First Synthetic Access to 6-(Methylene)oxapenems: A New Class of β-Lactamase Inhibitors

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Dedicated to Professor Ulrich Schöllkopf on the occasion of his 65th birthday

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The first synthetic route to racemic 6-(substituted methylene)oxapenems, an interesting new class of β-lactamase inhibitors, is described. In spite of their low hydrolytic stability, even the unprotected acids **9** and **10** can be isolated as their sodium salts. The 6-(unsubstituted methylene)oxapenem **7e**, however, is unstable and decomposes under the conditions of its formation.

The oxapenem class of β-lactams was first described in 1977.[1] Although some derivatives showed interesting activity as β-lactamase inhibitors,[2] the instability of the highly strained oxapenem ring system towards chemical hydrolysis precluded their use in biological systems. The recent discovery that 2-*tert*-alkyloxapenems are much more stable than expected[3-5] and the detailed description of the biological properties of 6-hydroxyethyloxapenems[6] revived our interest in this class of compounds. In particular we wanted to investigate whether a 6-methylene group would be compatible with the strained oxapenem skeleton, since several potent β-lactamase inhibitors possess a substituted methylene group in the 6-position of a penam-,[7] penem-[8] or carbapenem-system.[9] We report here the first synthetic route to 6-(substituted methylene)oxapenems. In this route a *tert*-butyl substituent was introduced in the 2-position in order to stabilize the oxapenem system.[3-5] An allyl ester was used as a carboxylic acid protecting group, because preliminary experiments had shown, that hydrogenolysis of a *p*-nitrobenzylic ester, which is most often used in oxapenem chemistry, is not compatible with the 6-methylene substituent.

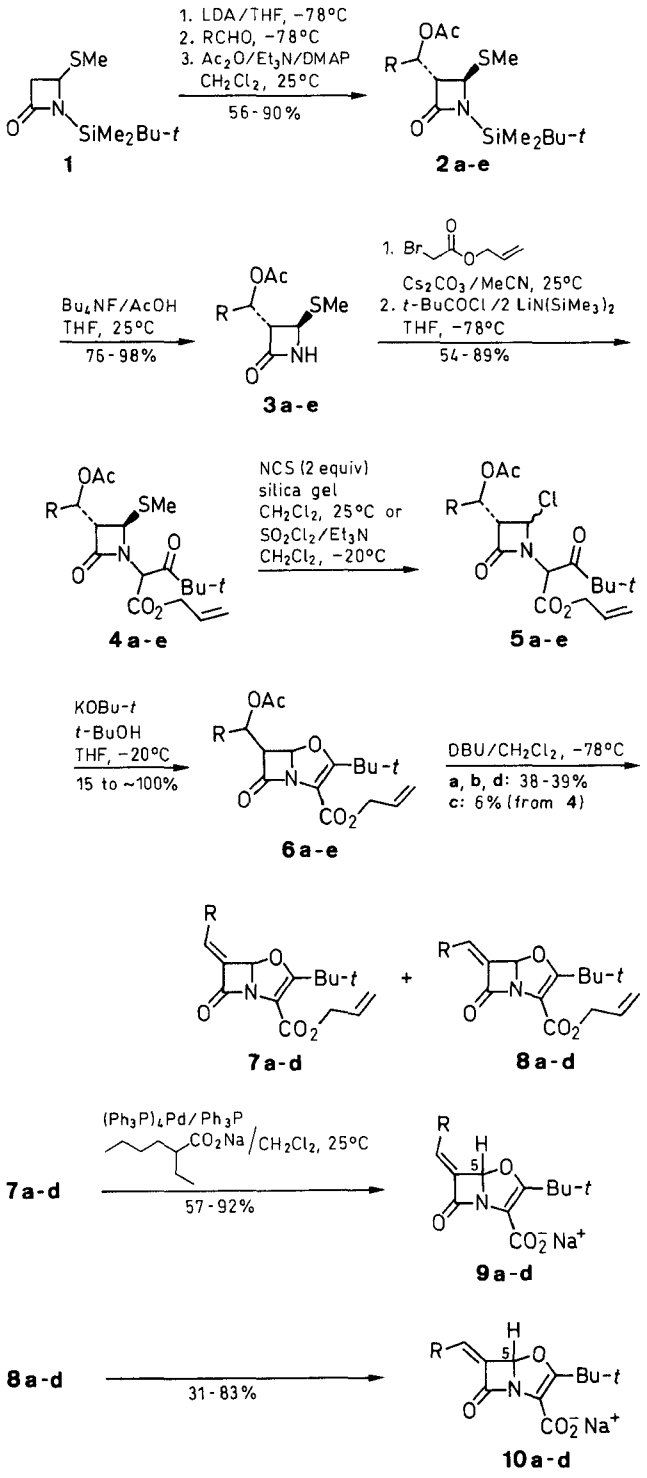
As shown in the Scheme, the cyclization precursors **4** were prepared by slight modifications of standard β-lactam methodology. The lithium enolate of β-lactam **1** was quenched with the corresponding aromatic or aliphatic aldehydes to yield a mixture of diastereomeric alcohols which subsequently were acetylated. Only trace amounts of 3,4-*cis*-azetidinones were produced in this hydroxyalkylation step. Mild deprotection gave rise to the *N*-unsubstituted β-lactam **3**.[10] The *N*-side chain was introduced in two steps, first alkylation with allyl bromoacetate and second acylation with pivaloyl chloride. Transformation of the methylthio group at the 4-position of the β-lactam **4** into a chlorine leaving group proved to be quite difficult. Elemental chlorine[11] could not be used because of the presence of the allyl ester double bond. The transformation was achievd by treating **4** with 2 equivalents of *N*-chlorosuccinimide in dichloromethane in the presence of silica gel as a catalyst.[12] However, furyl derivative **4c** gave rise to side products due to the reactivity of the furan system. In this case sulfuryl chloride/triethylamine at −20 °C was found to be the best reagent for chlorination,[13] although even under these conditions chloride **5c** contained considerable amounts of byproducts. After deprotonation with one equivalent of potassium *tert*-butylate, the *cis*/*trans*-mixture of chlorides **5** cyclized smoothly at −20 °C to give a *cis*/*trans*-mixture of the oxapenems **6**. Subsequent elimination of acetic acid at −78 °C under the influence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was extremely easy. The unsubstituted oxapenem **6e**, however, did not yield methylene derivative **7e**, but decomposed to products other than β-lactam derivatives under the elimination conditions. The mixture of *E*- and *Z*-isomers obtained from **6a–6d** could be separated by rapid chromatography on silica gel. Deprotection of the allyl ester using palladium catalyst[14] gave rise to the final products, the free 6-(methylene)oxapenems isolated as their sodium salts **9** and **10**. The compounds **9** and **10** are yellow to orange solids. The IR absorption of the β-lactam carbonyl is found between 1758 (**10b**) and 1792 cm^{-1} (**9d**), with the *E*-isomers **9** absorbing at higher frequency.

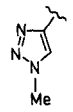
The geometry of the double bond of compounds **9** and **10** was deduced from their ^1H NMR spectra. Compared to the *Z*-oxapenems **10** the methylene proton as well as the ring proton at C-5 of *E*-oxapenems **9** are shifted downfield and the aromatic ortho-protons of compounds **9a–9c** are shifted upfield (see Tables 4 and 5). This corresponds well to shift differences found in 6-(methylene)penems.[8]

Although the unprotected oxapenems **9** and **10** were isolated with a purity of 80–90%, their stability against hydrolysis is limited (Table 1).

The *E*-oxapenems **9** are more stable than the *Z*-derivatives **10**. The least stable compound, the *Z*-(ethylidene)-oxapenem **10d** has a half-life of only 40 minutes at pH 7.0 and 20 °C! In spite of this instability the (methylene)oxapenems were proved to be interesting β-lactamase inhibitors even in cell culture. Their antibacterial activity however was rather low.

Melting points were determined on a Büchi capillary melting point apparatus and are uncorrected. IR spectra were determined on a Perkin-Elmer 281 IR spectrophotometer. ^1H NMR spectra were recorded on Bruker WM 250 and AM 300 spectrometers in either $CDCl_3$ or D_2O solution. Microanalyses were obtained using a Perkin-Elmer 240 element analyser. Mass spectra were obtained on the following mass spectrometers: Electron ionization (EI) on a KRATOS MS 80; desorption chemical ionization (DCI) on a Finnigan MAT 311 A; fast atom bombardment (FAB) on a Finnigan MAT 90. All reactions were performed under a positive pressure of Ar. Reactions were monitored by analytical TLC (silica gel 60 F-254, E. Merck). Silica gel 60 (230–400 mesh ASTM; E. Merck) was used for column chromatography which was performed under a low positive pressure.



2–10	R
a	
b	Ph
c	
d	Me
e (2–6)	H

Scheme

Table 1. Half-Life of Oxapenems **9** and **10** at pH 7.0 at 20 °C

E-Oxapenem	$t_{1/2}$ (h)	*Z*-Oxapenem	$t_{1/2}$ (h)
9a	3.6	**10a**	3.4
9b	4.3	**10b**	1.4
9c	7.9	**10c**	5.0
9d	1.6	**10d**	0.7

1-(*tert*-Butyldimethylsilyl)-4-methylthioazetidin-2-one (1):
A solution of 4-methylthioazetidin-2-one[15] (138.5 g, 1.18 mol) and *tert*-butyldimethylsilyl chloride (204.5 g, 1.36 mol) in DMF (760 mL) was treated portionwise with DABCO (165.5 g, 1.47 mol) at 0 °C. The mixture was stirred for 1 h at 0 °C and for 2 h at 25 °C and then partitioned between EtOAc and water. The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The residue was distilled; yield: 261 g (96%); bp 80–86 °C/0.05 mbar.

$C_{10}H_{21}NOSSi$ (231.4) calc. C 51.9 H 9.1 N 5.9
found 51.7 8.9 6.0

IR (KBr): $\nu = 1728\ cm^{-1}$.

^1H NMR ($CDCl_3$): $\delta = 0.30$ (s, 3 H), 0.32 (s, 3 H), 1.00 (s, 9 H), 2.10 (s, 3 H), 3.08 (dd, $J = 16$, 2.5 Hz, 1 H), 3.43 (dd, $J = 16$, 6 Hz, 1 H), 4.64 (dd, $J = 6$, 2.5 Hz, 1 H).

***trans*-1-*tert*-Butyldimethylsilyl-4-methylthio-3-[(1-methyl-1,2,3-triazol-4-yl)acetoxymethyl]azetidin-2-one (2a); Typical Procedure:**
To a freshly prepared solution of lithium diisopropylamide (LDA) (0.25 mol) in THF (500 mL) **1** (52.1 g, 225 mmol) in THF (100 mL) was added dropwise at −70 °C over 15 min. The solution was stirred for further 15 min at the same temperature, whence sometimes a white solid precipitated. 1-Methyl-1,2,3-triazole-4-carbaldehyde[16] (25 g, 225 mmol) in THF (400 mL) was then added over 10 min. During the addition the precipitate dissolved completely. After stirring for further 15 min at −70 °C, EtOAc (2 L) and water (2 L) were added, the aqueous phase was separated and extracted twice with EtOAc. The combined organic phases were dried ($MgSO_4$) and evaporated in vacuo to give the hydroxy intermediate as a crude oil. Yield: 69.2 g (90%).

The crude intermediate (15.3 g, 44.5 mmol) was dissolved in CH_2Cl_2 (250 mL). At 0 °C Et_3N (7.4 mL, 53.4 mmol), 4-dimethylaminopyridine (544 mg, 4.5 mmol) and Ac_2O (5.1 mL, 53.4 mmol) were added. The solution was kept at 0 °C for 1.5 h. Then sat. aq NH_4Cl (50 mL) was added and the mixture was diluted with CH_2Cl_2 (250 mL). The organic solution was washed with brine, sat. aq $NaHCO_3$ and water and dried ($MgSO_4$). The solvent was evaporated in vacuo and the residual oil was chromatographed on silica gel using toluene/EtOAc (1:1) as eluent. Compound **2a** was obtained as a 2:1 mixture of two diastereoisomers (Table 2). For the hydroxymethylation with gaseous formaldehyde **(2e)**, see Ref. 5.

***trans*-4-Methylthio-3-[(1-methyl-1,2,3-triazol-4-yl)acetoxymethyl]-azetidin-2-one (3a); Typical Procedure:**
To **2a** (11.75 g, 30.6 mmol) in THF (160 mL) containing AcOH (2 mL, 35 mmol) a 1 M solution of Bu_4NF in THF (30.6 mL, 30.6 mmol) was added dropwise at r.t. over 15 min. After stirring for a further 15 min CH_2Cl_2 (500 mL) was added and the solution was washed with brine, sat. aq $NaHCO_3$ and again with brine, dried ($MgSO_4$) and evaporated in vacuo. The residual oil was chromatographed on silica gel using EtOAc as eluent (Table 2).

Allyl 4,4-Dimethyl-2-[(*trans*)-4-methylthio-3-(1-methyl-1,2,3-triazol-4-yl)acetoxymethyl-2-oxoazetidin-1-yl]-3-oxopentanoate (4a); Typical Procedure:
To **3a** (6.24 g, 23.1 mmol) and allyl bromoacetate[17] (6.2 g, 34.7 mmol) in MeCN (140 mL) was added Cs_2CO_3 (9.0 g, 27.7 mmol) and the mixture was stirred at r.t. for 6.5 h. The precipitate was filtered on Celite. The filtrate was diluted with EtOAc (300 mL) and the solution was washed with sat. aq NH_4Cl, brine,

Table 2. Compounds **2** and **3** Prepared

Product	Yield[a] (%)	Molecular Formula[b]	IR ($CHCl_3$) $\nu_{C=O}$ (cm^{-1})	^1H NMR ($CDCl_3$/TMS)[c] δ, J (Hz)	MS m/z (%)
2a	56	$C_{16}H_{28}N_4O_3SSi$ (384.6)	–	0.25 (s, 3H), 0.35 (s, 3H), 0.97 (s, 9H), 2.10 (s, 3H), 2.15 (s, 3H), 3.81 (dd, J = 5, 1.5, 1H), 4.09 (s, 3H), 4.96 (d, J = 1.5, 1H), 6.22 (d, J = 5, 1H), 7.61 (s, 1H)	–
2b	87	$C_{19}H_{29}NO_3SSi$ (379.6)	–	0.25 (s, 3H), 0.31 (s, 3H), 0.97 (s, 9H), 1.85 (s, 3H), 2.10 (s, 3H), 3.68 (dd, J = 5, 1.5, 1H), 4.65 (d, J = 1.5, 1H), 6.15 (d, J = 5, 1H), 7.35 (s, 5H)	–
2c	90	$C_{17}H_{27}NO_4SSi$ (369.6)	1750	0.30 (s, 3H), 0.33 (s, 3H), 1.00 (s, 9H), 2.06 (s, 6H), 3.75 (dd, J = 5, 2.5, 1H), 4.85 (d, J = 2.5, 1H), 6.25 (d, J = 5, 1H), 6.38 (m, 1H), 6.46 (d, J = 3, 1H), 7.40 (m, 1H)	392 (M^+ + Na, 60), 153 (100)[d]
2d	83	$C_{14}H_{28}NO_3SSi$ (317.5)	–	0.29 (s, 3H), 0.32 (s, 3H), 1.00 (s, 9H), 2.03 (s, 3H), 1.38 (d, J = 6, 3H), 2.02 (s, 3H), 2.12 (s, 3H), 3.35 (dd, J = 6, 2, 1H), 4.61 (d, J = 2, 1H), 5.22 (quintet, 1H, J = 6)	318 ($M^+ + NH_3$, 100)[e]
2e	29	$C_{13}H_{25}NO_3SSi$ (303.5)	–	0.30 (s, 3H), 0.35 (s, 3H), 1.00 (s, 9H), 2.08 (s, 3H), 2.11 (s, 3H), 3.50 (td, J = 5, 2, 1H), 4.38 (d, J = 5, 2H), 4.58 (d, J = 2, 1H)	–
3a	77	$C_{10}H_{14}N_4O_3S$ (270.3)	1750	2.10 (s, 3H), 2.20 (s, 3H), 3.85 (dd, J = 5, 1.5, 1H), 5.01 (d, J = 1.5, 1H), 6.10 (br, 1H, NH), 6.30 (d, J = 5, 1H), 7.65 (s, 1H)	271 (M^+ + H, 100)[e]
3b	93	$C_{13}H_{15}NO_3S$ (265.3)	1759	2.00 (s, 3H), 2.20 (s, 3H), 3.62 (dd, J = 5, 1.5, 1H), 4.78 (d, J = 1.5, 1H), 6.05 (br, 1H, NH), 6.20 (d, J = 5, 1H), 7.35 (s, 5H)	283 ($M^+ + NH_3$, 75), 163 (100)[e]
3c	98	$C_{11}H_{13}NO_4S$ (255.3)	1776	2.10 (s, 3H), 2.15 (s, 3H), 3.72 (dd, J = 5, 2, 1H), 4.95 (d, J = 2, 1H), 6.03 (br, 1H, NH), 6.29 (d, J = 5, 1H), 6.37 (m, 1H), 6.48 (d, J = 4, 1H), 7.42 (m, 1H)	278 (M^+ + Na, 45), 153 (100)[d]
3d	96	$C_8H_{13}NO_3S$ (203.3)	–	1.40 (d, J = 6, 3H), 2.08 (s, 3H), 2.15 (s, 3H), 3.29 (dd, J = 7.5, 2, 1H), 4.72 (d, J = 2, 1H), 5.30 (m, 1H), 6.25 (br, 1H, NH)	221 ($M^+ + NH_3$, 22), 204 (M^+ + H), 100)[e]
3e	96	$C_7H_{11}NO_3S$ (189.2)	1772	2.10 (s, 3H), 2.15 (s, 3H), 3.47 (td, J = 6, 2, 1H), 4.40 (d, J = 6, 2H), 4.68 (d, J = 2, 1H), 6.13 (br, 1H, NH)	207 ($M^+ + NH_3$, 15), 190 (M^+ + H, 100)[e]

[a] Isolated yield over two steps, compounds **2** and **3** are oils or foams.
[b] Satisfactory microanalyses obtained: C ±0.4, H ±0.3, N ±0.4.
[c] Two diastereoisomers (except **2e**, **3e**), data of main diastereoisomer.
[d] FAB spectrum.
[e] DCI spectrum.

dried ($MgSO_4$) and evaporated in vacuo. The residual oil was chromatographed on silica gel using toluene/EtOAc (1:1) as eluent to give the intermediate acetic acid derivative as a pale yellow foam. Yield: 7.09 g (83%).

This intermediate (6.98 g, 18.9 mmol) and pivaloyl chloride (4.7 mL, 37.8 mmol) in THF (100 mL) were cooled to −78 °C. A 1 M solution of lithium bis(trimethylsilyl)amide in hexane (37.8 mL, 37.8 mmol) was added dropwise over 15 min. After stirring for further 30 min at the same temperature the reaction was quenched by addition of sat. aq NH_4Cl (20 mL). The resulting mixture was diluted with EtOAc (500 mL) and water (500 mL), the organic phase was separated, dried ($MgSO_4$) and evaporated in vacuo. The residual oil was chromatographed on silica gel using toluene/EtOAc (1:1) as eluent. Compound **4a** was obtained as a mixture of 4 diastereoisomers (Table 3).

Allyl 2-[(*cis*/*trans*)-4-Chloro-3-(1-methyl-1,2,3-triazol-4-yl)acetoxymethyl-2-oxoazetidin-1-yl]-4,4-dimethyl-3-oxopentanoate (5a); Typical Procedure:

A solution of **4a** (5.45 g, 12 mmol) in CH_2Cl_2 (80 mL, important: p.a. quality, not anhydrous) was treated at 0 °C with *N*-chlorosuccinimide (3.2 g, 24 mmol) and silica gel (6 g, 230–400 mesh ASTM, E. Merck). The mixture was stirred at r.t. for 30 min and evaporated in vacuo. The residue was dissolved in CCl_4 (50 mL), filtered and the filtrate evaporated. This procedure was repeated once to give **5a** as a crude oil (mixture of several diastereoisomers). *Note:* At least one diastereoisomer of **5a** was not distinguishable from **4a** by TLC (Table 3).

Allyl 2-[(*cis*/*trans*)-4-Chloro-3-(2-furyl)acetoxymethyl-2-oxoazetidin-1-yl]-4,4-dimethyl-3-oxopentanoate (5c):

4c (11.81 g, 27 mmol) in CH_2Cl_2 (250 mL) was treated at −20 °C with Et_3N (3.7 mL, 27 mmol) and SO_2Cl_2 (2.2 mL, 27 mmol). The mixture was stirred at the same temperature for 5 h and then washed with aq $NaHSO_3$/Na_2CO_3 (8 g/6.4 g in 160 mL water), brine, dried ($MgSO_4$) and evaporated in vacuo to give **5c** as a crude oil containing a considerable amount of impurities.

Allyl (*cis*/*trans*)-2-*tert*-Butyl-6-(1-methyl-1,2,3-triazol-4-yl)acetoxymethyl-1-oxa-2-penem-3-carboxylate (6a); Typical Procedure:

A solution of **5a** (4.3 g, 9.7 mmol) in THF (50 mL) was treated at −78 °C with a 0.9 N solution of KOBu-*t* in *t*-C_4H_9OH (10.8 mL, 9.7 mmol). The dark brown solution was stirred at −20 °C for 40 min, then sat. aq NH_4Cl (10 mL) was added and the mixture was diluted with EtOAc (250 mL). The organic phase was washed with brine (3 × 100 mL) dried ($MgSO_4$) and concentrated in vacuo to give **6a** as a crude yellow foam which already contained 10–20% of the elimination products **7a** and **8a** (Table 3).

Allyl (*E*)-2-*tert*-Butyl-6-(1-methyl-1,2,3-triazol-4-yl)methylene-1-oxa-2-penem-3-carboxylate (7a and 8a); Typical Procedure:

A solution of the crude oxapenem **6a** (3.64 g, 9 mmol) in CH_2Cl_2 (100 mL) was treated at −78 °C with DBU (1.34 mL, 9 mmol) and the mixture was stirred for 30 min at the same temperature. Then EtOAc (400 mL) was added and the solution was washed with sat. aq NH_4Cl and brine, dried ($MgSO_4$) and evaporated in vacuo. The residual oil was chromatographed on silica gel using toluene/EtOAc (2:1) as eluent. (*Z*)-Oxapenem **8a** was eluted first; yield: 455 mg (15%), then (*E*)-oxapenem **7a**; yield: 1.3 g (42%) (Table 4).

Compound **6e** decomposed under the reaction conditions to products other than β-lactams.

Sodium (*E*)-2-*tert*-Butyl-6-(1-methyl-1,2,3-triazol-4-yl)methylene-1-oxa-2-penem-3-carboxylate (9a); Typical Procedure:

A solution of **7a** (1.25 g, 3.6 mmol) in CH_2Cl_2 (50 mL) was treated with a 0.5 M solution of sodium 2-ethylhexanoate in EtOAc

Table 3. Compounds **4–6** Prepared

Product	Yield[a] (%)	Molecular Formula	IR ($CHCl_3$) $\nu_{C=O}$ (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)	MS[b] m/z (%)
4a	54	$C_{20}H_{28}N_4O_6S$ (452.5)	1768, 1752	mixture of 4 diastereoisomers, characteristic signals: 1.1–1.3 (s, 9H, t-C_4H_9), 4.6–4.7 (br d, 2H, OCH_2), 5.4–5.6 (s, 1H, $NCHCO_2$)	453 (M^++H, 100)
4b	89	$C_{23}H_{29}NO_6S$ (447.6)	1769, 1750	as above	465 (M^++H, 35), 163 (100)
4c	84	$C_{21}H_{27}NO_7S$ (437.5)	1770, 1752	as above	444 (M^++Li, 65), 153 (100)[c]
4d	65	$C_{18}H_{27}NO_6S$ (385.5)	–	as above	–
4e	55	$C_{17}H_{25}NO_6S$ (371.5)	1772, 1750	mixture of 2 diastereoisomers, characteristic signals: 1.20, 1.25 (2s, 9H, t-C_4H_9), 4.65 (br d, J = 5, 2H), 5.52, 5.58 (2s, 1H, $NCHCO_2$)	389 (M^++NH_3, 45), 372 (M^++H, 70), 87 (100)
5a	71	$C_{19}H_{25}ClN_4O_6$ (440.9)	1786, 1752	mixture of 8 diastereoisomers, characteristic signals: 5.8–6.3 (d, J = 1.0–1.5, *trans*-CHCl), 5.9–6.5 (d, J = 4, *cis*-CHCl)	441 (M^++H, 100)
5b	82	$C_{22}H_{26}ClNO_6$ (435.9)	1785, 1751	as above	–[d]
5c	99[e]	$C_{20}H_{24}ClNO_7$ (425.9)	–	as above	–
5d	~100	$C_{17}H_{24}ClNO_6$ (373.8)	1786, 1750	as above	–[d]
5e	~100	$C_{16}H_{22}ClNO_6$ (359.8)	1787, 1752	mixture of 4 diastereoisomers, characteristic signals: 5.90, 5.99 (2d, J = 1.5, *trans*-CHCl), 6.11, 6.15 (2d, J = 4, *cis*-CHCl)	377 (M^++NH_3, 25), 360 (M^++H, 15), 322 (M^+–Cl, 100)
6a	96	$C_{19}H_{24}N_4O_6$ (404.4)	1800, 1752	mixture of 4 diastereoisomers, characteristic signals: 5.50–5.80 (s, *trans* H-5), 5.35–5.85 (d, J = 3–4.5, *cis* H-5)	345 (M^+–$MeCO_2$, 8), 136 (100)
6b	84	$C_{22}H_{25}NO_6$ (399.4)	1803, 1743	as above	417 (M^++NH_3, 35), 399 (M^+, 60), 340 (M^+–$MeCO_2$, 100)
6c	95[e]	$C_{20}H_{23}NO_7$ (389.4)	–	as above	–
6d	~100	$C_{17}H_{23}NO_6$ (337.4)	1804, 1740	as above	338 (M^++H, 10), 278 (M^+–$MeCO_2$, 40), 210 (100)
6e	15[f]	$C_{16}H_{21}NO_6$ (323.3)	1804, 1744	*trans*-**6e**: 1.32 (s, 9H), 2.12 (s, 3H), 3.90 (m, 1H), 4.43 (m, 2H), 4.70 (m, 2H), 5.25 (d, J = 12, 1H), 5.43 (d, J = 19, 1H), 5.76 (s, 1H), 5.96 (m, 1H) *cis*-**6e**: 1.35 (s, 9H), 2.10 (s, 3H), 4.22 (m, 1H), 4.43 (m, 2H), 4.70 (m, 2H), 5.25 (d, J = 12, 1H), 5.43 (d, J = 19, 1H), 5.84 (d, J = 3, 1H), 5.96 (m, 1H)	–

[a] **4**: Isolated yield over two steps; **5** and **6**: yield of crude product; all compounds are oils or foams.
[b] DSI spectra.
[c] FAB spectra.
[d] No M^+ peak could be obtained.
[e] Crude product, see experimental for **7c**/**8c**.
[f] After chromatography on silica gel at –20°C with toluene/EtOAc (5 : 1) as eluent.

(7.2 mL, 3.6 mmol), PH_3P (94 mg, 0.36 mmol), and $[ph_3P]_4Pd$ (98 mg, 0.09 mmol). After 15 min at r.t., only a little precipitate appeared. The mixture was evaporated in vacuo, the residue was triturated with Et_2O and the solid material was filtered, washed once with Et_2O and dried. The sodium salt **9a** thus obtained was about 90% pure (HPLC, ^1H NMR) (Table 5).

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Table 4. 6-(Methylene)oxapenems **7** and **8** Prepared

Product	Yield[a] (%)	Molecular Formula[b]	IR ($CHCl_3$) $\nu_{C=O}$ (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)	MS[b] m/z (%)
7a	42	$C_{17}H_{21}N_4O_4$ (345.4)	1774	1.33 (s, 9H), 4.18 (s, 3H), 4.74 (m, 2H), 5.52 (d, J = 11, 1H), 5.48 (d, J = 19, 1H), 6.00 (m, 1H), 6.52 (s, 1H, H-5), 7.15 (s, 1H, CH=), 7.55 (s, 1H)	345 (M^+, 100)
7b	42	$C_{20}H_{21}NO_4$ (339.4)	1778	1.37 (s, 9H), 4.75 (m, 2H), 5.25 (d, J = 11, 1H), 5.46 (d, J = 19, 1H), 6.00 (m, 1H), 6.41 (s, 1H, H-5), 7.18 (s, 1H, CH=), 7.45 (m, 3H), 7.55 (m, 2H)	340 (M^+ + H, 55), 210 (100)
7c	4[c]	$C_{18}H_{19}NO_5$ (329.4)	1782	1.35 (s, 9H), 4.75 (m, 2H), 5.35 (d, J = 11, 1H), 5.47 (d, J = 19, 1H), 6.01 (m, 1H), 6.43 (s, 1H, H-5), 6.55 (dd, J = 3, 1.5, 1H, H-4, furyl), 6.78 (d, J = 3, 1H, H-3, furyl), 6.94 (s, 1H, CH=), 7.65 (d, J = 1.5, 1H, H-5, furyl)	330 (M^+, 100)
7d	21	$C_{15}H_{19}NO_4$ (277.3)	1794	1.33 (s, 9H), 1.97 (d, J = 7, 3H), 4.73 (m, 2H), 5.25 (d, J = 10, 1H), 5.45 (d, J = 18, 1H), 6.21 (s, 1H, H-5), 6.50 (q, J = 7, 1H, CH=)	277 (M^+, 7), 57 (100)[e]
8a	15	$C_{17}H_{21}N_4O_4$ (345.4)	1764	1.32 (s, 9H), 4.13 (s, 3H), 4.75 (m, 2H), 5.26 (d, J = 11, 1H), 5.45 (d, J = 19, 1H), 6.00 (m, 1H), 6.29 (s, 1H, H-5), 7.06 (s, 1H, CH=), 8.72 (s, 1H)	–
8b	16	$C_{20}H_{21}NO_4$ (339.4)	1768	1.35 (s, 9H), 4.75 (m, 2H), 5.28 (d, J = 11, 1H), 5.50 (d, J = 19, 1H), 6.02 (m, 1H), 6.25 (s, 1H, H-5), 6.83 (s, 1H, CH=), 7.45 (m, 3H), 7.98 (m, 2H)	357 ($M^+ + NH_3$), 340 (M^+, 100)
8c	2[c]	$C_{18}H_{19}NO_5$ (329.4)	1778	1.33 (s, 9H), 4.75 (m, 2H), 5.27 (d, J = 11, 1H), 5.48 (d, J = 19, 1H), 6.00 (m, 1H), 6.23 (s, 1H, H-5), 6.55 (dd, J = 3, 1.5, 1H, H-4, furyl), 6.70 (s, 1H, CH=), 7.50 (d, J = 3, 1H, H-3, furyl), 7.58 (d, J = 1.5, 1H, H-5, furyl)	–
8d	18	$C_{15}H_{19}NO_4$ (277.3)	1786	1.32 (s, 9H), 2.12 (d, J = 7, 3H), 4.72 (m, 2H), 5.25 (d, J = 10, 1H), 5.45 (d, J = 18, 1H), 5.99 (m, 1H), 6.10 (s, 1H, H-5), 6.20 (q, J = 7, 1H, CH=)	277 (M^+, 20), 57 (100)[d]

[a] Isolated yield of pure separated isomers **7** and **8**, compounds **7** and **8** are oils or foams.
[b] DCI spectra.
[c] Low yield because crude starting material was used.
[d] EI spectra.

Table 5. 6-(Methylene)oxapenems **9** and **10** Prepared

Product	Yield[a] (%)	mp (°C)	Molecular Formula[b]	IR ($CHCl_3$) $\nu_{C=O}$ (cm^{-1})	^1H NMR (D_2O/TPNA) δ, J (Hz)	MS[c] m/z (%)
9a	92[d]	140 (dec)	$C_{14}H_{15}N_4NaO_4$ (326.3)	1768	1.10 (s, 9H), 4.02 (s, 3H), 6.35 (s, 1H, H-5), 7.15 (s, 1H, CH=), 8.13 (s, 1H, Ar)	–[b]
9b	79[d]	175–180 (dec)	$C_{17}H_{16}NNaO_4$ (321.3)	1770	1.10 (s, 9H), 6.50 (s, 1H, H-5), 7.11 (s, 1H, CH=), 7.37 (m, 3H), 7.54 (m, 2H)	–[b]
9c	57[e]	–	$C_{15}H_{14}NNaO_5$ (311.3)	1768	1.22 (s, 9H), 6.50 (s, 1H, H-5), 6.68 (dd, J = 3.5, 1, 1H, H-4, furyl), 7.00 (d, J = 3.5, 1H, H-3, furyl), 7.15 (s, 1H, CH=), 7.78 (d, J = 1, 1H, H-5, furyl)	–[f]
9d	75[e]	–	$C_{12}H_{14}NNaO_4$ (259.2)	1792	1.10 (s, 9H), 1.80 (d, J = 8, 3H), 6.12 (s, 1H, H-5), 6.48 (q, J = 8, 1H, CH=)	282 (M^+ + Na, 65), 214 (100)
10a	81[d]	175–180 (dec)	$C_{14}H_{15}N_4NaO_4$ (326.3)	1760	1.09 (s, 9H), 4.01 (s, 3H), 6.13 (s, 1H, H-5), 6.92 (s, 1H, CH=), 8.58 (s, 1H)	–[b]
10b	83[d]	160–170 (dec)	$C_{17}H_{16}NNaO_4$ (321.3)	1758	1.10 (s, 9H), 6.11 (s, 1H, H-5), 6.91 (s, 1H, CH=), 7.38 (m, 3H), 7.80 (m, 2H)	–[b]
10c	31[e]	–	$C_{15}H_{14}NNaO_5$ (311.3)	1761	1.25 (s, 9H), 6.26 (s, 1H, H-5), 6.67 (d, J = 3, 1H, H-4, furyl), 6.88 (s, 1H, CH=), 7.20 (d, J = 3, 1H, H-3, furyl), 7.73 (s, 1H, H-5, furyl)	–[f]
10d	50[e]	–	$C_{12}H_{14}NNaO_4$ (259.2)	1774	1.05 (s, 9H), 1.89 (d, J = 7.5, 3H), 5.95 (s, 1H, H-5), 6.21 (q, J = 7.5, 1H, CH=)	282 (M^+ + Na, 90), 214 (100)

[a] Yield of isolated product.
[b] Satisfactory microanalyses (C ± 0.4, H ± 0.3, N ± 0.4) or HRMS values (± 0.002 amu) obtained.
[c] FAB spectra.
[d] Purity: > 90%.
[e] Purity: 80–85%.
[f] No M^+ peak could be obtained.

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