **6a** was obtained with 79% yield. Similarly the benzyl ester **1b** gave **6b** which was isolated as its acetate **7b** (excess acetic anhydride/pyridine; yield 95%). **6b** was also formed on stirring **1b** with conc. hydrochloric acid/tetrahydrofuran (24 h at 25 °C). In all experiments, no traces of the intermediate diols were found. It became clear that under acidic conditions the lactonization is a severe problem and the attack of the hydroxy function at the ß-lactam carbonyl group is, compared to that, a slow reaction.

Scheme 3



5

6: R^3 = H
7: R^3 = $OCCH_3$
a: R^2 = CH_2Ph
b: R^2 = Ph

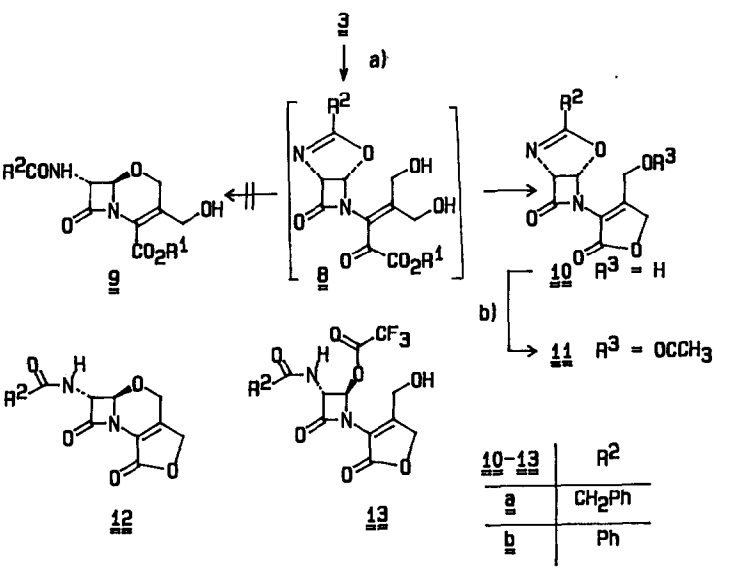
1; 5	a	b	c
R^1	CH_3	$PhCH_2$	Ph_2CH
R^2	CH_2Ph	Ph	Ph

After stirring the 1 M solution of the oxazolinoazetidinone **3b** in formic acid for 10 min at r. t., the starting material was consumed; LC on silica gel afforded the sensitive hydroxymethyl-

butenolide **10b** with 38% yield (Scheme 4). Trifluorocetic acid (at 20 °C) caused decomposition, whereas with zinc chloride etherate (2.2 M in dichloromethane, 15 h at 25 °C) a slow deprotection occurred; after acetylation the analytically pure acetate **11b** was isolated with 14% yield. With stronger Lewis acids (e.g. $BF_3 \cdot Et_2O$) complete decomposition was observed. When the crude chloride **2b** was kept in a solution of $CF_3CO_2H/CDCl_3$ (1:4, 80 MHz) in a NMR tube at r. t., after 10 min, besides acetone (δ = 2.09 ppm) and benzyl alcohol (δ = 4.58 ppm) a new trans-ß-lactam was detected (δ = 6.07 and 5.15 ppm, H-3 or H-4, J = 1.5 Hz) which probably is the 4-(trifluoroacetoxy)-azeti= dinone **13** It decomposed on attemps of isolation by crystallization or by LC with formation of **10b** in low yield. No evidence was found for the formation of strained 1-oxacephem butenolide **12b**.

The butenolide **10b** is prepared conveniently from **1b** in a one-pot procedure via the 4-methylthio-2-azetidinone **6b**: **1b** was stirred with trifluoroacetic acid/2-propanol/chloroform (4 h, 20 °C) followed by excess chlorine (3 h, r. t.) and aqueous work-up (pH 7) to yield 58% **10b**. The butenolides **10** are recognized by their absorptions in the IR-spectra: 1810 - 1750 cm^{-1} (C=O, ß-lactam and C=O, butenolide), and in ^1H NMR by a low-field shift of the 5-H absorption by 0.7 ppm compared to the benzhydryl ester **4c**. Many similar experiments carried out with the oxazolines **4b** and **c** or the chlorides **2a - c** resulted in the formation of small amounts of the butenolides **10a** or **b** and mainly in the destruction of the ß-lactam ring. In no case oxacephems **9** or **12** were detected.

Scheme 4



10-13	R^2
a	CH_2Ph
b	Ph

a) HCOOH, 10 min at r. t., or $ZnCl_2 \cdot OEt_2$, CH_2Cl_2, 15 h at r. t. b) Ac_2O/Et_3N, CH_2Cl_2, 8 h at r. t.

Conclusion

Although liberation of oxazolinoazetidinones **8** bearing hydroxymethyl groups in the side chain, could be accomplished under acidic conditions, which do not effect the ß-lactam or oxazoline ring, the butenolide formation could not be avoided. This latter result corresponds to a report given by S. Wolfe[7] without experimental details. For the synthesis of oxacephems by a strategy outlined before[9], the differentiation of the (E)- and (Z)-hydroxy protecting group seems inevitable. An example in which the (E)-hydroxy group remains blocked in the cyclization step is given in the following paper[13].

EXPERIMENTAL

All reactions were performed under N_2 or Ar with exclusion of air and, if necessary, in anhydrous solvents. 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 sep= arations for more then 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 "Silica gel 32 - 63", 0.032 -

0.063 mm, (ICN Biochemicals Eschwege) at 1 - 3 bar. - 0.1 M Phosphate buffer (pH 7) was used.

Oxazolinoazetidinones 3

Methyl (1'R*,5'S*)-2-(3-Benzyl-7-oxo-4-oxa-2,6-diazabicyclo[3.2.0]hept-2-ene-6-yl)-2-(2,2-dimethyl-1,3-dioxan-5-ylidene)acetate (**3a**): To methylthioazetidinone[9] **1a** (0.111 g, 0.255 mmol) in dichloromethane (5 mL) a 0.076 M chlorine soln in dichloromethane (1.2 mL, 0.26 mmol) was added at -40 °C and the mixture stirred for 3 h at -15 °C. Then all volatiles were removed i. vac. ($p < 10^{-4}$ torr). The residue was dissolved in acetone (5 mL) and stirred with phosphate buffer (5 mL) for 30 min. Extraction of the aqueous layer with dichloromethane (3 x 10 mL), and LC separation on silica gel (8 g) with dichloromethane/ether (1:1) gave 0.081 g **3a**; yield 82%, R_f = 0.36, mp 69 °C (ether). - IR (KBr): 1775 (NC=O), 1719 (OC=O), 1640 cm^{-1} (C=N). - ^1H NMR (100 MHz, $CDCl_3$): 1.40 (s, 2 x CH_3); 3.83 (s, CH_3O); 3.6 - 4.8 (AB of CH_2Ph and 2 x ABX of CH_2O); 5.27 (d, J = 3.6 Hz, 1-H); 6.13 (d, 5-H); 7.3 ppm (m, C_6H_5). - ^{13}C NMR ($CDCl_3$): 23.61 (2 CH_3), 35.60 (OCH_3), 52.32 (CH_2Ph), 59.77 and 60.60 (2 x CH_2O), 81.39 (C-1), 83.30 (C-5), 100.05 (C-2, dioxane), 114.53 (C-2, C=C), 156.10 (C-5, C=C), 126.93 - 133.28 (phenyl), 162.35, 165.27 and 169.45 (C=N, 2 C=O).

Benzyl (1'R*,5'S*)-2-(2,2-Dimethyl-1,3-dioxan-4-ylidene)-2-(7-oxo-3-phenyl-4-oxa-2,6-diaza-bicyclo[3.2.0]hept-2-ene-6-yl)acetate (**3b**): To **1b** (106 mg, 0.22 mmol) in dichloromethane (5 mL) a 0.292 M chlorine soln in tetrachloromethane (0.75 mL, 0.44 mmol) was added at -40 °C. After stirring at -15 °C for 3 h, the solvent, excess chlorine, and methylsulfenyl chloride were removed i. vac. ($p < 10^{-4}$ torr). The residue was dissolved in acetone (6 mL) and stirred with phosphate buffer (6 mL) for 1 h. Then the mixture was extracted with dichloromethane (3 x 10 mL) and the organic layer dried over sodium sulfate. After removal of the solvent and LC separation on silica gel (8 g) with tert.-butyl methyl ether/hexanes (1:1) **3b** (R_f = 0.25) was isolated as a white solid; yield 71 mg, 72%; mp 51 °C. IR (KBr): 1784 (NC=O), 1720 (OC=O), 1635 cm^{-1} (C=N). - ^1H NMR ($CDCl_3$), 100 MHz): 1.30 (2 x 5; CH_3); 3.88 and 4.30 (AB, J = 15.8 Hz, CH_2O); 4.63 and 4.67 (AB, CH_2O); 5.02 and 5.23 (AB, J = 11.7 Hz; $PhCH_2$); 5.46 (d, J = 3.4 Hz, 1-H); 6.88 (d, J = 3.4 Hz, 5-H); 7.25 - 7.45 and 7.80 - 7.95 ppm (m, phenyl). - ^{13}C NMR ($CDCl_3$): 23.4 (2 x CH_3), 60.3 and 60.9 (2 x CH_2O), 67.7 (CH_2Ph), 82.3 (C-1), 87.6 (C-5), 100.4 (C-2, dioxane), 115.1 (C-2, C=C), 126.8, 127.7, 128.8 - 129.3, 132.5 and 135.0 (phenyl), 156.7 (C-5, C=C), 162.0 (C=N), 165.8 (OC=O) and 67.0 (NC=O).

Diphenylmethyl (1'R*,5'S*)-2-(2,2-Dimethyl-1,3-dioxan-4-ylidene-2-(7-oxo-3-phenyl-4-oxa-2,6-diaza-bicyclo[3.2.0]hept-2-ene-6-yl)acetate (**3c**) and Diphenylmethyl (1'R*,5'S*,5R*,S*)-2-(2,2-Dimethyl-4,5-dehydrodioxan-5-yl)-2-(7-oxo-3-phenyl-4-oxa-2,6-diazabicyclo[3.2.0]hept-2-ene-6-yl)acetate (**4c**): A suspension of **1c**[9] (0.626 g, 1.09 mmol) in dichloromethane (3 mL) was treated with a 0.5 M chlorine soln in tetrachloromethane (4 mL, 2.0 mmol) at -22 °C. After 2 h stirring, excess chlorine, the solvent, and methylsulfenyl chloride were removed i. vac. ($p < 10^{-4}$ torr) at -22 °C, the residue was dissolved in dichloromethane (10 mL) and stirred with phosphate buffer (10 mL) over night. The organic layer was purified by LC on silica gel (8 g) with ether/pentane (1:1) as eluent; yield 100 mg (17%) **3c**; R_f = 0.24, white solid, mp 80 °C (ether); besides 97 mg (17%) of a 1:1 mixture of **3b** and **4c**.

In a similar experiment, after evaporation, the residue was dissolved with pyridine (0.15 mL)/dichloromethane (20 mL) and after 1 h the volatiles again removed i. vac.; yield 79% pure **3c**. **3b**, IR (KBr): 1780 (NC=O), 1720 (OC=O), 1630 cm^{-1} (C=N). - ^1H NMR ($CDCl_3$, 300 MHz): 1.31 (2 x s, CH_3); 3.97 and 4.38 (AB, J = 12 Hz, CH_2O); 4.75 (m, CH_2O); 5.38 (d, J = 3 Hz, 1-H); 6.20 (d, J = 3 Hz, 5-H); 6.89 (s, Ph_2CH); 7.28, 7.39, 7.51 and 8.07 (m, ArH). - ^{13}C NMR ($CDCl_3$): 23.50 (CH_3), 60.17 and 60.68 (CH_2O), 78.97 (Ph_2CH), 81.96 (C-1), 87.38 (C-5), 100.23 (C-2, dioxane), 115.07 (C-2, C=C), 126.69 - 139.16 (phenyl), 156.88 (C-5, C=C), 161.27 (C-3), 165.63 (OC=O) and 166.85 (NC=O). - **4c**: IR (KBr): 1780 (NC=O), 1730 cm^{-1} (OC=O). - ^1H NMR ($CDCl_3$, 100 MHz): 1.18 (s, CH_3); 1.39 (s, CH_3); 4.29 (s, 2-H, NCH); 4.28 and 4.44 (AB, J = 12 Hz, CH_2O); 5.63 (s, H-4, dioxane); 5.34 (d, J = 3.5 Hz, 1-H); 6.21 (d, J = 3.5 Hz, 5-H); 6.91 (s, Ph_2CH); 7.1 - 8.01 (m, phenyl).

Deprotection of Methylthioazetidinones 1

(3R*,4S*)-1-(4-Hydroxymethyl-2-oxo-2,5-dihydrofuran-3-yl)-4-methylthio-3-phenylacetamino-azetidin-2-one (**6a**): **1a** (0.196 g, 0.45 mmol) in formic acid (70%, 5 mL) was stirred at r. t. for 2 min, then the acid removed i. vac.. LC separation of the residue on silica gel (8 g) with tert.-butyl methyl ether/hexane/dichloromethane (2:1:1) gave 0.111 g (70%) **6a** as a colourless viscous oil. - IR (KBr): 3300 (NH), 1790 - 1680 (ß-lactam C=O, butenolide C=O, and amide C=O), 1620 (C=C) cm^{-1}. - ^1H NMR ($CDCl_3$, 100 MHz): 2.09 (SCH_3); 3.52 (s, CH_2OH); 3.78 (b, OH); 4.37 and 4.64 (AB, J = 16 Hz, butenolide CH_2); 4.75 - 5.0 (m, 3'-H and $PhCH_2$); 5.42 (d, J = 2.5 Hz, 4'-H); 7.1 - 7.45 (phenyl). - ^{13}C NMR ($CDCl_3$): 11.59 (SCH_3), 42.71 (CH_2OH), 56.2 (5'-C), 61.2 and 63.8 (C-3 and C-4), 69.6 ($PhCH_2$), 117.63 (C-3), 127.38, 128.89, 129.46 and 134.12 (phenyl), 154.96 (C-4), 164.18 (NC=O, amide), 169.07 (NC=O, ß-lactam), 172.47 ppm (OC=O).

(3R*,4S*)-1-(4-Acetoxymethyl-2-oxo-2,5-dihydrofuran-3-yl)-3-benzoylamino-4-methylthio-azetidin-2-one (**7b**): After 2 min stirring **1b** (102 mg, 0.205 mmol) in formic acid (2 mL) at r. t. the solvent was removed i. vac., the residue dissolved in acetic anhydride (2 mL) and pyridine (33 mg) was added. Stirring over night, removal of excess acetic anhydride i. vac. (8 torr), and LC separation on silica gel (8 g) 76 mg (95%) **7b** were isolated as a colourless viscous oil. - IR (KBr): 3350 (NH), 1790 - 1720 (ß-lactam C=O), butenolide C=O, and ester C=O, 1650 cm^{-1} (NC=O). ^1H NMR ($CDCl_3$, 100 MHz): 2.09 (s, SCH_3); 2.21 (s, $CH_3C=O$); 4.87 (m, AB, CH_2OAc); 5.09 and 5.10 (AB, 5'-Hz); 4.23 (d, J = 10 Hz, N-H); 4.32 (dd, J_1 = 10 Hz, J_2 = 2.6 Hz, 3-H); 5.59 (d, J = 2.6 Hz, 4-H); 7.2 - 7.5 and 7.7 - 8.0 (m, phenyl).
$C_{18}H_{18}N_2SO_6$ (390.41). Calc. C 55.38 H 4.65. Found C 55.78 H 4.93.

(3R*,4S*)-3-Benzoylamino-1-(4-hydroxymethyl-2-oxo-2,5-dihydrofuran-3-yl)-4-methylthio-azetidin-2-one (**6b**): A soln **1b** (0.203 g, 0.409 mmol) and conc. hydrochloric acid (67 mg) in THF (6 mL) was

stirred until the starting material was consumed (TLC, 24 h). Then phosphate buffer (8 mL) was added and the mixture extracted with tert.-butyl methyl ether. The solvent of the organic layer was removed i. vac. and the residue purified by LC; yield 120 mg (86%) **6b**; white solid, mp 105 °C. - IR (KBr): 3365 (OH), 1740 - 1800 (ß-lactam C=O and butenolide C=O), 1650 cm^{-1} (NC=O). - ^1H NMR ($CDCl_3$, 90 MHz): 2.12 (s, SCH_3); 3.88 (b, OH); 4.68 (b, CH_2OH); 4.98 (s, 5'-Hz); 5.28 (dd, J_1 = 8 Hz, J_2 = 2 Hz, 3-H); 5.67 (d, J = 2 Hz, 4-H); 7.2 - 8.0 (phenyl), 8.08 (d, J = 10 Hz, N-H).
MS: $C_{16}H_{16}N_2O_5S$ Calc. 348.0780. Found 348.0777.

Butenolides 10 and 11

(1'R*,5'S*)-3-(7-Oxo-3-phenyl-4-oxa-2,6-diazabicyclo[3.2.0]hept-2-ene-6-yl)-4-hydroxymethyl-2,5-dihydrofuran-2-one (**10b**): **3b** (79 mg, 0.179 mmol) was stirred in formic acid (10 mL) for 10 min. Then the acid was removed i. vac. and the residue separated by LC on silica gel (8 mg) with tert.-butyl methyl ether/toluene (1:1); yield 20 mg, 38%. - IR (KBr): 1773 (ß-lactam C=O), 1757 (butenolide C=O), 1673 (C=C), 1632 cm^{-1} (C=N). - ^1H NMR ($CDCl_3$, 100 MHz): 2.81 (s, OH); 4.40 and 4.70 (AB, J = 15.3 Hz, 5-Hz); 4.91 and 4.92 (AB, CH_2OH); 5.46 (d, J = 3.4 Hz, 1'-H); 6.88 (d, J = 3.4 Hz, 5'-H); 7.20 - 8.10 (phenyl).
MS: $C_{15}H_{12}N_2O_5$ Calc. 300.0746. Found 300.0746.

10b, One-Pot Procedure via **6b**: A soln of **1b** (0.169 g, 0.34 mmol) in 2-propanol (2 mL), trichloromethane (2 mL), and trifluoroacetic acid (0.6 mL) was stirred for 4 h at r. t.. Then a 1.04 M chlorine soln in tetrachloromethane (2 mL) was added. After 3 h stirring, the mixture was poured into phosphate buffer (10 mL), extracted with dichloromethane, and purified by LC as above; yield 60 mg (58%) **10b**.

(1'R*,5'S*)-3-(7-Oxo-3-phenyl-4-oxa-2,6-diazabicyclo[3.2.0]hept-2-ene-6-yl)-4-acetoxymethyl-2,5-dihydrofuran-7-one (**11b**): **3b** (0.102 g, 0.227 mmol) and zinc chloride etherate soln in dichloromethane (2.2 M, 0.6 mL, 1.32 mmol) were stirred for 12 h at r. t.. Then acetic anhydride (1 mL) and triethyl amine (0.32 mL, 2.3 mmol) were added and the mixture stirred for another 8 h. The volatiles were removed i. vac. and the residue was purified by LC on silica gel (8 g) with ether; yield 11 mg (14%) **11b**; white solid, mp 119 °C. - IR (KBr): 1810 - 1730 (butenolide C=O, ß-lactam C=O, and ester C=O), 1630 cm^{-1} (C=C). - ^1H NMR ($CDCl_3$, 100 MHz): 1.93 (s, CH_3); 4.82 (b, 5-Hz); 5.19 (b, CH_2OAc); 5.45 (d, J = 3.6 Hz, 1'-H); 6.82 (d, J = 3.6 Hz, 5'-H); 7.42, 7.49 and 8.02 (m, phenyl).
$C_{17}H_{14}N_2O_6$ (342.31). Calc. C 59.65 H 4.12. Found C 59.72 H 4.11.

Deprotection of the chloride (**2b**): The chloride **2b** (18 mg, 0.04 mmol), $CDCl_3$ (0.5 mL), and trifluoroacetic acid (0.1 mL) were kept in a NMR tube. After 10 min equimolar amounts of acetone (δ = 2.1) and benzyl alcohol (δ = 4.58) were detected besides the signals of a trans-ß-lactam at 6.07 and 5.15 ppm (J = 1.5 Hz). After LC, a mixture of the butenolide **10b** and the trans-ß-lactam, probably the trifluoroacetate **13**, was obtained; yield 2 mg, 15%.

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