Stable Oxapenem-3-carboxylic Acids – A New Class of β-Lactam Antibiotics. Influence of 2- and 6-Alkyl Substituents

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Dedicated to Prof. Wolfgang Beck on the occasion of his 60th birthday

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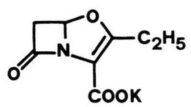
β-Lactam Antibiotics, Stable Oxapenem-3-carboxylic Acids, X-Ray

Novel antibacterially active oxapenem-carboxylic acids were prepared. Their increased stability depends on the 2-*tert*-butyl substituent and arises from its electron releasing inductive effect. The geometry and reactivity of oxapenems are discussed on the basis of two X-ray structure determinations and compared to those of related antibiotics.

Introduction

In 1988, the β-lactam antibiotics accounted for more than two thirds of the world-wide antibacterial market sales and the penicillins and cephalosporins were the most popular members in the therapy of bacterial infection diseases [1]. Growing resistance of some bacteria against these classical antibiotics has promoted the search for other antibacterials. This has led to the discovery of the so-called nonclassical β-lactams [2]. Two milestones in this development were the isolation of thienamycin [3], a natural compound of superior activity and that of clavulanic acid [4], a potent betalactamase inhibitor. On the other hand, efforts have been undertaken to provide β-lactam antibiotics of unusual structures by chemical synthesis [5].

A promising class of such compounds, the oxapenem-3-carboxylic acids was discovered [6] in 1978 and later several preparations of 6-mono- or unsubstituted oxapenem esters have been reported [7–16]. In most cases the authors pointed to the extreme lability of these compounds and some derivatives could not be purified [8, 14, 16]. More recently, a relatively stable sodium oxapenem-3-carboxylate has been prepared by Japanese chemists [17].



1a

The salt **1a** was reported to be a more powerful inhibitor than clavulanic acid of isolated staphylococcal penicillinase PC 1 and of P99 cephalosporinase from Enterobacter cloacae. It was, however, too unstable in aqueous solution to determine its antibacterial activity or its synergy with penicillin against intact bacteria [7].

Results and Discussion

With the idea to stabilize compound **1a** and to retain its betalactamase inhibitory properties, we started a systematic study of the oxapenems using various model compounds **1b–1h** in 1983 [18].

The racemic model compounds **1b–1h** were prepared according to the following scheme (Method A). For this preparation a Hg^{2+} mediated cyclization was used as key step. A related process* has been applied for a synthesis of benzooxacephems [19].

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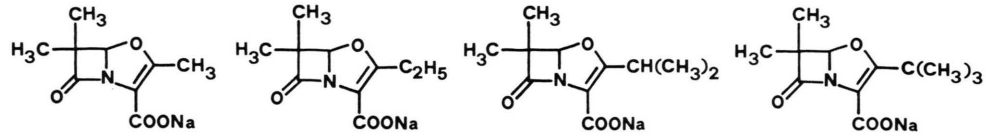
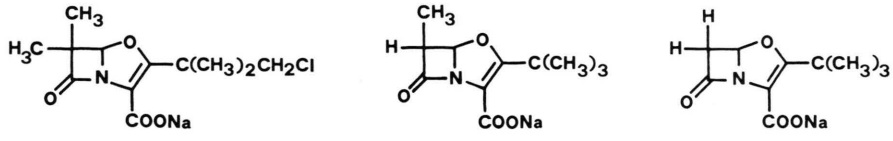
* This process based on an intramolecular reaction of a thioether moiety with an alcohol group.

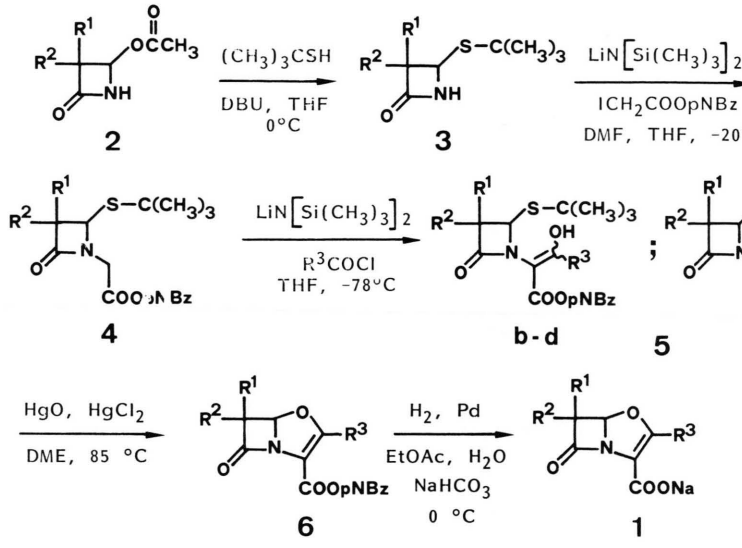


1b **1c** **1d** **1e**



1f **1g** **1h**

Method A

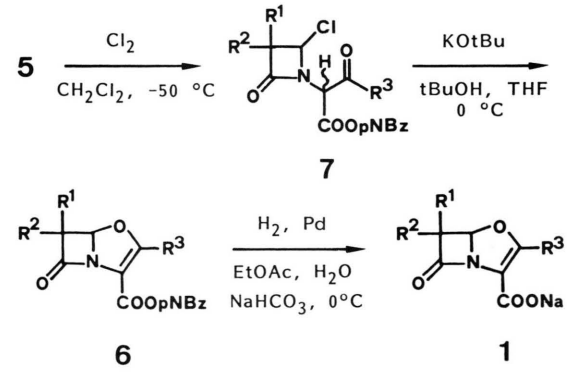


2 **3** **4** **b-d** **5** **e-h** **6** **1**

b: $R^1 = R^2 = R^3 = CH_3$
c: $R^1 = R^2 = CH_3$, $R^3 = C_2H_5$
d: $R^1 = R^2 = CH_3$, $R^3 = CH(CH_3)_2$
e: $R^1 = R^2 = CH_3$, $R^3 = C(CH_3)_3$
f: $R^1 = R^2 = CH_3$, $R^3 = C(CH_3)_2CH_2Cl$
h: $R^1 = R^2 = H$, $R^3 = C(CH_3)_3$

Starting with 4-acetoxyazetidinone **2** ($R^1 = R^2 = CH_3$) [20] the highly substituted oxapenem-*p*-nitrobenzyl esters **6** were obtained in good yields. However, during the preparation of the low substituted oxapenem-3-carboxylic acid **1h** ($R^1 = R^2 = H$), the thermal cyclization step **5** → **6** was accompanied by substantial decomposition of the sensitive oxapenem system. Therefore, by preference, this compound was prepared according to the method of Eglington *et al.* [8] (Method B).

Method B

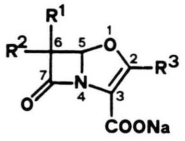


5 **7** **6** **1**

g: $R^1 = CH_3$, $R^2 = H$, $R^3 = C(CH_3)_3$
h: $R^1 = R^2 = H$, $R^3 = C(CH_3)_3$

Having these compounds in hand, we determined the stability of **1b–1h** in aqueous phosphate buffer of pH 7.4 at 37 °C by UV spectroscopy, according to our established method with penems [21]. It was found (Table I) that, with increasing alkyl substitution of the oxapenem nucleus, the hydrolysis half life was substantially increased. As for 6-substitutions, this effect was already known from the field of penems [22]. However, the observed stabilization with 2-substituents, especially that with the *tert*-butyl group, was most surprising.

Table I. Hydrolysis half lives of substituted sodium oxapenemcarboxylates **1** in physiological phosphate buffer at 37 °C, determined by UV-spectroscopy.



1

	R^1	R^2	R^3	$T_{1/2}$ (37 °C, pH 7.4)
1b	CH_3	CH_3	CH_3	50 min
1c	CH_3	CH_3	C_2H_5	70 min
1d	CH_3	CH_3	$CH(CH_3)_2$	2.0 h
1e	CH_3	CH_3	$C(CH_3)_3$	29.5 h
1f	CH_3	CH_3	$C(CH_3)_2CH_2Cl$	9.0 h
1g	CH_3	H	$C(CH_3)_3$	2.6 h
1h	H	H	$C(CH_3)_3$	1.6 h

Investigation of the novel 2-alkyl substituted sodium oxapenem-carboxylates **1b–1h** by the agar diffusion method revealed that, in contrast to the above mentioned labile 2-ethyl derivative **1a,** the compounds **1e, 1g** or **1h,** having a 2-*tert*-butyl group, as well as **1f** with a 2-(chloro-*tert*-butyl) group, were biologically active against intact bacteria. It was found that the 6-unsubstituted and the 6-methyl-oxapenems **1h** and **1g** were the most active compounds of the above mentioned series, being equally effective against *Staphylococcus aureus* DSM 1104, penicillin resistant *Staph. aureus* 25466 and *Escherichia coli* DSM 1103 (see Fig. 1).

The increase in hydrolysis stability of the oxapenem system by bulky 2-substituents led us to investigate this surprising effect. Consequently, **6b** and **6e,** two of the crystalline oxapenem-carboxylic acid *p*-nitrobenzyl esters, were investigated by X-ray analyses. It was anticipated that the geometry of the oxapenem esters **6b** and **6e** would not be dramatically changed during the deprotection step leading to **1b** and **1e.** We hoped that the investigation of compounds **6b** (R^3 = CH_3) and **6e** (R^3 = *tert*-butyl) would provide a significant difference in molecular structures, allowing eventually to explain the lower hydrolysis reactivity of **1e.** However, no such significant difference of the molecular data (bond lengths and angels) was observed and surprisingly, the bulky *tert*-butyl substitution did not lead to a considerable out-of-plane-distortion of the double bond substituents. This led us to the conclusion, that other than geometric factors cause the dramatic increase in hydrolysis half life observed with the *tert*-butyl substituted oxapenems.

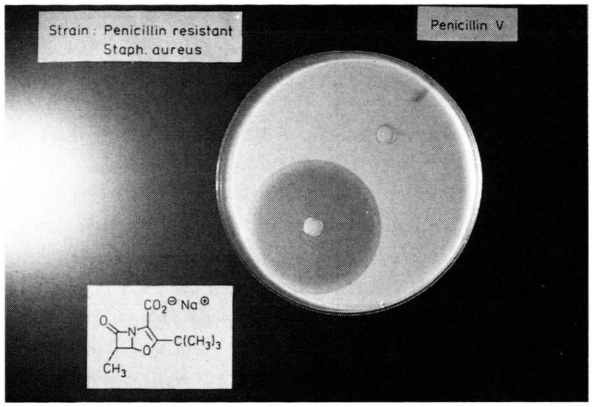


Fig. 1. Plate agar assay of **1g** (240 μg, racemic) and penicillin V (250 μg). Difco Nutrient Agar. Staph. aureus 25466. Diameters of inhibition zones: 47 mm and 7 mm.

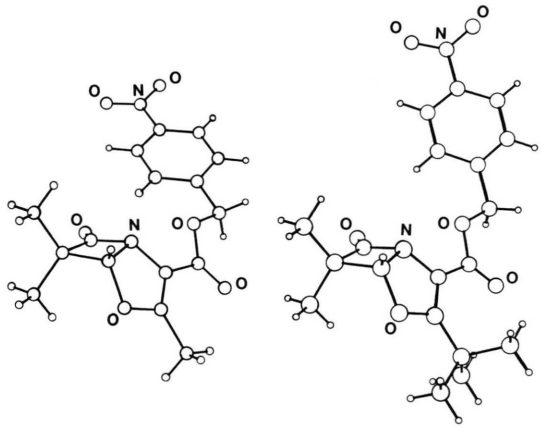
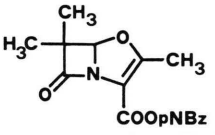
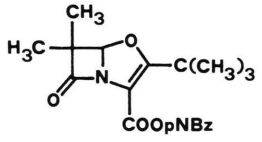
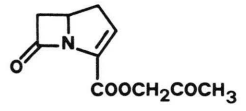
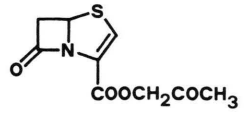


Fig. 2. X-ray models of *p*-nitrobenzyl oxapenemcarboxylates **6b** and **6e.**

The high reactivity of bicyclic β-lactams has been associated with their pyramidal character. The pyramid is defined by the nitrogen atom (apex) and the atomic neighbours (basis). As the orbital on nitrogen is no longer parallel to that of the amide carbonyl, the free nitrogen electron pair cannot enter into a stabilizing amide resonance as it does with monocyclic or noncyclic amides. Consequently, the C–N bond has diminished double bond character, leading to increased electrophilicity. In addition, the amide C=O bond becomes shorter with increasing height of the pyramid, leading to a higher IR stretching frequency.

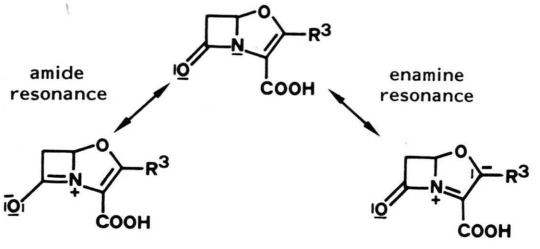
Such increased C–N and decreased C=O bond lengths can indeed be observed with the X-ray models and can be deduced from the IR spectra of the investigated oxapenems. As expected, due to the oxazoline ring being smaller than the other relevant 5-membered heterocycles, the pyramidalities of the oxapenems are more pronounced than those of the other related bicyclic β-lactams (Table II). The extraordinarily high reactivity of the 2-methyl or 2-ethyl substituted oxapenems can be explained on this basis. However, the increased hydrolytic stability of the corresponding *tert*-butyl compounds is not obvious from these results.

Table II. β-Lactam IR frequency (CH_2Cl_2), relevant bond lengths, altitude of pyramid with N (apex) and adjacent atoms as basis, and hydrolysis half life of selected bicyclic β-lactams.

	β-lactam νC=O (cm^{-1})	Bond lengths[a] (Å) O=C(7)	C(7)–N(4)	Altitude of pyramid (Å)	Hydrolysis[c] $T_{1/2}$ of sodium salt
	1805	1.196/1.198[b]	1.420/1.417[b]	0.535	50 min
oxapenem **6b**					
	1797	1.197	1.421	0.529	29.5 h
oxapenem **6e**					
	1785	1.194	1.419	0.500	3 h
2-carbapenem [21]					
	1798	1.204	1.419	0.441	20 h
penem [21]					
Penicillins [23]	1770–1780	1.20	1.37	~0.40	
Cephalosporins [23]	1764–1776	1.21[d]	1.38[d]	~0.24	

[a] Maximum standard deviation 0.006 Å; [b] two molecules of identical structure in the crystal were calculated; [c] phosphate buffer pH 7.4, 37 °C; [d] corresponding bond lengths.

Another possible (destabilizing) effect in oxapenems and related substances arises from the contribution of the C=C bond. This leads to an enamine resonance which restricts the (stabilizing) amide resonance and increases β-lactam reactivity as shown in the following scheme:



It was assumed, therefore, that the inductive effect of the *tert*-butyl group causes the decrease of β-lactam reactivity. As depicted above, an inductively electron releasing group R^3 should indeed restrict the enamine resonance and lead to more stable oxapenems.

To prove this hypothesis we prepared another model compound **1f,** the chloro-*tert*-butyl group of which is even more bulky than the *tert*-butyl group of **1e.** On the other hand, the additional electron attracting chlorine substituent makes **1f** electronically different from **1e.** Consequently, a comparison of the hydrolysis half lives of **1f** and **1e** would allow to determine whether the steric or inductive effect of substituent R^3 predominates. The reduced half life (9 h) of the chlorinated oxapenem **1f,** compared to that (29.5 h) of **1e** (Table I), clearly revealed that the electron releasing inductive effect of the substituent R^3 indeed plays a leading role in the observed stabilization of oxapenems.

Experimental

Melting points are uncorrected. – IR: Perkin-Elmer 125 and Bruker Fourier-IR-Spectrometer IFS 45. – ^{1}H NMR: Bruker WP 80CW and AM 360. – UV: Perkin-Elmer Lambda 3. – Optical rotation: Zeiss 0.005°. Mass spectra: MS 902 (AEI Manchester). X-ray: Nicolett P3 (graphite monochromator, Mo–K_α-radiation, λ = 0.71069 Å). Structure elucidation was made by the SHELXTL 4.1 program. The progress of all reactions was monitored on TLC plates 60 F_{254} (Merck, 0.25 mm). Special care was taken to develop TLCs immediately after spotting (without intermediate drying). Column chromatography was performed with Kieselgel 60 (Merck 0.063–0.200 mm) or Florisil (Fluka, 60–100 mesh). Dry THF or glyme was obtained by refluxing the commercial grade (Janssen) solvent over $LiAlH_4$ and by distillation. Dry DMF was prepared by storing the commercial grade solvent (Janssen) over molecular sieves 4 Å (Union Carbide).

Preparation of sodium oxapenem-3-carboxylates **1b–1h**

Method A, general procedure

4-tert-Butylthioazetidinones **3b** *($R^1 = R^2 = CH_3$),* **3g** *($R^1 = CH_3$, $R^2 = H$), and* **3h** *($R^1 = R^2 = H$)*

To a stirred solution of **2** [20] (125 mmol) and *tert*-butyl-mercaptan (12.4 g, 15.6 ml, 137 mmol) in dry THF (100 ml) at 0 °C was slowly added 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (20.9 g, 20.6 ml, 137 mmol) in order that the reaction temperature did not exceed 0 °C. After additional stirring for 2 h at 0 °C the yellow solution was stirred overnight at room temperature, methylene chloride (500 ml) added and the resulting solution washed four times with portions (100 ml) of 2N HCl, twice with saturated $NaHCO_3$ solution (100 ml portions) and with saturated NaCl solution (100 ml). The organic layer was dried over $MgSO_4$ and the solvent removed *in vacuo.* The crude product was chromatographed on silica gel (400 g, 63–200 μm) with toluene-ethyl acetate (4:1) or (3:1).

3b ($R^1 = R^2 = CH_3$): yield 59%, m.p. 122.5–123.5 °C (from CH_2Cl_2/hexane). – DC: R_f = 0.27 (toluene/ethyl acetate 1:1), I_2-straining. – ^{1}H NMR ($CDCl_3$): δ = 1.22 (s, 3H, CH_3), 1.36 (s, 12H, CH_3 and *tert*-butyl), 4.50 (s, 1H, 4-H), 6.69 (broad s, 1H, NH). – IR (CH_2Cl_2): 3405 m (NH), 2965 m, 2895 w and 2860 w (aliph. CH), 1765 s (β-lactam C=O), 1460 m, (C–H def.), 1390 m and 1370 m (*tert*-butyl), 1340 w, 1200 m, 1155 m, 1115 w, 985 w, 950 m.

$C_9H_{17}NOS$ (187.31)
Calcd C 57.71 H 9.15 N 7.48 S 17.12%,
Found C 57.99 H 9.23 N 7.46 S 17.18%.

3g ($R^1 = CH_3$, $R^2 = H$): yield 71%, crude product is *cis, trans*-isomer mixture (1:9).

$C_8H_{15}NOS$ (173.28)
Calcd C 55.45 H 8.73 N 8.08 S 18.50%,
Found C 55.90 H 8.58 N 7.72 S 18.21%.

trans-**3g:** m.p. 98.5–100 °C (from CH_2Cl_2/hexane). – DC: R_f = 0.31 (toluene/ethyl acetate 1:1), I_2-staining. – ^{1}H NMR (CCl_4): δ = 1.35 (d, J = 7.5 Hz, 3H, CH_3), 1.36 (s, 9H, *tert*-butyl), 2.75–

3.12 (m, 1H, 3-H), 4.41 (d, J = 2.5 Hz, 1H, 4-H), 7.99 (broad s, 1H, NH). – IR (CH_2Cl_2): 3405 m (NH), 2930 m (aliph. CH), 1770 s (β-lactam C=O), 1460 m (C–H def.), 1375 and 1365 m (*tert*-butyl), 1340 m, 1230 w, 1160 s, 1065 m, 940 s, 835 w.

cis-**3g:** m.p. 98.5–100.5 °C (from CH_2Cl_2/hexane). – DC: R_f = 0.22 (toluene/ethyl acetate 1:1), I_2-staining. – ^{1}H NMR ($CDCl_3$): δ = 1.23 (d, J = 7.5 Hz, 3H, CH_3), 1.37 (s, 9H, *tert*-butyl), 3.27–3.68 (m, 1H, 3-H), 4.88 (d, J = 5.5 Hz, 1H, 4-H), 7.83 (broad s, 1H, NH). – IR (CH_2Cl_2): 3395 m (NH), 2925 m (aliph. CH), 1765 s (β-lactam C=O), 1455 m, (C–H def.), 1375 m and 1365 m (*tert*-butyl), 1335 w, 1180 m, 1155 s, 945 s, 875 w, 830 w.

3h (R^1 = R^2 = H): yield 79%, m.p. 119–121 °C (from CH_2Cl_2/hexane). – DC: R_f = 0.23 (toluene/ethyl acetate 1:1), I_2-staining. – ^{1}H NMR ($CDCl_3$): δ = 1.37 (s, 9H, *tert*-butyl), 2.84 (ddd, J = 15 Hz, J = 3 Hz, J = 2 Hz, *trans*-3-H), 3.43 (ddd, J = 15 Hz, J = 5 Hz, J = 2 Hz, 1H, *cis*-3-H), 4.87 (dd, J = 5 Hz, J = 3 Hz, 1H, 4′-H), 6.78 (broad s, 1H, NH). – IR (CH_2Cl_2): 3410 m (NH), 2955 m, 2905 w and 2865 w (aliph. CH), 1770 s (β-lactam C=O), 1460 w, 1410 w (C–H def.), 1370 m (*tert*-butyl), 1340 m, 1230 w, 1160 s, 1085 w, 970 w, 925 m.

$C_7H_{13}NOS$ (159.25)
Calcd C 52.80 H 8.23 N 8.80 S 20.13%,
Found C 52.97 H 8.08 N 8.94 S 20.26%.

p-Nitrobenzyl (4-tert-butylthio-2-oxo-1-azetidinyl)-acetates **4b** *(R^1 = R^2 = CH_3),* **4g** *(R^1 = CH_3, R^2 = H), and* **4h** *(R^1 = R^2 = H)*

To a stirred solution of **3** (25 mmol) in dry THF (110 ml) and dry DMF (15 ml) at –78 °C within 5 min a 1N solution (27.5 mmol) of lithium[bis-(trimethylsilyl)]amide was added under nitrogen by a syringe through a septum. Immediately after addition of the base a solution of *p*-nitrobenzyl iodoacetate (25 mmol) in dry DMF (30 ml) was added within 5 min and the reaction mixture allowed to stir for 2 h at –40 °C to –30 °C. A red-brown suspension was thus formed. Dry ether (600 ml) was added, the suspension filtered and the filtrate washed twice with portions of 20% aqueous NaCl solution (400 ml). The aqueous phases were reextracted with ether (200 ml) and the combined organic extracts dried over $MgSO_4$, filtered and the solvent removed *in vacuo*, leaving crude **4.** It was chromatographed on silica gel (63–200 μm) with toluene/ethyl acetate 4:1 to give pure **4.**

4b (R^1 = R^2 = CH_3): yield 74%, m.p. 142.5–144.5 °C (CH_2Cl_2/hexane). – DC: R_f = 0.44 (toluene/ethyl acetate 1:1). – ^{1}H NMR ($CDCl_3$): δ = 1.22 (s, 3H, 3-CH_3), 1.28 (s, 9H, *tert*-butyl), 1.38 (s, 3H, 3-CH_3), 3.75 (d, J = 18 Hz, 1H, 2-H), 4.27 (d, J = 18 Hz, 1H, 2-H), 4.64 (s, 1H, 4′-H), 5.24 (s, 2H, –O–CH_2–Ar), 7.48 (d, J = 8.5 Hz, 2H, Ar–H), 8.19 (d, J = 8.5 Hz, 2H, Ar–H). – IR (CH_2Cl_2): 2960 m, 2925 w, and 2860 w (aliph. CH), 1765 s (β-lactam C=O), 1750 s (ester C=O), 1610 m (C=C), 1530 s (NO_2), 1460 w and 1405 w (C–H def.), 1370 m (*tert*-butyl), 1350 s (NO_2), 1210 m, 1185 s (C–O), 1135 w, 1105 m, 930 m, 860 w, 850 w (Ar–H), 805 w. – UV (dioxane): λ_{max} = 265 nm (ε = 10040).

$C_{18}H_{24}N_2O_5S$ (380.46)
Calcd C 56.83 H 6.35 N 7.36 S 8.43%,
Found C 56.57 H 6.57 N 7.13 S 8.40%.

trans-**4g** (R^1 = CH_3, R^2 = H): yield *ca.* 70%, m.p. 84.5–86 °C (isopropanol). – DC: R_f = 0.42 (toluene/ethyl acetate 1:1). – ^{1}H NMR ($CDCl_3$): δ = 1.29 (s, 9H, *tert*-butyl), 1.39 (d, J = 7.5 Hz, 3H, 3′-CH_3), 3.13 (dq, J = 7.5 Hz, J = 2.5 Hz, 1H, 3′-H), 3.73 (d, J = 18 Hz, 1H, 2-H), 4.31 (d, J = 18 Hz, 1H, 2-H), 4.55 (d, J = 2.5 Hz, 1H, 4′-H), 5.24 (s, 2H, –O–CH_2–Ar), 7.48 (d, J = 9 Hz, 2H, Ar–H), 8.20 (d, J = 9 Hz, 2H, Ar–H). – IR (CH_2Cl_2): 2925 m (aliph. CH), 1755 s (β-lactam C=O and ester C=O), 1610 m (C=C), 1525 s (NO_2), 1450 w, 1390 m and 1360 m (*tert*-butyl), 1345 s (NO_2), 1185 s (C–O), 1120 m, 1090 m, 1055 w, 965 w, 935 m, 855 m (Ar–H). – UV (ethanol): λ_{max} = 264 nm (ε = 10400).

$C_{17}H_{22}N_2O_5S$ (366.44)
Calcd C 55.72 H 6.05 N 7.64 S 8.75%,
Found C 56.08 H 6.11 N 7.40 S 8.79%.

cis-**4g** (R^1 = CH_3, R^2 = H): yield 69%, m.p. 83.5–85.5 (CH_2Cl_2/hexane). – DC: R_f = 0.35 (toluene/ethyl acetate 1:1). – ^{1}H NMR ($CDCl_3$): δ = 1.26 (d, J = 7 Hz, 3H, 3′-CH_3), 1.29 (s, 9H, *tert*-butyl), 3.60 (dq, J = 7 Hz, J = 5 Hz, 1H, 3′-H), 3.79 (d, J = 18 Hz, 1H, 2-H), 4.30 (d, J = 18 Hz, 1H, 2-H), 5.06 (d, J = 5 Hz, 1H, 4′-H), 5.25 (s, 2H, –O–CH_2–Ar), 7.49 (d, J = 9 Hz, 2H, Ar–H), 8.21 (d, J = 9 Hz, 2H, Ar–H). – IR (CH_2Cl_2): 2955 m (aliph. CH), 1755 s (β-lactam C=O and ester C=O), 1610 m, (C=C), 1525 s (NO_2), 1450 w, 1395 m, 1375 m and 1365 m (CH_3 def. and *tert*-butyl), 1345 s (NO_2), 1190 s (C–O), 1090 m, 1010 w, 970 w, 930 m, 855 m (Ar–H). – UV (ethanol): λ_{max} = 263 nm (ε = 10110).

$C_{17}H_{22}N_2O_5S$ (366.44)
Calcd C 55.72 H 6.05 N 8.75 S 7.64%,
Found C 55.92 H 5.88 N 8.78 S 7.46%.

4h (R^1 = R^2 = H): yield 78%, m.p. 82.5–84 °C (isopropanol). – DC: R_f = 0.38 (toluene/ethyl acetate 1:1). – ^{1}H NMR (CCl_4): δ = 1.29 (s, 9H, *tert*-butyl), 2.88 (dd, *J* = 15 Hz, *J* = 2.5 Hz, 1H, *trans*-3′-H), 3.47 (dd, *J* = 15 Hz, *J* = 5 Hz, 1H, *cis*-3′-H), 3.62 (d, *J* = 18 Hz, 1H, 2-H), 4.26 (d, *J* = 18 Hz, 1H, 2-H), 4.90 (dd, *J* = 5 Hz, *J* = 2.5 Hz, 1H, 4′-H), 5.21 (s, 2H, $-O-CH_2-Ar$), 7.46 (d, *J* = 9 Hz, 2H, Ar–H), 8.16 (d, *J* = 9 Hz, 2H, Ar–H). – IR (CH_2Cl_2): 2955 m (aliph. CH), 1770 s (β-lactam C=O), 1755 (ester C=O), 1610 m (C=C), 1530 s (NO_2), 1455 w (C–H def.), 1390 m and 1375 m (CH_3 def.), 1365 m (*tert*-butyl), 1345 s (NO_2), 1180 s (C–O), 1110 m, 1080 w, 1060 w, 945 m, 915 m, 855 m, 845 m (Ar–H), 800 w. – UV (ethanol): λ_{max} = 263.5 nm (ε = 10140).

$C_{16}H_{20}N_2O_5S$ (352.41)
Calcd C 54.53 H 5.72 N 7.95 S 9.10%,
Found C 54.71 H 5.63 N 7.99 S 9.14%.

p-Nitrobenzyl 2-(4-tert-butylthio-3,3-dimethyl-2-oxo-1-azetidinyl)-3-hydroxybut-2-enoate
5b *(R^1 = R^2 = R^3 = CH_3), -3-hydroxypent-2-enoate*
5c *(R^1 = R^2 = CH_3, R^3 = C_2H_5) and -3-hydroxy-4-methylpent-2-enoate*
5d *(R^1 = R^2 = CH_3, R^3 = $CH(CH_3)_2$)*

To a stirred mixture of **4b–d** (2.0 mmol) in dry THF (6 ml) at −78 °C a 1 N solution of lithium[bis-(trimethylsilyl)]amide (4.2 ml) was added within 5 min and immediately after addition of the base a solution of acid chloride (2.0 mmol) in dry THF (6 ml) was added at −78 °C where upon the initially dark reaction mixture turned yellow. The reaction mixture was allowed to stir for 40 min at −78 °C and after removal of the cooling bath acetic acid (180 μl) was added. The reaction mixture was diluted with toluene (200 ml) and the resulting solution washed with 20% aqueous NaCl (100 ml), 2N HCl (100 ml) and again with 20% NaCl (100 ml). The aqueous layers were reextracted with toluene (50 ml) and the combined organic solutions dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. The orange viscous crude product was chromatographed on silica gel (50 g) using toluene/ethyl acetate (4:1) affording pure enol **5.**

5b (R^1 = R^2 = R^3 = CH_3): yield 69%, m.p. 88.5–90.5 °C (CH_2Cl_2/hexane). – DC: R_f = 0.43 (toluene/ethyl acetate 1:1, oval shaped spot. – ^{1}H NMR ($CDCl_3$): δ = 1.19, 1.27, and 1.39 (3 signals, 15H, *tert*-butyl and 3′-CH_3), 2.12 (s, 3H, $-C=C(OH)-CH_3$), 4.58 (s, 1H, 4′-H), 5.26 and 5.28 (2 s, 2H, $-O-CH_2-Ar$), 7.47 (d, *J* = 8.5 Hz, 2H, Ar–H), 8.17 (d, *J* = 8.5 Hz, 2H, Ar–H), 12.02 and 12.20 (2 s, 1H, enol-H of E- and Z-isomer). – IR (CH_2Cl_2): 2960 m and 2865 w (aliph. CH), 1760 s (β-lactam C=O), 1660 s (ester C=O), 1610 (C=C), 1530 s (NO_2), 1385 m and 1370 s (*tert*-butyl), 1355 s (NO_2), 1230 s (C–O), 1145 m, 1100 m, 1065 m, 1045 w, 1015 w, 980 m, 855 m (Ar–H). – UV (ethanol): λ_{max} = 265 nm (ε = 19380).

$C_{20}H_{26}N_2O_6S$ (422.50)
Calcd C 56.86 H 6.20 N 6.63 S 7.59%,
Found C 56.84 H 6.16 N 6.72 S 7.60%.

5c (R^1 = R^2 = CH_3, R^3 = C_2H_5): yield 64%, noncrystalline solid, – DC: R_f = 0.50 (toluene/ethyl acetate 1:1). – ^{1}H NMR ($CDCl_3$): δ = 1.12, 1.18, 1.26 and 1.41 (4 s, 18H, 3′-CH_3, $-C=C(OH)-CH_2-C\underline{H}_3$), and *tert*-butyl), 2.47 (q, *J* = 7.5 Hz, 2H, $-C=C(OH)-C\underline{H}_2-CH_3$), 4.59 (s, 1H, 4′-H), 5.26 and 5.32 (2 s, 2H, $-O-CH_2-Ar$), 7.32 (d, *J* = 8.5 Hz, 2H, Ar–H), 8.21 (d, *J* = 8.5 Hz, 2H, Ar–H), 12.21 and 12.39 (2 s, 1H, enol-H of E- and Z-isomer). – IR (CH_2Cl_2): 2960 m (aliph. CH), 1760 s (β-lactam C=O), 1660 s (ester C=O), 1610 s (C=C), 1530 s (NO_2), 1460 w and 1410 m (C–H def.), 1385 m, 1375 m and 1365 m (CH_3 def. and *tert*-butyl), 1350 s (NO_2), 1225 s (C–O), 1145 m, 1100 m, 1050 w, 1015 m, 975 w, 880 w, 850 m (Ar–H). – UV (ethanol): λ_{max} = 264 nm (ε = 20100).

$C_{21}H_{28}N_2O_6S$ (436.53)
Calcd C 57.78 H 6.47 N 6.42 S 7.35%,
Found C 57.97 H 6.47 N 6.49 S 7.36%.

5d (R^1 = R^2 = CH_3, R^3 = $CH(CH_3)_2$): yield 84%, m.p. 97–99 °C (CH_2Cl_2/hexane). – DC: R_f = 0.56 (toluene/ethyl acetate 1:1). – ^{1}H NMR ($CDCl_3$): δ = 1.14, 1.17, 1.18, 1.22, 1.24 and 1.39 (6 signals, 21H, 3′-CH_3, *t*-butyl, $-CH(C\underline{H}_3)_2$), 2.75–3.16 (m, 1H, $-C\underline{H}(CH_3)_2$), 4.57 (s, 1H, 4′-H), 5.27 and 5.31 (2 s, 2H, $O-CH_2-Ar$), 7.51 (d, *J* = 8.5 Hz, 2H, Ar–H), 8.21 (d, *J* = 8.5 Hz, 2H, Ar–H), 12.22 and 12.45 (2 d, *J* = 1.5 Hz, 1H, enol-H of E- and Z-isomer). – IR (CH_2Cl_2): 2960 m and 2865 w (aliph. CH), 1760 s (β-lactam C=O), 1665 s (ester C=O), 1610 s (C=C), 1530 (NO_2), 1460 w and 1410 m (C–H def.) 1390 m and 1380 m (isopropyl), 1370 m (*tert*-butyl), 1355 s (NO_2), 1320 m, 1225 s (C–O), 1445 m, 1100 w, 1080 m, 1050 w, 1010 m, 860 m, 845 m, 825 m. – UV (ethanol): λ_{max} = 263 nm (ε = 19090).

$C_{22}H_{30}N_2O_6S$ (450.55)
Calcd C 58.65 H 6.71 N 6.22 S 7.12%,
Found C 58.64 H 6.66 N 5.82 S 6.98%.

p-Nitrobenzyl 2-(4-tert-butylthio-2-oxo-1-azetidinyl)-4,4-dimethyl-3-oxopentanoates **5e** *($R^1 = R^2 = CH_3$, R^3 = tert-butyl,* **5g** *($R^1 = CH_3$, $R^2 = H$, R^3 = tert-butyl) and* **5h** *($R^1 = R^2 = H$, R^3 = tert-butyl) and -5-chloro-4,4-dimethyl-3-oxopentanoate* **5f** *($R^1 = R^2 = CH_3$, $R^3 = C(CH_3)_2CH_2Cl$)*

To a stirred mixture of **4e–h** (1 mmol) and acid chloride (1.08 mmol) in dry THF (12 ml) at −78 °C a 1N solution of lithium [bis(trimethylsilyl)]amide in THF (2.2 ml, 2.2 mmol) was added within 5 min and the orange-red mixture stirred for 1 h at −70 °C. The reaction mixture was diluted with toluene (40 ml) and the obtained solution washed subsequently with 2 N HCl (30 ml) and twice with portions (40 ml) of saturated NaCl solution. The aqueous phases were reextracted with toluene (20 ml) and the combined organic layers dried over $MgSO_4$, filtered and the solvent removed *in vacuo*, leaving a pale yellow oil. It was chromatographed on silica gel (63–200 μm) (20 g) with toluene/ethyl acetate 19:1 affording pure noncrystalline **5** as mixture of stereoisomers.

5e ($R^1 = R^2 = CH_3$, R^3 = *tert*-butyl): yield 79%, m.p. 87.5–90.5 °C (CH_2Cl_2/hexane). – DC: R_f = 0.59 (toluene/ethyl acetate 1:1). – ^{1}H NMR (CD_3CN): δ = 1.11, 1.13, 1.16, 1.22, 1.25 and 1.28 (6 signals, 24H, 3′-CH_3, $-S-C(CH_3)_3$ and $-CO-C(CH_3)_3$ of both diastereoisomers), 4.58 (s, ~0.5H, 4-H, diastereomer I), 4.77 (s, ~0.5H, 4H, diastereomer II), 5.17 (s, ~0.5H, 2-H, diastereomer I), 5.25 (s, 2H, $-O-CH_2-Ar$), 5.35 (s, ~0.5H, 2-H, diastereomer II), 7.49 (broad d, J = 9 Hz, 2H, Ar–H), 8.13 (d, J = 9 Hz, 2H, Ar–H). – IR (CH_2Cl_2): 2955 m and 2865 w (aliph. CH), 1765 s (β-lactam C=O), 1755 s (ester C=O), 1715 s (ketone C=O), 1610 m (C=C), 1525 s (NO_2), 1460 m (C–H def.) 1390 m and 1370 m (*tert*-butyl), 1350 s (NO_2), 1315 m, 1185 s (C–O), 1135 m, 1105 m, 1060 w, 1015 w, 995 m, 930 w, 890 w, 860 w, 850 m (Ar–H). – UV (ethanol): λ_{max} = 264.5 nm (ε = 10930).

$C_{23}H_{32}N_2O_6S$ (464.58)

Calcd	C 59.46	H 6.94	N 6.03	S 6.90%,
Found	C 59.42	H 6.91	N 5.63	S 6.92%.

5f ($R^1 = R^2 = CH_3$, $R^3 = C(CH_3)_2CH_2Cl$): yield 80%. – DC: R_f = 0.62 (toluene/ethyl acetate 1:1). – ^{1}H NMR (CD_3CN): δ = 1.04, 1.27 and 1.34 (3 signals, 21H, 3′-CH_3, *tert*-butyl and $-C(CH_3)_2CH_2Cl$ of both diastereomers), 3.69 (s, 2H, $-CH_2Cl$), 4.61 (s, ~0.5H, 4′-H), 4.80 (s, ~0.5H, 4′-H), 5.24 (s, ~0.5H, 2-H), 5.30 (s, 2H, $-O-CH_2Ar$), 5.34 (s, ~0.5H, 2-H), 7.54 (broad d, J = 8.5 Hz, 2H, Ar–H), 8.17 (d, J = 8.5 Hz, 2H, Ar–H). – IR (CH_2Cl_2): 3040 w (CH_2-Cl), 2965 m, 2895 w and 2860 w (aliph. CH), 1765 s (β-lactam C=O), 1755 s (ester C=O), 1720 s (ketone C=O), 1610 m (C=C), 1525 s (NO_2), 1460 m (C–H def.), 1390 m and 1370 m (*tert*-butyl), 1350 s (NO_2), 1315 m, 1190 s (C=O), 1135 m, 1105 m, 990 m, 890 m, 860 w, 845 m (Ar–H). – UV (ethanol): λ_{max} = 264 nm (ε = 12350).

$C_{23}H_{31}N_2O_6SCl$ (499.03)

Calcd	C 55.36	H 6.26	N 5.61	S 6.42%,
Found	C 55.38	H 6.11	N 6.00	S 6.43%.

trans-**5g** ($R^1 = CH_3$, $R^2 = H$, R^3 = *tert*-butyl): yield 65%. – DC: R_f = 0.58 (toluene/ethyl acetate 1:1). – ^{1}H NMR (CD_3CN): δ = 1.17 (s, ~4.5H, $-C(CH_3)_3$), 1.20 (s, ~4.5H, $-C(CH_3)_3$), 1.29, 1.33 and 1.36 (m, 12H, 3′-CH_3 and $S-C(CH_3)_3$), 2.92–3.32 (m, 1H, 3′-H), 4.49 (d, J = 2 Hz, ~0.5H, 4′-H), 4.64 (d, J = 2 Hz, ~0.5H, 4′-H), 5.21 (s, ~0.5H, 2-H), 5.26 (s, 2H, $-O-CH_2-Ar$), 5.39 (s, ~0.5H, 2-H), 7.52 (d, J = 9 Hz, 2H, Ar–H), 8.16 (d, J = 9 Hz, 2H, Ar–H). – IR (CH_2Cl_2): 2955 m (aliph. CH), 1765 s (β-lactam C=O and ester C=O), 1725 s (ketone C=O), 1610 s (C=C), 1525 s (NO_2), 1460 m (C–H def.), 1380 w and 1365 m (*tert*-butyl), 1350 s (NO_2), 1315 m, 1205 m, 1180 s (C–O), 1120 m, 1050 m, 990 w, 960 w, 905 w, 890 w, 855 m, 840 m (Ar–H), 790 w. – UV (ethanol): λ_{max} = 264 nm (ε = 10160).

$C_{22}H_{30}N_2O_6S$ (450.56)

Calcd	C 58.65	H 6.71	N 6.22	S 7.12%,
Found	C 58.72	H 6.87	N 6.20	S 7.44%.

cis-**5g** ($R^1 = CH_3$, $R^2 = H$, R^3 = *tert*-butyl): yield 43%. – DC: R_f = 0.54 (toluene/ethyl acetate 1:1). – ^{1}H NMR (CD_3CN): δ = 1.13, 1.18, 1.20 (m, 12H, 3′-CH_3 and $-C(CH_3)_3$), 1.27 (s, 9H, $S-C(CH_3)_3$), 3.33–3.77 (m, 1H, 3′-H), 5.04 (d, J = 5 Hz, ~0.5H, 4′-H), 5.20 (d, J = 5 Hz, ~0.5H, 4′-H), 5.26 (s, 2H, $-O-CH_2-Ar$), 5.26 (s, ~0.5H, 2-H), 5.40 (s, ~0.5H, 2-H), 7.54 (d, J = 8.5 Hz, 2H, Ar–H), 8.17 (d, J = 8.5 Hz, 2H, Ar–H). – IR (CH_2Cl_2): 2960 m (aliph. CH), 1760 s (β-lactam C=O and ester C=O), 1715 s (ketone C=O), 1610 s (C=C), 1525 s (NO_2), 1455 m (C–H def.), 1365 m (*tert*-butyl), 1350 s (NO_2), 1315 m, 1170 s (C–O), 1090 m, 1055 m, 1000 w, 965 w, 875 w, 845 m (Ar–H). – UV (ethanol): λ_{max} = 264 nm (ε = 12830).

$C_{22}H_{30}N_2O_6S$ (450.56)

Calcd	C 58.65	H 6.71	N 6.22	S 7.12%,
Found	C 58.46	H 6.54	N 6.35	S 7.15%.

5h ($R^1 = R^2 = H$, R^3 = *tert*-butyl): yield 65%. – DC: R_f = 0.55 (toluene/ethyl acetate 1:1). – ^{1}H

NMR (CD_3CN): δ = 1.18 (s, ~4.5H, $-C(CH_3)_3$), 1.21 (s, ~4.5H, $-C(CH_3)_3$), 1.29 (s, 9H, $-S-C(CH_3)_3$), 2.91 (dd, J = 15 Hz, J = 2.5 Hz, ~0.5H, *trans*-3′-H), 2.94 (dd, J = 15 Hz, J = 2.5 Hz, ~0.5H, *trans*-3′-H), 3.55 (dd, J = 15 Hz, J = 5 Hz, ~0.5H, *cis*-3′-H), 3.61 (dd, J = 15 Hz, J = 5 Hz, ~0.5H, *cis*-3′-H), 4.95 (dd, J = 5 Hz, J = 2.5 Hz, ~0.5H, 4′-H), 5.07 (dd, J = 5 Hz, J = 2.5 Hz, ~0.5H, 4′-H), 5.29 (s, ~2.5H, $-O-CH_2-Ar$ and 2-H), 5.43 (s, ~0.5H, 2-H), 7.56 (d, J = 9 Hz, 2H, Ar–H), 8.19 (d, J = 9 Hz, 2H, Ar–H). – IR (CH_2Cl_2): 2970 m, 2905 w and 2870 w (aliph. CH), 1770 s (β-lactam C=O), 1760 s (ester C=O), 1715 s (ketone C=O), 1610 m (C=C), 1530 s (NO_2), 1480 w, 1460 w (C–H def.), 1370 (*tert*-butyl), 1350 s (NO_2), 1315 m, 1180 s (C–O), 1125 w, 1110 w, 1060 w, 1040 w, 995 m, 845 m (Ar–H). – UV (ethanol): λ_{max} = 265 nm (ε = 11790).

$C_{21}H_{28}N_2O_6S$ (436.53)
Calcd C 57.78 H 6.47 N 6.42 S 7.35%,
Found C 57.52 H 6.47 N 6.34 S 7.35%.

p-Nitrobenzyl 7-oxo-4-oxa-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylates **6b** *($R^1 = R^2 = R^3 = CH_3$),*
6c *($R^1 = R^2 = CH_3$, $R^3 = C_2H_5$),*
6d *($R^1 = R^2 = CH_3$, $R^3 = CH(CH_3)_2$),*
6e *($R^1 = R^2 = CH_3$, $R^3 = C(CH_3)_3$),*
6f *($R^1 = R^2 = CH_3$, $R^3 = C(CH_3)_2CH_2Cl$),*
6h *($R^1 = R^2 = H$, $R^3 = C(CH_3)_3$)*

To a solution of **5b–f** or **5h** (2.0 mmol) in dry dimethoxyethane (460 ml) yellow mercuric (II) oxide (5 mmol) and mercuric (II) chloride (5 mmol) were added and the mixture refluxed for 1.5 to 3 h. After cooling the reaction mixture was filtered through Cellite in order to remove insoluble mercuric salts and the filtrate was evaporated *in vacuo* to a volume of approx. 50 ml. Benzene (500 ml) was then added and the mixture left for 2 d at 0 °C where upon some insoluble material deposited. After filtration, the obtained clear solution was subsequently washed with saturated NaCl solution (250 ml), 0.5 M phosphate buffer pH 7 (250 ml) and again with saturated NaCl solution (250 ml). The aqueous phases were reextracted with benzene (100 ml). The combined organic solutions were dried over $MgSO_4$, filtered, the filtrate evaporated to a volume of approx. 50 ml and the resulting solution stored at 0 °C. Some additional deposited material was removed by filtration and the filtrate evaporated *in vacuo* leaving a yellow, slightly turbid oil. For purification and removal of ultimately deposited mercuric salts the crude material was chromatographed on Florisil (25 g) with toluene/ethyl acetate 7:1 (5 ml fractions) and afforded pure **6.**

6b ($R^1 = R^2 = R^3 = CH_3$): yield 58%, m.p. 116.5–119 °C (CH_2Cl_2/*n*-hexane). – DC: R_f = 0.59 (toluene/ethyl acetate 1:1). – ^1H NMR (CCl_4): δ = 1.30 (s, 3H, 6-CH_3), 1.48 (s, 3H, 6-CH_3), 2.25 (s, 3H, 3-CH_3), 5.03 (d, J = 14 Hz, 1H, $-O-CH_2-Ar$), 5.37 (d, J = 14 Hz, 1H, $-O-CH_2-Ar$), 5.46 (s, 1H, 5-H), 7.51 (d, J = 9 Hz, 2H, Ar–H), 8.16 (d, J = 9 Hz, 2H, Ar–H). – IR (CH_2Cl_2): 2930 w (aliph. CH), 1805 s (β-lactam C=O), 1710 s (ester C=O), 1630 s (C=C), 1605 m, 1525 s (NO_2), 1380 m (C–H def.), 1345 s (NO_2), 1330 s (C–O), 1295 w, 1160 m, 1095 s (C–O), 1050 w, 1025 w, 1010 m, 985 m, 950 w, 925 w, 850 m (Ar–H). – UV (dioxane): λ_{max} = 273.5 nm (ε = 16050). – MS (70 eV, 80 °C): m/e = 332 M^+, 304 (–CO), 290 ($-C_2H_2O$), 263 ($-C_4H_6O$, $+H^\cdot$), 217, 136 ($O_2N-C_6H_4-CH_2^+$), 111, 70 ($C_4H_6O^+$), 55 ($C_3H_3O^+$). – X-ray*.

$C_{16}H_{16}N_2O_6$ (332.32)
Calcd C 57.83 H 4.85 N 8.43%,
Found C 57.78 H 5.07 N 8.11%.

6c ($R^1 = R^2 = CH_3$, $R^3 = C_2H_5$): yield 67%, noncrystalline solid. – DC: R_f = 0.61 (toluene/ethyl acetate 1:1). – ^1H NMR (CCl_4): δ = 1.16 (t, J = 7.5 Hz, 3H, $-CH_2-C\underline{H}_3$), 1.28 (s, 3H, 6-CH_3), 1.47 (s, 3H, 6-CH_3), 2.69 (q, J = 7.5 Hz, 2H, $-C\underline{H}_2-CH_3$), 5.02 (d, J = 13 Hz, 1H, $-O-CH_2-Ar$), 5.35 (d, J = 13 Hz, 1H, $-O-CH_2Ar$), 5.44 (s, 1H, 5-H), 7.49 (d, J = 8.5 Hz, 2H, Ar–H), 8.09 (d, J = 8.5 Hz, 2H, Ar–H). – IR (CH_2Cl_2): 2950 m and 2870 w (aliph. CH), 1802 s (β-lactam C=O), 1715 s (ester C=O), 1625 s (C=C), 1610 s (C=C), 1525 s (NO_2), 1465 m (C–H def.), 1380 m (CH_3 def.), 1350 s (NO_2), 1335 s (C–O), 1300 w, 1240 w, 1205 w, 1165 s (C–O), 1105 s (C–O), 1070 m, 1050 m, 1000 m, 920 w, 855 m (Ar–H). – UV (dioxane): λ_{max} = 272.5 nm (ε = 16450). – MS (70 eV, 80 °C): m/e = 346 M^+, 318 (–CO), 277 ($-C_4H_6O$, $+H^\cdot$), 217, 166 ($-O_2N-C_6H_4-CH_2-OCO^\cdot$), 136 ($O_2N-C_6H_4-CH_2^+$), 70 ($C_4H_6O^+$), $m^\star$ = 222 (346/277).

$C_{17}H_{18}N_2O_6$ (346.34)
Calcd C 58.96 H 5.24 N 8.09%,
Found C 58.80 H 5.02 N 7.86%.

* X-ray data may be obtained from: Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftlich-technische Information mbH, D-W-7514 Eggenstein-Leopoldshafen 2, by quoting the Registry-No. CSD 56278, the names of the authors and the journal citation.

6d (R^1 = R^2 = CH_3, R^3 = $CH(CH_3)_2$: yield 64%, m.p. 90.5–92 °C (CH_2Cl_2/*n*-hexane). – DC: R_f = 0.63 (toluene/ethyl acetate 1:1). – ^{1}H NMR (CCl_4): δ = 1.15 (d, J = 7 Hz, 3H, $-CH(C\underline{H}_3)_2$), 1.18 (d, J = 7 Hz, 3H, $-CH(C\underline{H}_3)_2$), 1.27 (s, 3H, 6-CH_3), 1.46 (s, 3H, 6-CH_3), 3.52 (m, J = 7 Hz, 1H, $-C\underline{H}(CH_3)_2$), 5.01 (d, J = 14 Hz, 1H, $-O-C\underline{H}_2-Ar$), 5.35 (d, J = 14 Hz, 1H, $-O-CH_2-Ar$), 5.43 (s, 1H, 5-H), 7.49 (d, J = 8.5 Hz, 2H, Ar–H), 8.09 (d, J = 8.5 Hz, 2H, Ar–H). – IR (CH_2Cl_2): 2965 m, 2930 m and 2870 w (aliph. CH), 1800 s (β-lactam C=O), 1710 s (ester C=O), 1625 s (C=C), 1525 s (NO_2), 1470 m (C–H def.), 1390 m and 1380 m (isopropyl), 1350 s (NO_2), 1340 s (C–O), 1315 m, 1220 w, 1170 m, 1150 m, 1095 s (C–O), 1045 m, 1010 m, 935 w, 860 m, 850 m (Ar–H). – UV (dioxane): λ_{max} = 275 nm (ε = 17500). – MS (70 eV, 80–90 °C): m/e = 360 M^+, 332 (–CO), 317 ($-C_3H_7^{\cdot}$), 291 ($-C_4H_6O$, $+H^{\cdot}$), 217, 180 ($O_2N-C_6H_4-CH_2-OCO^+$), 136 ($O_2N-C_6H_4-CH_2^+$), 70 ($C_4H_6O^+$), m = 235.2 (360/291).

$C_{18}H_{20}N_2O_6$ (360.37)
Calcd C 59.99 H 5.59 N 7.77%,
Found C 59.94 H 5.32 N 7.78%.

6e (R^1 = R^2 = CH_3, R^3 = *tert*-butyl): yield 75%, m.p. 119–120.5 °C (CH_2Cl_2/*n*-hexane). – DC: R_f = 0.63 (toluene/ethyl acetate 1:1). – ^{1}H NMR (CCl_4): δ = 1.30 (s, 12H, 6-CH_3 and *tert*-butyl), 1.47 (s, 3H, 6-CH_3), 5.02 (d, J = 14 Hz, 1H, $-O-CH_2-Ar$), 5.36 (d, J = 14 Hz, 1H, $-O-CH_2-Ar$), 5.40 (s, 1H, 5-H), 7.53 (d, J = 8.5 Hz, 2H, Ar–H), 8.12 (d, J = 8.5 Hz, 2H, Ar–H). – IR (CH_2Cl_2): 2935 m and 2870 w (aliph. CH), 1797 s (β-lactam C=O), 1715 s (ester C=O), 1610 m, 1585 s (C=C), 1525 s (NO_2), 1460 w (C–H def.), 1350 s (NO_2), 1315 s (C–O), 1155 m, 1140 m, 1085 s (C–O), 1030 w, 1010 m, 920 w, 850 m (Ar–H). – UV (dioxane): λ_{max} = 278 nm (ε = 14980). – MS (20 eV, 80 °C): m/e = 374 M^+, 346 (–CO), 331 (–CO, $-CH_3$), 305 ($-C_4H_6O$, $+H^{\cdot}$), 289 (–CO, $-C_4H_9^{\cdot}$), 217, 194 ($-O_2N-C_6H_4-CH_2-OCO^{\cdot}$), 152 ($O_2N-C_6H_4-CH_2O^+$), 136 ($O_2N-C_6H_4-CH_2^+$), 70 ($C_4H_6O^+$), 57 ($C_4H_9^+$). – X-ray*.

$C_{19}H_{22}N_2O_6$ (374.40)
Calcd C 60.95 H 5.92 N 7.48%,
Found C 60.54 H 5.79 N 7.23%.

6f (R^1 = R^2 = CH_3, R^3 = $C(CH_3)_2CH_2Cl$): yield 86%, m.p. 95–97 °C (CH_2Cl_2/hexane). – DC: R_f = 0.65 (toluene/ethyl acetate 1:1). – ^{1}H NMR CCl_4): δ = 1.34, 1.38, 1.40 and 1.48 (4 s, 12H, 6-CH_3 and $-C(C\underline{H}_3)_2CH_2Cl$), 3.66 (d, J = 10 Hz, 1H, $-C(CH_3)_2C\underline{H}_2Cl$), 3.91 (d, J = 10 Hz, 1H, $-C(CH_3)_2C\underline{H}_2Cl$), 5.06 (d, J = 14 Hz, 1H, $-O-CH_2-Ar$), 5.41 (d, J = 14 Hz, 1H, $-O-CH_2-Ar$), 5.48 (s, 1H, 5-H), 7.55 (d, J = 9 Hz, 2H, Ar–H), 8.16 (d, J = 9 Hz, 2H, Ar–H). – IR (CH_2Cl_2): 2930 m and 2875 w (aliph. CH), 1803 s (β-lactam C=O), 1710 s (ester C=O), 1590 s (C=C), 1525 s (NO_2), 1460 w, 1370 m (CH_3 def.), 1350 s (NO_2), 1315 s (C–O), 1255 m, 1160 s, 1130 m, 1115 m, 1090 s (C–O), 1010 s, 990 m, 920 m, 890 w, 850 m (Ar–H). – UV (dioxane): λ_{max} = 279 nm (ε = 14400). – MS (70 eV, 110 °C): m/e = 408 M^+, 380 (–CO), 339 ($-C_4H_6O$), $+H^{\cdot}$), 303 ($-C_4H_6O$, $-Cl^{\cdot}$), 289 (–CO, $-C_4H_8Cl^{\cdot}$), 217, 186 ($-C_4H_6O$, $-O_2N-C_6H_4-CH_2-O^{\cdot}$), 136 ($O_2N-C_6H_4-CH_2^+$), 70 ($C_4H_6O^+$).

$C_{19}H_{21}N_2O_6Cl$ (408.84)
Calcd C 55.82 H 5.18 N 6.85 Cl 8.67%,
Found C 55.96 H 5.26 N 6.84 Cl 8.81%.

6h (R^1 = R^2 = H, R^3 = *tert*-butyl): yield 12% (see also Method B), m.p. 142–144 °C (CH_2Cl_2/hexane). – DC: R_f = 0.62 (toluene/ethyl acetate 1:1). – ^{1}H NMR (CD_3CN): δ = 1.29 (s, 9H, *tert*-butyl), 3.40 (dd, J = 17 Hz, J = 1 Hz, 1H, *trans*-6-H), 3.79 (dd, J = 17 Hz, J = 2.5 Hz, 1H, *cis*-6-H), 5.16 (d, J = 14 Hz, 1H, $-O-CH_2-Ar$), 5.42 (d, J = 14 Hz, 1H, $-O-CH_2-Ar$), 5.85 (dd, J = 2.5 Hz, J = 1 Hz, 1H, 5-H), 7.61 (d, J = 8.5 Hz, 2H, Ar–H), 8.17 (d, J = 8.5 Hz, 2H, Ar–H). – IR (CH_2Cl_2): 2955 m, (aliph. CH), 1804 s (β-lactam C=O), 1715 s (ester C=O), 1610 m, 1585 s (C=C), 1525 s (NO_2), 1350 s (NO_2), 1315 s (C–O), 1200 m, 1165 s, 1145 s, 1120 m, 1080 s (C–O), 1040 m, 1025 s, 1015 m, 885 m, 855 m (Aryl-H), 840 m. – UV (dioxane): λ_{max} = 277 nm (ε = 15340). – MS (70 eV, 130 °C): m/e = 346 M^+, 318 (–CO), 304 ($-C_2H_2O$), 289 ($-C_4H_9^{\cdot}$), 168 ($-O_2N-C_6H_4-CH_2^{\cdot}$), 153 ($O_2N-C_6H_4-CH_2OH^+$), 152 ($O_2N-C_6H_4-CH_2-O^+$), 136 ($O_2N-C_6H_4-CH_2^+$), 57 ($C_4H_9^+$).

$C_{17}H_{18}N_2O_6$ (346.34)
Calcd C 58.96 H 5.24 N 8.09%,
Found C 58.81 H 5.24 N 7.96%.

Sodium 7-oxo-4-oxa-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylates **1b** *(R^1 = R^2 = R^3 = CH_3),* **1c** *(R^1 = R^2 = CH_3, R^3 = C_2H_5),* **1d** *(R^1 = R^2 = CH_3, R^3 = $CH(CH_3)_2$),* **1e** *(R^1 = R^2 = CH_3, R^3 = $C(CH_3)_3$),* **1f** *(R^1 = R^2 = CH_3, R^3 = $C(CH_3)_2CH_2Cl$),* **1h** *(R^1 = R^2 = H, R^3 = $C(CH_3)_3$)*

In a hydrogenation apparatus fitted with a rubber septum and magnetic stirrer a mixture of

4.7 mg (56 μmol) $NaHCO_3$ in water (1 ml), ethyl acetate (2 ml), 10% Pd on C (30 mg) was prehydrogenated at 0 °C. After 5 min the uptake of H_2 ended and a solution of **6** (50 μmol) in ethyl acetate (1 ml) was added at 0 °C through the septum by a syringe. Within 20 min 5.4 ml of H_2 was taken up (theoretical volume: 4.6 ml). The reaction mixture was diluted with ethyl acetate (2 ml) and removed from the catalyst by filtration through a glass filter. The organic layer was removed and the aqueous phase washed twice with portions (1 ml) of ethyl acetate. Residual ethyl acetate was removed from the aqueous layer by short evacuation at 13 Torr. A 10 μl sample of the aqueous layer was diluted in a quartz UV cell with water (2.7 ml) and the extinction at 260 nm measured in a UV-spectrometer. Lyophilisation *in vacuo* (10^{-3} Torr) at −20 °C afforded pure **1** as noncrystalline voluminous and colourless powder. The product was stored at −80 °C. From the organic phases *p*-toluidine could be identified by TLC.

1b ($R^1 = R^2 = R^3 = CH_3$): yield after lyophilisation 79%. – ^{1}H NMR (D_2O): δ = 1.28 (s, 3H, 6-CH_3), 1.42 (s, 3H, 6-CH_3), 2.17 (s, 3H, 3-CH_3), 5.55 (s, 1H, 5-H). – UV (H_2O): λ_{max} = 259 nm (ε = 5800).

1c ($R^1 = R^2 = CH_3$, $R^3 = C_2H_5$): yield in solution 89%, yield after lyophilisation 64%. – ^{1}H NMR (D_2O): δ = 1.11 (t, J = 7 Hz, 3H, $-CH_2-C\underline{H}_3$), 1.27 (s, 3H, 6-CH_3), 1.42 (s, 3H, 6-CH_3), 2.64 (q, J = 7 Hz, 2H, $-C\underline{H}_2-CH_3$), 5.56 (s, 1H, 5-H). – UV (H_2O): λ_{max} = 259 nm (ε = 5800).

1d ($R^1 = R^2 = CH_3$, $R^3 = CH(CH_3)_2$): yield in solution 100%, yield after lyophilisation 59%. – ^{1}H NMR (D_2O): δ = 1.12 (d, J = 7 Hz, 3H, $-CH(C\underline{H}_3)_2$), 1.15 (d, J = 7 Hz, 3H, $-CH(C\underline{H}_3)_2$), 1.27 (s, 3H, 6-CH_3), 1.43 (s, 3H, 6-CH_3), 3.52 (m, 1H, $-C\underline{H}(CH_3)_2$), 5.55 (s, 1H, 5-H). – IR (KBr): 2970 m, 2935 m and 2880 w (aliph. CH), 1780 s (β-lactam C=O), 1635 s (C=C), 1590 s (carboxylate C=O), 1470 m and 1445 w (C–H def.), 1405 s (carboxylate C=O), 1370 m (isopropyl), 1325 m, 1305 m, 1260 m (=C–O–C), 1220 w, 1195 m, 1125 m, 1040 m (=C–O–C), 995 m, 945 w, 865 w, 835 w, 800 w, 755 w. – UV (H_2O): λ_{max} = 260 nm (ε = 5800).

1e ($R^1 = R^2 = CH_3$, R^3 = *tert*-butyl): yield after lyophilisation 68%, ^{1}H NMR (D_2O): δ = 1.23 (s, 9H, *tert*-butyl), 1.26 (s, 3H, 6-CH_3), 1.39 (s, 3H, 6-CH_3), 5.50 (s, 1H, 5-H). – UV (H_2O): λ_{max} = 261 nm (ε = 5800).

o-Nitrobenzyl 3-tert-butyl-6,6-dimethyl-7-oxo-4-oxa-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (derivative of **1e***)*

1e (66 mg, 0.25 mmol) and *o*-nitrobenzyl bromide (43 mg, 0.20 mmol) in dry DMSO (0.3 ml) were stirred under argon for 46 h. A substochiometric amount of *o*-nitrobenzyl bromide was used in order to facilitate separation of the lipophilic product. Benzene (40 ml) was added to the reaction mixture and the solution washed three times with portions (40 ml) of H_2O. The aqueous phases were reextracted with benzene (30 ml), the combined organic layers dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. A pale yellow noncrystalline solid (70 mg) was obtained. Chromatography on silica gel (1 g) using hexane/ethyl acetate 9:1 afforded pure title compound (10 mg, 13%, only a part of chromatography fractions containing pure product) as a colourless noncrystalline solid. – DC: R_f = 0.59 (toluene/ethyl acetate 1:1). – ^{1}H NMR (CCl_4): δ = 1.31 (s, 12H, *tert*-butyl and 6-CH_3), 1.49 (s, 3H, 6-CH_3), 5.32 (d, J = 16 Hz, 1H, $-O-CH_2-Ar$), 5.86 (d, J = 16 Hz, 1H, $-O-CH_2-Ar$), 5.45 (s, 1H, 5-H), 7.20–8.18 (m, 4H, Ar–H). – IR (CH_2Cl_2): 2945 m (aliph. CH), 1796 s (β-lactam C=O), 1710 s (ester C=O), 1580 s (C=C), 1525 s (NO_2), 1345 s (NO_2). – UV (dioxane): λ_{max} = 273 nm (ε = 10270). – MS (20 eV, 110 °C): m/e = 376 ($M^+ + H_2$), 374 M^+, 346 (−CO), 317 ($-C_4H_9^{\cdot}$), 305 ($-C_4H_6O$, $+H^{\cdot}$), 289 ($-CO$, $-C_4H_9^{\cdot}$), 258, 194 ($-O_2N-C_6H_4-CH_2-OCO^{\cdot}$), 152 ($O_2N-C_6H_4-CH_2-O^+$), 136 ($O_2N-C_6H_4-CH_2^+$), 85 ($C_4H_9CO^+$), 70 ($C_4H_6O^+$), 57 ($C_4H_9^+$).

$C_{19}H_{22}N_2O_6$ (374.40)
Calcd C 60.95 H 5.92 N 7.48%,
Found C 61.02 H 5.95 N 7.09%.

1f ($R^1 = R^2 = CH_3$, $R^3 = C(CH_3)_2CH_2Cl$): yield after lyophilisation 60%. – ^{1}H NMR (D_2O): δ = 1.27, 1.30, 1.33 and 1.39 (4 s, 12H, 6-CH_3 and $-C(C\underline{H}_3)_2CH_2Cl$), 3.74 (d, J = 10 Hz, 1H, $-C(CH_3)_2C\underline{H}_2Cl$), 4.05 (d, J = 10 Hz, 1H, $-C(CH_3)_2C\underline{H}_2Cl$), 5.52 (s, 1H, 5-H). – IR (KBr): 2975 m, 2935 m and 2875 w (aliph. CH), 1780 s (β-lactam C=O), 1610 s (braod, C=C and carboxylate C=O), 1465 w and 1445 w ($-C(CH_3)_2-$), 1390 s (carboxylate C=O), 1310 m, 1255 m (=C–O–C), 1195 m, 1175 m, 1140 m, 1120 m, 1090 m (=C–O–C), 1030 w, 1000 m, 935 w, 860 w, 845 w, 795 m (C-Hal), 750 w. – UV (H_2O): λ_{max} = 265 nm (ε = 5800).

1h ($R^1 = R^2 = H$, R^3 = *tert*-butyl): yield in solution 75%. – ^{1}H NMR (D_2O): δ = 1.23 (s, 9H, *tert*-butyl), 3.43 (dd, J = 18 Hz, J = 1 Hz, 1H, *trans*-

6-H), 3.72 (dd, J = 18 Hz, J = 2.5 Hz, *cis*-6-H), 5.82 (s, 1H, 5-H).

Method B, general procedure

p-Nitrobenzyl 2-(4-chloro-2-oxo-1-azetidinyl)-4,4-dimethyl-3-oxopentanoates **7g** *($R^1 = CH_3$, $R^2 = H$, $R^3 = C(CH_3)_3$) and* **7h** *($R^1 = R^2 = H$, $R^3 = C(CH_3)_3$)*

Into a stirred solution of *trans*-**5g** or **5h** (1.0 mmol) in dry CH_2Cl_2 (40 ml) at −50 °C through a rubber septum Cl_2 gas (44.8 ml, 2.0 mmol) was added by a syringe in order that the needle reached below the surface of the reaction solution. The mixture was allowed to stir at −50 °C for 30 min and it was warmed to 0 °C. TLC monitoring was difficult because of identical R_f of starting material and product. The obtained solution was washed with a aqueous solution (50 ml) containing $NaHSO_3$ (3.5 g) and K_2CO_3 (2.0 g) and then with saturated NaCl solution (50 ml). The organic layer was dried over $MgSO_4$, filtered and the solvent removed *in vacuo* leaving a noncrystalline solid. It was rapidly chromatographed on silica gel (4 g) with toluene/ethyl acetate 9:1 at −10 °C.

cis-**7g** ($R^1 = CH_3$, $R^2 = H$, R^3 = *tert*-butyl): yield 84%, noncrystalline solid, mixture of two *cis*-diastereomers I and II. – ^{1}H NMR (CD_3CN): δ = 1.19, 1.21 and 1.32 (3 signals, 12H, 4′-CH_3 and *tert*-butyl, I and II), 3.59–3.98 (m, 1H, 3′-H), 5.30 (s, 2H, −O−CH_2−Ar), 5.50 (s, ~0.25 H, 2-H, I), 5.70 (s, ~0.75 H, 2-H, II), 5.94 (d, J = 5 Hz, ~0.25 H, 4′-H, I), 6.09 (d, J = 5 Hz, ~0.75 H, 4′-H, II), 7.43–7.64 (m, 2H, Ar−H), 8.17 (d, J = 9 Hz, 2H, Ar−H).

$C_{18}H_{21}N_2O_6Cl$ (396.83)
Calcd C 54.48 H 5.33 N 7.06%,
Found C 54.61 H 5.32 N 7.57%.

7h ($R^1 = R^2 = H$, R^3 = *tert*-butyl): yield 83%, m.p. 96–100.5 °C (CH_2Cl_2/hexane), mixture of two diastereomers I and II. – ^{1}H NMR (CD_3CN): δ = 1.04 (s, ~5.4 H, *tert*-butyl, I), 1.21 (s, ~3.6 H, *tert*-butyl, II), 3.05–3.86 (m, 1H, 3′-H), 5.29 (s, 2H, −O−CH_2−Ar), 5.52 (s, ~0.6 H, 2-H, I), 5.71 (s, ~0.4 H, 2-H, II), 5.84 (dd, J = 4 Hz, J = 2 Hz, ~0.6 H, 4′-H, I), 5.98 (dd, J = 4 Hz, J = 2 Hz, ~0.4 H, 4′-H, II), 7.51 (d, J = 9 Hz, ~0.8 H, Ar−H, II), 7.55 (d, J = 9 Hz, ~1.2 H, Ar−H, I), 8.19 (d, J = 9 Hz, 2H, Ar−H, I and II).

$C_{17}H_{18}N_2O_6Cl$ (417.25)
Calcd C 53.34 H 5.00 N 7.32%,
Found C 53.29 H 5.04 N 7.22%.

p-Nitrobenzyl 3-tert-butyl-7-oxo-4-oxa-1-aza-bicyclo[3.2.0]hept-2-ene-2-carboxylates **6g** *($R^1 = CH_3$, $R^2 = H$, $R^3 = C(CH_3)_3$) and* **6h** *($R^1 = R^2 = H$, $R^3 = C(CH_3)_3$)*

To a stirred solution of **7g** or **7h** (0.25 mmol) in dry THF (5 ml) at −30 °C a 1 N solution of potassium *tert*-butoxide (260 µl, 0.26 mmol) in dry *tert*-butanol was added within 5 min and the brown-red solution stirred for 30 min at −30 °C. TLC (toluene/acetate 4:1) indicated a complete reaction. The reaction mixture was diluted with ethyl acetate (50 ml) and subsequently washed with H_2O (50 ml) and saturated NaCl solution (50 ml). The organic layer was dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The residue was chromatographed on silica gel (4 g) with toluene/ethyl acetate 9:1 affording pure product **6g** or **6h.**

6g ($R^1 = CH_3$, $R^2 = H$, $R^3 = C(CH_3)_3$): yield 58%, m.p. 104–106.5 °C (CH_2Cl_2/hexane), mixture of *cis*-, *trans*-diastereomers. – DC: R_f = 0.63 (toluene/ethyl acetate 1:1). – ^{1}H NMR (CD_3CN): δ = 1.22, 1.29 and 1.44 (3 signals, 12H, 6-CH_3 and *tert*-butyl, *cis* and *trans*), 3.68 (q, J = 7.5 Hz, ~0.5 H, 6-H, *trans*), 4.02 (dq, J = 7.5 Hz, J = 3 Hz, ~0.5 H, 6-H, *cis*), 5.15 (d, J = 14 Hz, 1H, −O−CH_2−Ar), 5.42 (d, J = 14 Hz, 1H, −O−CH_2−Ar), 5.59 (s, ~0.5 H, 5-H, *trans*), 5.82 (d, J = 3 Hz, ~0.5 H, 5-H, *cis*), 7.61 (d, J = 8.5 Hz, 2H, Ar−H), 8.15 (d, J = 8.5 Hz, 2H, Ar−H). – IR (CH_2Cl_2): 2965 m (aliph. CH), 1800 s (β-lactam C=O), 1715 s (ester C=O), 1585 s (C=C), 1525 s (NO_2), 1345 s (NO_2), 1310 s (C−O), 1165 m, 1140 m, 1085 s (C−O), 1025 m, 1015 w, 935 m, 850 m (Ar−H). – UV (dioxane): λ_{max} = 277.5 nm (ε = 15200). – MS (70 eV, 110–120 °C): m/e = 360 M^+, 332 (−CO), 305 (−CH_3−C=C=O·), 152 ($O_2N-C_6H_4-CH_2-O^+$), 136 ($O_2N-C_6H_4-CH_2^+$), 57 ($C_4H_9^+$), 56 ($CH_3-CH=C=O^+$), m = 258.4 (360/305).

$C_{18}H_{20}N_2O_6$ (360.37)
Calcd C 59.99 H 5.59 N 7.77%,
Found C 60.16 H 5.61 N 8.26%.

6h ($R^1 = R^2 = H$, R^3 = *tert*-butyl): yield 62%, m.p. 142–144 °C (CH_2Cl_2/hexane); see also Method A.

Sodium 3-tert-butyl-6-methyl-7-oxo-4-oxa-1-aza-bicyclo[3.2.0]hept-2-ene-2-carboxylate **1g**

Following procedure A from **6g** the pure title compound was obtained. Yield after lyophylisation 37%, colourless powder. – ^{1}H NMR (D_2O): δ = 1.24 and 1.27 (2 s, 9 H, *tert*-butyl, *cis* and *trans*), ~1.38 (2d, J ~7.5 Hz, 3H, 6-CH_3), 3.67 (q, J = 7.5 Hz, ~0.5 H, 6-H, *trans*), 3.96 (dq, J =

7.5 Hz, J = 3 Hz, ~0.5H, 6-H, *cis*), 5.55 (s, ~0.5H, 5-H, *trans*), 5.80 (d, J = 3 Hz, ~0.5H, 5-H, *cis*). – UV (H_2O): λ_{max} = 260 nm (ε = 5800). The product was stored at −80 °C.

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