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A CONVERGENT SCHEME FOR THE STEREOSELECTIVE SYNTHESIS OF 3'-NOR-1-OXACEPHEMS

D. Häbich* and W. Hartwig

Chemisch-wissenschaftliches Labor Pharma der BAYER AG
Postfach 10 17 09, D-5600 Wuppertal 1, W-Germany.

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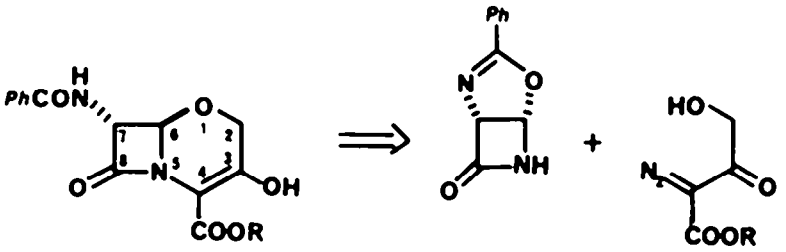
Abstract - A convergent approach to the construction of the 3-hydroxy-oxacephems **1**, valuable intermediates for the synthesis of 3'-nor-1-oxacephems, is presented. The key step utilizes the Lewis acid catalyzed stereoselective ring-opening of the oxazoline **2** by an appropriately functionalized alcohol **3**.

The oxacephem class of β-lactam antibiotics has been under intense investigation in recent years[1] since the "simple" replacement of sulfur by oxygen in cephalosporins was found to afford compounds of up to four to eight fold higher antibacterial activity[2]. These efforts have yielded various syntheses of oxacephems[3]. Oxacephems of the 3'-nor type have also been synthesized in this context[4], some showing considerable antibacterial activity[2c,4g,4k,5]. All the procedures known to date for the preparation of the corresponding oxacephem nuclei are multistep linear syntheses in which every reaction step is carried out in the presence of the sensitive β-lactam ring. Linear syntheses have, however, a marked strategic disadvantage compared with convergent syntheses[6]. Our aim was to establish a convergent access to this class of β-lactam derivatives.†



1 **2** **3**

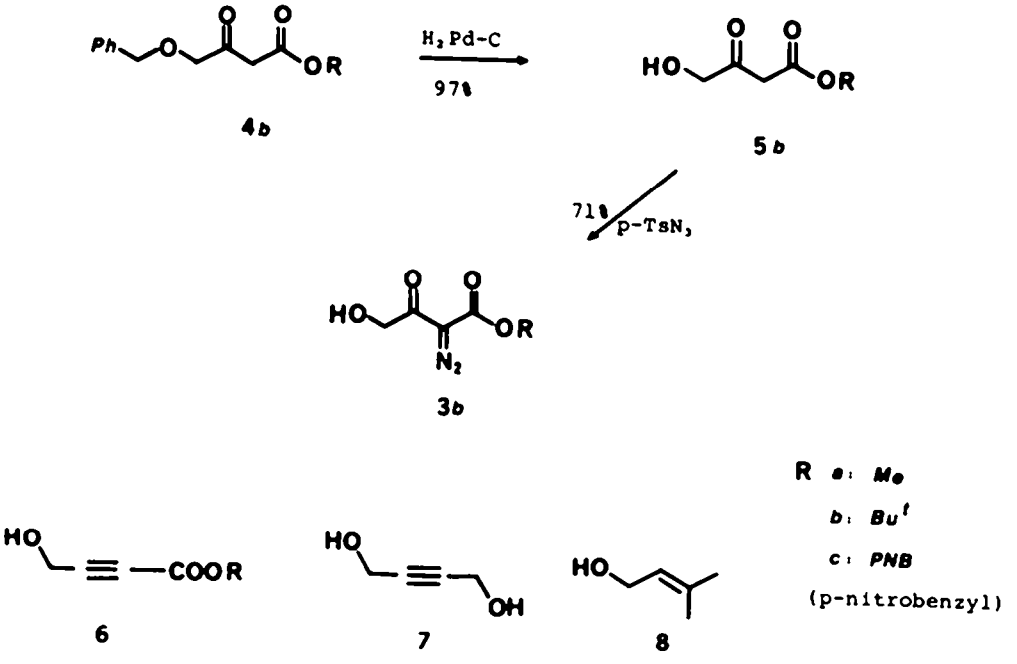
Scheme I. Synthetic strategy for 3'-nor-oxacephem synthesis

† A recently published patent application[7] claiming almost the same synthetic strategy has prompted us to report our results. In contrast to this work we found no need to use the oxazoline **2** in its N-6 protected form for the key transformation.

For the synthesis of 3'-nor-oxacephems, the 3-hydroxy-derivative **1** was envisaged as a common key intermediate allowing further elaboration of the nucleus[4b-e]. The retro-synthetic disconnection (scheme I) of the C_4-O and the C_4-N bond suggested the use of a chiral synthetic building block **2** and an achiral partner **3** that would possess both the necessary carbon skeleton and the appropriate stereochemistry to permit correct configuration in forming the critical C_4-O bond. Oxazolino-azetidinones substituted at nitrogen can be opened stereoselectively by alcohols in the presence of proton or Lewis acids[8]. Intramolecular variants of this reaction have been used by Nagata et al. for the construction of oxacephems[9]. N-6 unsubstituted oxazolines **2**, recently described by us[10], should, in contrast to the N-substituted congeners, react with bifunctional reagents such as **3** to give the bicyclic β-lactams directly.

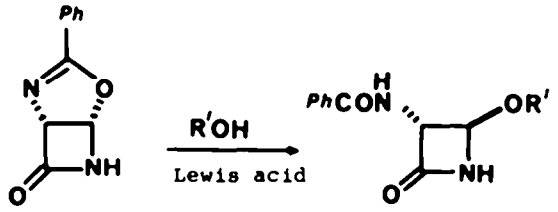
The present report describes a convergent approach to the construction of 3'-nor-oxacephems utilizing the Lewis acid catalyzed stereoselective ring-opening of the oxazoline **2** by a functionalized alcohol **3** and subsequent ring closure by Merck-type[11] carbene insertion (scheme I).

In the preparation of the reaction partner **3b**, the β-ketoester **4b** was synthesized (scheme II) from tert.-butyl 4-chloroacetoacetate[12] by substitution with sodium benzylate in analogy to known methods[12,13]. The 4-hydroxyaceto-acetate **5b** was obtained successfully from **4b** by hydrogenolysis in ethanol in the presence of 10% palladium on charcoal [14], thus providing access to its diazo derivative **3b**. Less sensitive masked 4-hydroxyacetoacetate equivalents such as 4-hydroxybutynoates **6** and 2-butyne-1,4-diol **7** were also considered as possible alternatives.



Scheme II. Synthesis of the 4-hydroxyacetates

The synthetic feasibility and the stereochemistry of the crucial oxazoline ring-opening reaction was first investigated using 3-methyl-2-buten-1-ol **8** (table I). Reaction of **2** with excess alcohol **8** in dichloromethane in the presence of tin (II) chloride yielded the ring-cleavage product **9** within 15 minutes (0°→ room temp.) in 70% yield with a trans stereoselectivity of > 30:1 (NMR). Prolonged reaction times led to the chiral acetals **10** (R'=3-methyl-



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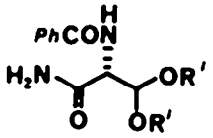

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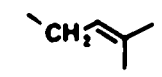
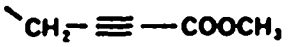
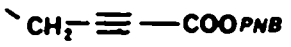
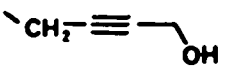
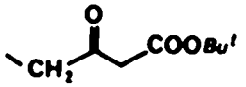
9 R': 

11 a 

11 c 

12 

14 b 

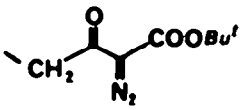
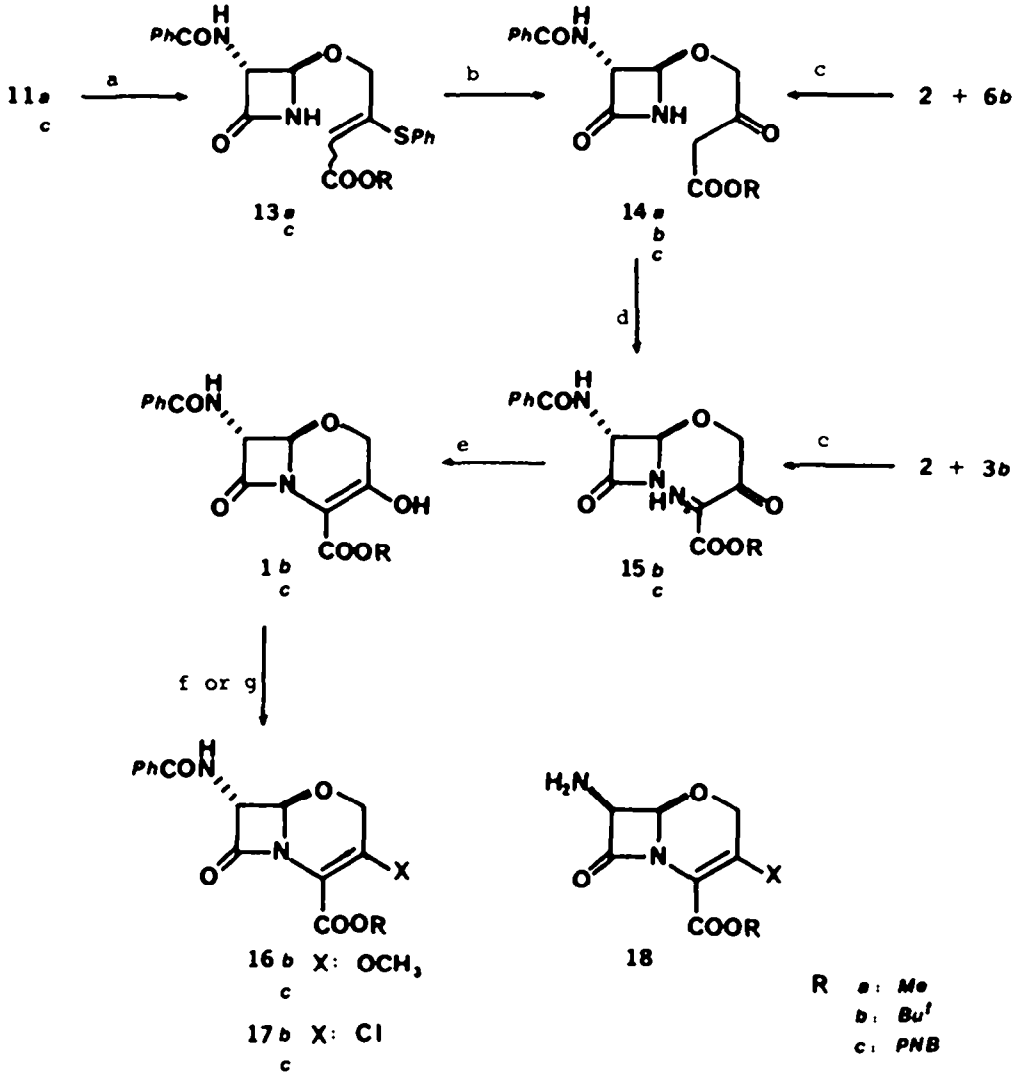
15b 

Table I. Stereoselective ring-opening of oxazoline **2** by alcohols.

entry	alcohol (equiv.)	Lewis acid	solvent	time [h]	product	isol.yield [%]
1	**8** (10)	$SnCl_2$	CH_2Cl_2	0.25	**9**	70
2	**6a** (5)	$SnCl_2$	CH_2Cl_2	1	**11a**	23
3	**6a** (5)	$BF_3 \cdot Et_2O$	CH_2Cl_2	1	**11a**	63
4	**6c** (2)	$BF_3 \cdot Et_2O$	THF	0.5	**11c**	66
5	**7** (2)	$BF_3 \cdot Et_2O$	THF	2	**12**	8
6	**5b** (2)	$BF_3 \cdot Et_2O$	THF	0.5	**14b**	31
7	**3b** (1.8)	$BF_3 \cdot Et_2O$	THF	0.3	**15b**	74
8	**3b** (1.1)	$BF_3 \cdot Et_2O$	THF	0.3	**15b**	71



Scheme III. Elaboration of the 3'-nor-oxacephem nuclei

reagents: (a) $HSPh$, NEt_3, THF, 0°C → r.t.

(b) N-bromoacetamide, dioxane:H_2O 10:1, 0°C; Na_2SO_3

(c) $BF_3 \cdot Et_2O$, THF, 0°C → r.t.

(d) p-TsN$_3$ or p-HOOC-C_6H_4-SO_2N_3, NEt_3, CH_3CN, 0°C → r.t.

(e) cat. $Rh_2(OAc)_4$, C_6H_6 or $ClCH_2CH_2Cl$, 80°C

(f) CH_2N_2, Et_2O-CH_2Cl_2, r.t.

(g) PCl_5, DMF, 0°C → r.t.

2-butenyl) via the intermediate **9** . The use of boron trifluoride etherate instead of tin (II) chloride was found to be more favorable in the reaction with methyl 4-hydroxy-2-butynoate **6a**[15] (entries 2, 3) . Owing to the better solubility of the oxazoline **2** , the use of THF instead of dichloromethane as solvent enabled both the reaction time and the excess of alcohol used to be reduced (entries 4-8). We ascribe the low yield of **12** to the poor solubility of **7** in THF and the subsequent rapid reaction of **12** to ring-opened products e.g. **10** . Side-reactions that were not further investigated are responsible for the moderate yield of **14b** in the reaction of **2** with the sensitive 4-hydroxyacetoacetate **5b** . Tert.Butylester protection, although problematic in oxacephems, was chosen to counteract sterically the possible formation of tetronic acid[15,16] under the reaction conditions. A highly convergent access to the 3'-nor-oxacephem skeleton was achieved by reacting the building blocks **2** and **3b** under almost the same conditions (entry 7) affording the crystalline oxacephem-precursor **15b** directly in 74% yield. Due to the greater stability of **3b** compared to **5b** the conversion could be carried out employing almost equimolar amounts of the reactants without adversely affecting yield (entry 8).

Less convergent but also favorable in terms of overall yield was the route via the butynoates **11a,c** , which were converted to the ß-ketoesters **14a,c** (scheme III) by formal addition of water according to the mild method of Ikegami[17]. In one case in the methyl ester series the thioaddition product **13a** was isolated and characterized. One-pot conversion of **11** to **14** generally gave yields exeeding 80%. The ß-ketoesters **14b,c** were smoothly converted to the diazo derivatives **15b,c** by reaction with p-toluenesulfonyl[18] - or the saver[19] 4-carboxybenzenesulfonyl azide[20]. The ring-closure of the diazo-ß-ketoesters **15** to the 3-hydroxy-oxacephems **1** was achieved using the rhodium (II) acetate catalyzed carbene insertion method developed by Christensen et al.[11] to form carbapenems.†

Further derivatization was carried out by reacting the 3-hydroxy derivatives **1** with diazomethane to give the 3-methoxy compounds **16** , and with phosphorus trichloride in DMF to give the 3-chloro compounds **17**[4e,21].

Compounds of the type **16** and **17** have already been prepared as benzhydryl[4e] and PNB[4j] esters during the course of other oxacephem syntheses. Their further conversion to the corresponding nor-oxacephem nuclei **18** by cleavage of the benzoyl protecting group and subsequent isomerization of the amino function can be effected by various well-known methods[4k,22].

In conclusion the convergent sequence **2** + **3** ⟶ **15** ⟶ **1** represents the shortest route to the 3'-nor-oxacephem ring system known so far. The synthetic operations carried out in the presence of the sensitive ß-lactam ring have been reduced to a minimum.

EXPERIMENTAL

Melting points were determined on a Büchi capillary melting point apparatus and are uncorrected. IR spectra were determined on a Perkin-Elmer 281 infrared spectrophotometer. UV spectra were recorded on a Perkin-Elmer 554 spectrophotometer and optical rotations were determined using a Perkin-Elmer 241 MC polarimeter. The NMR spectra were recorded on Bruker WP 200, WM 250 and AM 300 spectrometers in either $CDCl_3$ or $(CD_3)_2SO$ solution. Chemical shifts are reported as δ values in ppm relative to tetramethylsilane (δ 0.0) as an internal standard. Data are reported as follows: chemical shift (multiplicity, coupling constants, integrated intensity, assignment). Mass spectra were obtained on a Kratos MS 80 mass spectrometer. All reactions were performed under a positive atmosphere of N_2 with the aid of a Firestone valve. Reactions

† see also ref. 4j

were monitored by analytical thin-layer chromatography using 5 x 10 cm TLC plates: silica gel 60 F-254, layer thickness 0.25 mm, E. Merck. Silica gel columns for chromatography utilized E. Merck silica gel 60 (230-400 mesh ASTM) and a slightly positive pressure of air. "Anhydrous" solvents were distilled shortly before use from an appropriate drying agent.

tert.-Butyl 4-benzyloxyacetoacetate (**4b**). A solution of 64.9 g = 62.1 ml (0.6 mol) of benzyl alcohol in 50 ml of tetrahydrofuran (THF) was added to an ice-cooled suspension of 18.0 g (0.6 mol) of sodium hydride (80% in paraffin oil) in 150 ml of anhydrous THF in the course of 1 h at 0°C and the mixture was stirred at room temp. for 0.5 h. A solution of 57.8 g (0.3 mol) of tert.-butyl 4-chloroacetoacetate[12] in 50 ml of THF was added at 0°C in the course of 1 h. The ice-bath was removed and the reaction mixture was stirred at room temp. for a further hour and neutralized by careful addition of 0.5 N HCl with cooling (pH control). The mixture was extracted with ether and the extracts were washed with water and dried over $MgSO_4$. Evaporation of the ether in vacuo gave an oil, which was purified by chromatography on 1.7 kg of silica gel (toluene:ethyl acetate 95:5), to afford 41.7 g (53%) of **4b**, Rf: 0.47 (toluene:ethyl acetate 9:1). ^1H NMR (200 MHz, $CDCl_3$) δ 1.50 (s, 9H, $C(CH_3)_3$), 3.48 (s, 2H, CH_2), 4.18 (s, 2H, CH_2), 4.63 (s, 2H, CH_2) and 7.40 (s, 5H, Ph). IR ($CHCl_3$) 1740-1710 (C=O, β-keto ester), 1656 cm^{-1} (C=C, enol form). Anal.Calcd. for $C_{15}H_{20}O_4$: C 68.16, H 7.63. Found: C 68.2, H 7.6%.

tert.-Butyl 4-hydroxyacetoacetate (**5b**). A mixture of 6.61 g (25 mmol) of **4b** and 1.32 g of palladium (10% on charcoal) in 345 ml of methanol was stirred at room temp. under a hydrogen atmosphere (1 atm.) for 1.5 h. The catalyst was removed by filtration, the filtrate solution was evaporated off in vacuo and the oil which remained was dried under a high vacuum to afford 4.24 g (97%) of **5b** as an oil. Rf: 0.31 (toluene:ethyl acetate 3:2). ^1H NMR (200 MHz, $CDCl_3$) δ 1.50 (s, 9H, $C(CH_3)_3$), 3.05 (bs, 1H, OH), 3.43 (s, 2H, CH_2) and 4.38 (bs, 2H, CH_2). Anal.Calcd. for $C_8H_{14}O_4$: C 55.16, H 8.10. Found: C 55.2, H 8.3%.

tert.-Butyl 2-diazo-4-hydroxy-3-oxobutanoate (**3b**). 6.72 ml (48.2 mmol - 2 equiv.) of triethylamine was added dropwise to a solution, cooled to 0°C, of 4.20 g (24.1 mmol) of **5b** and 5.22 g (26.5 mmol) of 4-toluenesulfonyl azide[18] in 48 ml of anhydrous acetonitrile. The mixture was stirred for 3 h at 0°C and 0.5 h at room. temp., treated with 10 g of Celite and evaporated in vacuo. Chromatography of the residue on 200 g of silica gel (toluene:ethyl acetate 85:15) afforded 3.43 g (71%) of **3b** as light colored crystals, mp. 35°C, Rf: 0.36 (toluene:ethyl acetate 4:1). IR ($CHCl_3$): 3495 (OH), 2982, 2141 (N_2), 1709 (C=O), 1643 (C=O), 1335, 1137, 990 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 1.52 (s, 9H, $C(CH_3)_3$), 3.48 (t, J=5Hz, 1H, CH_2OH), 4.59 (d, J=5Hz, 2H, CH_2OH). Anal.Calcd. for $C_8H_{12}N_2O_4$: C 48.00, H 6.04. Found: C 48.0, H 6.1%.

4-Nitrobenzyl 4-hydroxy-2-butynoate (**6c**). A solution of 3.3 ml (23.3 mmol) of tetrahydro-2-(2-propynyloxy)-2H-pyran[15] in 23 ml of anhydrous THF was added to 7.8 ml (23.2 mmol) of a 3 molar solution of ethyl-magnesium bromide in ether at room temp. in the course of 0.5 h. The mixture was then stirred at room temp. for 1.5 h. This solution was added dropwise to a stirred solution, cooled to -20°C, of 5.0 g (23.2 mmol) of 4-nitrobenzyl chloroformate in 25 ml of THF in the course of 1.5 h. The mixture was stirred at -15°C for 0.5 h and at 0°C for 1.5 h, and was then left to stand at 0°C for 12 h, whereupon the magnesium salts crystallized. The salts were removed by filtration and the filtrate solution was washed with brine and dried over $MgSO_4$. The solvent was evaporated in vacuo, the residue was dissolved in 25 ml of anhydrous methanol and stirred with 1 ml of Dowex-50-X4 (H^+ form) at room temp. for 1 h. The ion exchanger was removed by filtration, the filtrate solution was concentrated in vacuo and the residue was dried under high vacuum. The treatment with the ion exchanger was repeated as described above. The crude product was chromatographed on 300 g of silica gel (toluene:ethyl acetate 4:1) to afford 2.07 g (38%) of **6c** as colorless crystals, mp. 93-94°C, Rf: 0.27 (toluene: ethyl acetate 4:1). IR (KBr): 3475 (OH), 2235 (-C≡C-), 1690 (C=O, ester), 1524 (NO_2, as.) and 1348 cm^{-1} (NO_2, sym.). ^1H NMR (200 MHz, DMSO) δ 4.30 (d, J=6Hz, 2H, CH_2OH), 5.38 (s, 2H, CH_2-), 5.63 (t, J=6Hz, 1H, CH_2OH), 7.68 (d, J=20Hz, 2H, H-aromatic) and 8.15 (d, J=20Hz, 2H, H-aromatic). Anal.Calcd. for $C_{11}H_9NO_5$: C 56.17, H 3.86, N 5.96. Found: C 56.2, H 3.9, N 6.1%.

3(R)-Benzoylamino-4-(R)-[3-methyl-2-butenyloxy]-2-azetidinone (**9**). 181 mg (0.96 mmol - 1.2 equiv.) of anhydrous tin-II chloride (dried by fusing briefly under a high vacuum) was added, at 0°C, to a suspension of 150 mg (0.78 mmol) of (1R,5S)-3-phenyl-4-oxa-2,6-diazabicyclo[3.2.0]hept-2-en-7-one (**2**)[10] in 1.3 ml of anhydrous CH_2Cl_2 and 0.81 ml (7.8 mmol - 10 equiv.) of **8**. The cooling bath was removed and the reaction mixture was stirred for 15 min. at room temp., poured into dilute $NaHCO_3$ solution and extracted with CH_2Cl_2 and the extract was washed with water and dried over $MgSO_4$. Evaporarion of the solvent in vacuo and filtration of the residue on 5 g of silica gel (toluene:ethyl acetate 3:7) afforded 153 mg (70%) of **9** as colorless crystals, mp. 92°C, Rf: 0.38 (toluene:ethyl acetate 3:7). IR (KBr): 1775 (C=O, β-lactam), 1667 (C=O, amide), 1633 (C=C) and 1529 cm^{-1} (amide II-band). ^1H NMR (200 MHz, $CDCl_3$) δ 1.70, 1.77 (s, 6H, CH_3), 4.18 (m, 2H, $-OCH_2-CH=$), 4.74 (dd, J=9Hz, 1Hz, 1H, H-3), 5.23 (d, J=1Hz, 1H, H-4), 5.38 (m, 1H, $-CH=$), 6.78 (s, 1H, NH), 7.18 (d, J=9Hz, 1H, NH), 7.4-7.6 (m, 3H, C_6H_5) and 7.8 (m, 2H, o-C_6H_5). MS (70eV): m/e = 274 (M^+); calculated: 274.32. Anal.Calcd. for $C_{15}H_{18}N_2O_3$: C 65.68, H 6.61,

N 10.21. Found: C 65.4, H 6.5, N 10.0%.

2(R)-Benzoylamino-3,3-bis(3-methyl-2-butenyloxy)propionic amide (**10**). As described for the preparation of **9**, 94 mg (0.5 mmol) of **2** after 7 h at room temp. and chromatography of the crude product on 15 g of silica gel (toluene: ethyl acetate 3:7) afforded 63 mg (46%) of **9** (data see above) and 77 mg (43%) of **10** as colorless crystals, mp. 159-160°C, Rf: 0.46 (toluene:ethyl acetate 3:7). IR (KBr): 1667 and 1528 (C=O, amide), 1633 cm^{-1} (C=C). ^1H NMR (250 MHz, $CDCl_3$) δ 1.61, 1.64 1.72, 1.78 (s, 12H, CH_3), 4.0-4.3 (m, 2H, $-CH_2-CH=$), 4.73 (dd, J=6Hz, 2Hz, 1H, H-2), 4.95 (d, J=2Hz, 1H, $-CH(OR)_2$), 5.23, 5.37 (t, J=6Hz, 2H, $-CH_2-CH=$), 5.54, 6.67 (s, 2H, $CONH_2$), 7.23 (s, 1H, NHCOPh), 7.35-7.5 (m, 3H, Ph), 7.8 (m, 2H, o-benzoyl-H). MS (70eV): 275 ($M^+-OC_5H_9$). Anal.Calcd. for $C_{20}H_{28}N_2O_4$: C 66.64 H 7.83, N 7.77. Found: C 66.3, H 7.6, N 7.8%.

Methyl 4-[3(R)-benzoylamino-2-azetidinon-4(R)-yloxy]-2-butynoate (**11a**). a) As described for the preparation of **9**, 94 mg (0.5 mmol) of the oxazoline **2** and 290 mg (2.5 mmol - 5 equiv.) of methyl 4-hydroxy-2-butynoate (**6a**)[15] after 1 h at room temp. afforded 35 mg (23%) of the adduct **11a** as colorless crystals, mp. 142-143°C, Rf: 0.29 (toluene:EtOAc 2:3), $[\alpha]_D^{20}$ = 18.37° (c 1.035, acetone). IR ($CHCl_3$): 2240 (C≡C), 1784 (C=O, β-lactam), 1717 (C=O, ester) and 1662 cm^{-1} (C=O, amide). ^1H NMR (250 MHz, DMSO) δ 3.70 (s, 3H, $COOCH_3$), 4.54 (AB, J=15Hz, 2H, CH_2O), 4.66 (dd, J=8Hz, 1Hz, 1H, H-3), 5.24 (d, J=1Hz, 1H, H-4), 7.5-7.65 (m, 3H, Ph), 7.9 (m, 2H, ortho-benzoyl-H), 9.08 (s, 1H, NH) and 9.18 (d, J=8Hz, 1H, NH). Anal.Calcd. for $C_{15}H_{14}N_2O_5$: C 59.60, H 4.67, N 9.27. Found: C 59.2, H 4.7, N 9.2%. b) 0.41 ml (3.33 mmol - 13 mol %) of boron trifluoride etherate was added to a suspension of 4.70 g (25.0 mmol) of the oxazoline **2** and 14.3 g (125 mmol - 5 equivalents) of the butynoate **6a**[15] in 40 ml of anhydrous CH_2Cl_2 at room temp.. The mixture was stirred at room temp. for 1 h, whereupon a clear solution formed. The solution was poured into dilute $NaHCO_3$ solution, the mixture was extracted with CH_2Cl_2 and the extracts were washed with water and dried over $MgSO_4$. Evaporation of the solvent in vacuo and chromatography of the residue on 120 g of silica gel (toluene:ethyl acetate 2:3) afforded 4.74 g (63%) of **11a**, the physical data being identical to those of the substance prepared according to method a).

4-Nitrobenzyl 4-[3(R)-benzoylamino-2-azetidinon-4(R)-yloxy]-2-butynoate (**11c**). 10 µl (0.08 mmol - 4 mol %) of boron trifluoride etherate was added to a suspension of 376 mg (2 mmol) of **2** and 941 mg (4 mmol) of the butynoate **6c** in 8 ml of anhydrous THF at 0°C. The mixture was stirred at room temp. for 0.5 h and was then poured into dilute $NaHCO_3$ solution and extracted with CH_2Cl_2. The extract was washed with water and dried over $MgSO_4$. Evaporation of the solvent in vacuo and chromatography of the residue on 60 g of silica gel (toluene:ethyl acetate 35:65) gave 557 mg (66%) of the adduct **11c** as a colorless foam. Rf: 0.55 (ethyl acetate), $[\alpha]_D^{20}$ = -35.28° (c 0.5, $CHCl_3$). IR (KBr): 3330 (NH), 2244 (C≡C), 1780 (C=O, β-lactam), 1715 (C=O, ester), 1651 and 1524 (amide), 1524 (NO_2-as) and 1350 cm^{-1} (NO_2-sym.). ^1H NMR (250 MHz, $CDCl_3$) δ 4.54 (AB, J=16Hz, 2H, CH_2O), 4.69 (d, J=9Hz, 1H, H-3), 5.28 (s, 2H, CH_2-benzyl), 5.34 (s, 1H, H-4), 7.08 (s, 1H, NH), 7.4-7.6, 7.8 (m, Ph, NH), 7.51, 8.21 (d, J=9.5Hz, AB-4-nitrobenzyl) together 10H. Anal.Calcd. for $C_{21}H_{17}N_3O_7$: C 59.58, H 4.05, N 9.92. Found: C 58.9, H 4.0, N 9.8%.

4-[3(R)-Benzoylamino-2-azetidinon-4(R)-yloxy]-2-butyn-1-ol (**12**). As described for the preparation of **11c**, 941 mg (5 mmol) of the oxazoline **2**, 861 mg (10 mmol) of the diol **7** and 100 µl (0.8 mmol - 16 mol %) of boron trifluoride etherate in 20 ml of anhydrous THF after 2 h at room temp. and chromatography of the crude product on 100 g of silica gel (toluene:ethyl acetate 1:9) afforded 74 mg (8%) of the adduct **12** as a foam, Rf = 0.21 (toluene:ethyl acetate 1:9). IR ($CHCl_3$): 3351 (NH, OH), 1779 (C=O, β-lactam), 1664 and 1528 cm^{-1} (amide). ^1H NMR (200 MHz, DMSO) δ 4.11 (d, J=6Hz, 2H, CH_2OH), 4.32 (AB, J=17Hz, 2H, CH_2O), 4.65 (dd, J=9Hz, 1Hz, 1H, H-3), 5.21 (d, J=1Hz, H-4), 5.21 (t, J=6Hz, CH_2OH), together 2H, 7.5-7.6 (m, 3H, Ph), 7.75 (m, 2H, o-benzoyl-H), 9.02 (s, 1H, NH) and 9.18 (d, J=9Hz, 1H, NH). Anal.Calcd. for $C_{14}H_{14}N_2O_4$: C 61.31, H 5.15, N 10.21. Found: C 61.1, H 5.2, N 10.3%.

Methyl E,Z-4[3(R)-benzoylamino-2-azetidinon-4(R)-yloxy]-3-phenylthio-2-butenoate (**13a**). 113 µl (1.1 mmol) of thiophenol and 153 µl (1.1 mmol) of triethylamine was added to a solution, cooled to 0°C, of 302 mg (1 mmol) of **11a** in 5 ml of THF. The ice-bath was removed and the mixture was stirred at room temp. for 3 h. It was then poured into saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 and the extract was washed with water and dried over $MgSO_4$. The solvent was evaporated in vacuo and the crude product was crystallized from CH_2Cl_2/ether to afford 280 mg (68%) of **13a**, mp. 178°C, Rf: 0.48 (toluene: ethyl acetate 1:4). IR (KBr): 3317 (NH), 1807 (C=O, β-lactam), 1704 (C=O, ester), 1642 and 1533 (amide) and 1602 cm^{-1} (S-C=C). ^1H NMR (250 MHz, DMSO) δ 3.61, 3.63 (s, 3H, $COOCH_3$), 3.95 (s, 2H, CH_2O), 4.48 (d, J=8Hz, 1H, H-3), 4.78 (s, 1H, H-4), 6.14, 6.16 (s, 1H, -CH=C), 7.3-7.6 (m, 8H, Ph), 7.85 (m, 2H, o-benzoyl-H), 8.85 (s, 1H, NH-β-lactam) and 9.05, 9.10 (d, J=8Hz, 1H, PhCONH). Anal.Calcd. for $C_{21}H_{20}N_2O_5S$: C 61.15, H 4.89, N 6.79, S 7.77. Found: C 61.1, H 4.9, N 6.8, S 7.7%.

Methyl 4-[3(R)-benzoylamino-2-azetidinon-4(R)-yloxy]-acetoacetate (**14a**). By the procedure described by Ikegami et al.[17], 635 mg (2.1 mmol) of the butynoate **11a** after chromatography of the crude product on 30 g of silica gel (toluene: ethyl acetate 1:4) afforded 546 mg (81%) of the β-keto ester **14a** as a foam. Rf: 0.22 (toluene:ethyl acetate 1:4). IR ($CHCl_3$): 3328 (NH), 1777 (C=O, β-lactam),

1737 (C=O, ketone), 1725 (C=O, ester), 1658 and 1525 cm^{-1} (amide). ^1H NMR (250 MHz, $CDCl_3$) δ 3.53 (s, 2H, $COCH_2COOR$), 3.71 (s, 3H, $COOCH_3$), 4.46, 4.58 (AB, J=17Hz, 2H, CH_2O), 4.77 (d, J=7.5Hz, 1H, H-3), 5.14 (s, 1H, H-4) and 7.4-7.7 (m, 7H, Ph, NH).

tert.-Butyl 4-[3(R)-benzoylamino-2-azetidinon-4(R)-yloxy]-acetoacetate (**14 b**). As described for the preparation of **11 c**, 216 mg (1.15 mmol) of the oxazoline , 400 mg (2.3 mmol) of the alcohol **5b** and 30 µl (0.24 mmol - 21 mol %) of boron trifluoride etherate in 4 ml of anhydrous THF after 0.5 h at room temp. and chromatography of the crude product on 60 g of silica gel (toluene:ethyl acetate 1:3) afforded 128 mg (31%) of the adduct **14 b** as colorless crystals, mp. 142°C, Rf: 0.36 (toluene:ethyl acetate 1:4), $[\alpha]_D^{20}$ = -32.24° (c 0.955, $CHCl_3$). IR (KBr): 3320 (NH), 1763 (C=O, β-lactam), 1738 (C=O, ketone), 1720 (C=O, ester), 1656 and 1524 cm^{-1} (amide). ^1H NMR (200 MHz, $CDCl_3$) δ 1.45 (s, 9H, $C(CH_3)_3$), 3.43 (s, 2H, $COCH_2COOR$), 4.50 (AB, J=15Hz, 2H, OCH_2CO), 4.78 (dd, J=1Hz, 8Hz, 1H, H-3), 5.15 (d, J=1Hz, 1H, H-4), 7.13 (s, 1H, NH), 7.3-7.6 (m, 4H, Ph, NH), 7.8 (m, 2H, ortho-benzoyl-H). Anal.Calcd. for $C_{18}H_{22}N_2O_6$: C 59.66, H 6.12, N 7.73. Found: C 59.5, H 6.2, N 7.6%.

4-Nitrobenzyl 4[3(R)-benzoylamino-2-azetidinon-4(R)-yloxy]-acetoacetate (**14 c**). By the procedure described by Ikegami et al.[17], 551 mg (1.3 mmol) of the butynoate after crystallisation of the crude product from CH_2Cl_2/ether afforded 479 mg (83%) of the β-keto ester **14 c** as colorless crystals, mp. 138-139°C, Rf: 0.27 (toluene:ethyl acetate 1:4). IR (KBr): 3338 (NH), 1174 (C=O, β-lactam), 1740 (C=O, ketone), 1720 (C=O, ester), 1641 and 1512 (amide) and 1346 cm^{-1} (NO_2-sym.). ^1H NMR (200 MHz, DMSO) δ 3.75 (s, 2H, $COCH_2COOR$), 4.43 (s, 2H, CH_2O), 4.65 (d, J=9Hz, 1H, H-3), 5.18 (s, 1H, H-4), 5.30 (s, 2H, CH_2-benzyl), 7.45-7.9 (m, Ph), 7.65, 8.25 (d, J=9.5Hz, AB-4-nitrobenzyl) together 9H, 9.00 (s, 1H, NH) and 9.14 (d, J=9Hz, 1H, PhCONH). Anal.Calcd. for $C_{21}H_{19}N_3O_8$: C 57.14, H 4.34, N 9.52. Found: C 56.9, H 4.3, N 9.2%.

tert.-Butyl 4-[3(R)-benzoylamino-2-azetidinon-4(R)-yloxy]-2-diazo-3-oxo-butanoate (**15 b**). a) As described for the preparation of **11 c**, 941 mg (5.0 mmol) of the oxazoline **2**, 1.10 g (5.5 mmol - 1.1 equiv.) of the alcohol **3b** and 123 µl (1.0 mmol - 20 mol %) of boron trifluoride etherate in 20 ml of anhydrous THF after 20 minutes at room temp. afforded 1.36 g (71%) of the adduct **15 b** as colorless crystals, mp. 103°C (analytical sample mp. 127°C), Rf: 0.30 (toluene:ethyl acetate 35:65), $[\alpha]_D^{20}$ = -15.4° (c 0.867, $CHCl_3$). IR (KBr): 3307 (NH); 2154 (N_2), 1786 (C=O, β-lactam), 1699 (C=O, ester), 1643 (amide I) and 1527 cm^{-1} (amide II). ^1H NMR (250 MHz, $CDCl_3$) δ 1.54 (s, 9H, $C(CH_3)_3$), 4.77 (dd, J=7Hz, ~ 1Hz, 1H, H-3), 4.89 (AB, J=17Hz, 2H, CH_2O), 5.26 (d, J= ~ 1Hz, 1H, H-4), 7.1-7.5 (m, 5H, NH, NH, Ph) and 7.8 (m, 2H, o-benzoyl-H). Anal.Calcd. for $C_{18}H_{20}N_4O_6$: C 55.67, H 5.19, N 14.43. Found: C 55.7, H 5.4, N 14.0%.

b) 258 µl (1.85 mmol) of triethylamine was added to a solution of 184 mg (0.5 mmol) of **14 b** and 100 mg (0.55 mmol) of p-toluenesulfonyl azide[18] in 10 ml of anhydrous acetonitrile at 0°C. The cooling bath was removed and the mixture was stirred at room temp. for 1.5 h. The mixture was concentrated in vacuo and chromatographed on 8 g of silica gel (toluene:ethyl acetate 35:65) to afford 186 mg (96%) of the diazo compound **15 b** the physical data being identical to those of the substance prepared according to method a).

4-Nitrobenzyl 4-[3-(R)-benzoylamino-2-azetidinon-4(R)-yloxy]-2-diazo-3-oxo-butanoate (**15 c**). 0.75 ml (5.4 mmol) of triethylamine was added to a suspension of 662 mg (1.5 mmol) of **14 c** and 395 mg (1.74 mmol) of 4-carboxybenzenesulphonyl azide[20] in 15 ml of anhydrous acetonitrile at 0°C. The cooling bath was removed and the mixture was stirred at room temp. for 1 h. 100 ml of ethyl acetate was added and the precipitate was removed by filtration and discarded. The filtrate solution was evaporated in vacuo and ether was added to the residue to afford 540 mg (77%) of **15 c** as colorless crystals, mp. 135°C, Rf: 0.44 (toluene:ethyl acetate 1:9). IR (KBr): 3317 (NH), 2154 (N_2), 1789 (C=O, β-lactam), 1709 (C=O, ester), 1660 and 1521 cm^{-1} (amide). ^1H NMR (200 MHz, DMSO) δ 4.64 (dd, J=9Hz, 1Hz, 1H, H-3), 4.72 (s, 2H, CH_2O), 5.27 (d, J=1Hz, 1H, H-4), 5.44 (s, 2H, CH_2-benzyl), 7.5-7.9 (m, Ph), 7.71, 8.26 (d, J=9.5Hz, AB-4-nitrobenzyl) together 9H, 9.00 (s, 1H, NH), 9.15 (d, J=9Hz, 1H, PhCONH). Anal.Calcd. for $C_{21}H_{17}N_5O_8$: C 53.97, H 3.67, N 14.98. Found: C 53.6, H 3.8, N 14.8%.

tert.-Butyl (6R,7R)-7-benzoylamino-3-hydroxy-8-oxo-5-oxa-1-azabicyclo[4.2.0] oct-2-ene-2-carboxylate (**1b**). A suspension of 341 mg (0.88 mmol) of the diazo derivative **15b** and 0.5 mg of rhodium(II)acetate in 18 ml of anhydrous oxygen free benzene was heated at 80°C for 1 h. The mixture was then allowed to cool, filtered (Celite) to remove the catalyst, and the filtrate was concentrated in vacuo. Chromatography of the residue on 20 g of silica gel (toluene:ethyl acetate 35:65) afforded 260 mg (82%) of **1b** as a colorless foam, Rf: 0.36 (toluene:ethyl acetate 3:7). IR (KBr). 3324 (OH, NH), 1771 (C=O, β-lactam), 1655 (β-keto ester, enol form), 1655 and 1532 cm^{-1} (amide). ^1H NMR (250 MHz, $CDCl_3$) δ 1.59 (s, 9H, $C(CH_3)_3$), 4.42 (AB, J=17.5Hz, 2H, CH_2O), 4.93 (d, J=7.5Hz, 1H, H-7), 5.05 (s, 1H, H-6), 7.05 (d, J=7.5Hz, 1H, NH), 7.3-7.6 (m, 3H, Ph) and 7.8 (m, 2H, ortho-benzoyl-H). Anal.Calcd. for $C_{18}H_{21}N_3O_6$: C 59.83, H 5.86, N 7.75. Found: C 59.8, H 5.6, N 7.9%.

4-Nitrobenzyl (6R,7R)-7-benzoylamino-3-hydroxy-8-oxo-5-oxa-1-azabicyclo[4.2.0] oct-2-ene-2-carboxylate (**1 c**). As described for the preparation of the 3-hydroxy-oxacephem **1b**, 295 mg (61%) of **1c**, Rf: 0.37 (ethyl acetate), was obtained from 510 mg (1.1 mmol) of **15 c** after trit. of the crude product with ether.IR (KBr):

3320 (b, OH, NH), 1776 (C=O, β-lactam), 1652 (β-keto ester, enol form), 1660 and 1525 cm^{-1} (amide). ^1H NMR (200 MHz, DMSO) δ 4.38 (AB, J=18Hz, 2H, CH_2O), 4.98 (d, J=9Hz, 1H, H-7), 5.20 (s, 1H, H-6), 5.45 (s, 2H, CH_2-benzyl), 7.5-8.2 (m, 9H, H-aromatic) and 9.24 (d, J=9Hz, 1H, NH). The light colored powder was used for subsequent conversions without further purification.

tert.-Butyl (6R,7R)-7-benzoylamino-3-methoxy-8-oxo-5-oxa-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (**16b**). A solution of diazomethane in ether was added to a solution of 760 mg (2.1 mmol) of **1b** in 20 ml of CH_2Cl_2 at room temp. until a yellow coloration remained. Evaporation of the solvent in vacuo and chromatography of the residue on 30 g of silica gel (toluene:ethyl acetate 2:3) afforded 565 mg (72%) of **16b** as a colorless foam, Rf: 0.53 (toluene:ethyl acetate 1:4). IR (KBr): 3354 (NH), 1775 (C=O, β-lactam), 1722 (C=O, ester), 1650 and 1531 cm^{-1} (amide). ^1H NMR (250 MHz, $CDCl_3$) δ 1.53 (s, 9H, $C(CH_3)_3$), 3.78 (s, 3H, OCH_3), 3.36, 4.48 (d, J=18Hz, 2H, CH_2O), 5.00 (s, 1H, H-6), 5.04 (d, J=7.5Hz, 1H, H-7), 7.3-7.6 (m, 4H, Ph, NH) and 7.85 (m, 2H, o-benzoyl-H). Anal.Calcd. for $C_{19}H_{22}N_2O_6$: C 60.95, H 5.92, N 7.48. Found: C 60.9, H 5.8, N 7.3%.

4-Nitrobenzyl (6R,7R)-7-benzoylamino-3-methoxy-8-oxo-5-oxa-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (**16c**). As described for the preparation of **16b**, 130 mg (0.3 mmol) of **1c**, after chromatography of the crude product on 15 g of silica gel (toluene:ethyl acetate 35:65), afforded 75 mg (56%) of **16c** as colorless crystals, mp. 195°C [lit. [4j] 192-193°C], Rf: 0.33 (toluene:ethyl acetate 3:7). IR (KBr): 3361 (NH), 1771 (C=O, β-lactam), 1724 (C=O, ester), 1650 and 1517 (amide), 1605 (C=C) and 1349 cm^{-1} (NO_2-sym.). ^1H NMR (250 MHz, $CDCl_3$) δ 3.85 (s, 3H, OCH_3), 4.50, 4.63 (AB, J=17Hz, 2H, CH_2O), 4.97 (d, J=8Hz 1H, H-7), 5.10 (s, 1H, H-6), 5.30, 5.45 (AB, J=15Hz, CH_2-benzyl), 7.11 (d, J=8Hz, 1H, NH), 7.4-7.9 (m, Ph) and 7.65, 8.24 (AB, J=10Hz, 4-nitrobenzyl, 9H). Anal.Calcd. for $C_{27}H_{25}N_3O_8$: C 58.28, H 4.22, N 9.27. Found: C 58.0, H 4.3, N 9.1%.

tert.-Butyl (6R,7R)-7-benzoylamino-3-chloro-8-oxo-5-oxa-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (**17b**). 30.5 ml (349 mmol) of phosphorus trichloride was added to a solution of 7.82 g (21.7 mmol) of **1b** in 430 ml of anhydrous DMF at 0°C. The cooling bath was removed and the mixture was stirred at room temp. for 2 h. The mixture was then poured into a mixture of CH_2Cl_2 and ice-water and extracted with CH_2Cl_2. The extract was washed with $NaHCO_3$ solution and water and dried over $MgSO_4$. Evaporation of the solvent in vacuo and chromatography of the residue on 340 g of silica gel (toluene:ethyl acetate 7:3) afforded 2.47 g (30%) of **17b** as a foam. IR (KBr): 3360 (NH), 1787 (C=O, β-lactam), 1721 (C=O, ester), 1650 and 1518 cm^{-1} (amide). ^1H NMR (250 MHz, $CDCl_3$) δ 1.55 (s, 9H, $C(CH_3)_3$), 4.35-4.48 (AB, J=17.5Hz, 2H, CH_2O), 4.92 (s, 1H, H-6), 5.18 (d, J=7.5Hz, 1H, H-7), 7.3-7.6 (m, 4H, Ph, NH) and 7.9 (m, 2H, o-benzoyl-H).

4-Nitrobenzyl(6R,7R)-7-benzoylamino-3-hydroxy-8-oxo-5-oxa-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (**17c**). As described for the preparation of **17b**, 1.22 g (26%) of **17c** was obtained as colorless crystals from 4.39 g (10 mmol) of **1c** and 1.40 ml (16 mmol) phosphorus trichloride, mp. 192°C, Rf: 0.35 (toluene:ethyl acetate 7:3). IR (KBr): 1791 (C=O, β-lactam), 1733 (C=O, ester), 1642 and 1516 (amide), 1346 cm^{-1} (NO_2, sym.). ^1H NMR (250 MHz, $CDCl_3$-DMSO) δ 4.48, 4.54 (AB, J=17Hz, 2H, CH_2O), 4.99 (d, J=7.5Hz, 1H, H-7), 5.33 (s, 1H, H-6), 5.43, 5.54 (AB, J=13Hz, 2H, CH_2-benzyl), 7.4-7.6 (m, 3H, Ph), 6.75 (d, J=10Hz, 2H, PNB), 7.96 (m, 2H, o-benzoyl-H), 8.24 (d, J=10Hz, 2H, PNB), 9.18 (d, J=7.5Hz, 1H, NH). Anal.Calcd. for $C_{21}H_{16}ClN_3O_7$: C 55.09, H 3.52, N 9.18. Found: C 55.4, H 3.7, N 9.0%.

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