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# SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF (1'R,5R,6R)-2-TERT-BUTYL-6-(1'-HYDROXYETHYL)OXAPENEM-3-CARBOXYLIC ACID

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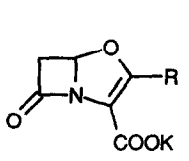
**Abstract:** The synthesis of (1'R,5R,6R) potassium 2-tert-butyl-6-(1'-hydroxyethyl)oxapenem-3-carboxylate **2** is described. **2** showed excellent in vitro activity against clinical isolates of Staphylococcus aureus.

In 1976, at the occasion of the first conference on "Recent Advances in the Chemistry of ß-Lactam Antibiotics" in Cambridge, England, R. B. Woodward announced the synthesis of the first non-classical ß-lactam, a penem, possessing the structural features of the penicillins (penams) and cephalosporins (cephems).[1] Later, numerous research groups have prepared hundreds of derivatives of penems and carbapenems.

Replacing the sulfur atom in the formula of the penems by oxygen, leads to the 1-oxadethiapenems, called "oxapenems". This class of ß-lactams was successfully developed already in 1977.[2] One year later, a powerful inhibitor of isolated ß-lactamases was found among the oxapenems. Unfortunately, this compound **1a** was very unstable and consequently not active as antibiotic or ß-lactamase inhibitor against intact bacteria.[3]

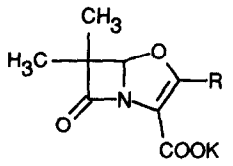
Unlike in the development of penems or carbapenems, the hope of finding a clinically useful oxapenem was soon abandoned because of the low stability in this class of compounds. This reduced interest in the novel class of oxapenems was reflected by the number of publications which decreased from nine in 1978 to none in 1984 and 1985.

With the idea to achieve more stable derivatives by introducing bulky substituents, we prepared several 2-substituted oxapenemcarboxylic acids of type **1**. We discovered that the half-life of hydrolysis of the 2-tert-butyl substituted compound **1b** was **increased 30-fold** in comparison with that of methyl substituted **1c**. When compared with that of 6-unsubstituted oxapenem **1d**, an additional, approximately two-fold increase in stability, was achieved with a 6-methyl substituent (compound **1e**).[4]



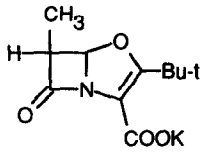

**1a** R = ethyl

**1d** R = Bu-t

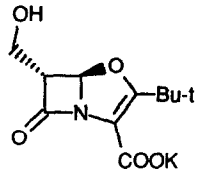



**1b** R = Bu-t

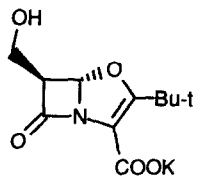
**1c** R = methyl




**1e**

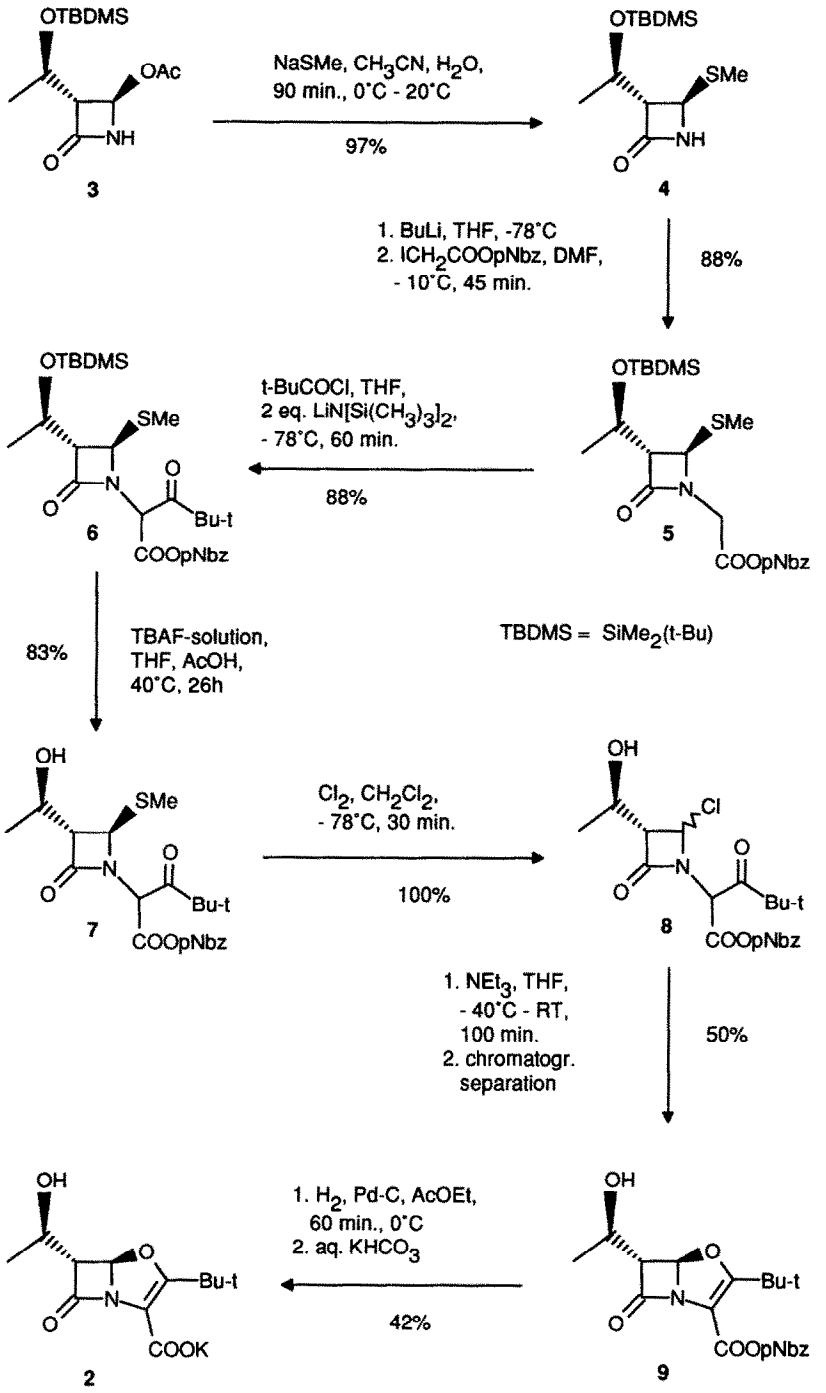



**1f**




**1g**

Interestingly, it was found that 6-alkylidene substitution lowered the stability of oxapenemcarboxylic acids.[5]


OTBDMS
OAc
NH
3
NaSMe, CH3CN, H2O,
90 min., 0°C - 20°C
97%
OTBDMS
SMe
NH
4
1. BuLi, THF, -78°C
2. ICH2COOpNbz, DMF,
- 10°C, 45 min.
88%
OTBDMS
SMe
5
COOpNbz
t-BuCOCl, THF,
2 eq. LiN[Si(CH3)3]2,
- 78°C, 60 min.
88%
OTBDMS
SMe
Bu-t
6
COOpNbz
TBDMS = SiMe2(t-Bu)
83%
TBAF-solution,
THF, AcOH,
40°C, 26h
OH
SMe
Bu-t
7
COOpNbz
Cl2, CH2Cl2,
- 78°C, 30 min.
100%
OH
Cl
Bu-t
8
COOpNbz
1. NEt3, THF,
- 40°C - RT,
100 min.
2. chromatogr.
separation
50%
OH
Bu-t
COOK
2
1. H2, Pd-C, AcOEt,
60 min., 0°C
2. aq. KHCO3
42%
OH
Bu-t
9
COOpNbz

We have recently reported the preparations and biological activities of enantiomeric 2-tert-butyl-6-hydroxymethyloxapenemcarboxylic acids **1f** and **1g**.[6] The "natural enantiomer **1f**" was a potent ß-lactamase inhibitor in vitro, superior to clavulanic acid. Those compounds were prepared from **racemic** 4-benzoyloxyazetidin-2-one. In the preparation of the (1'R,5R,6R)-6-hydroxyethyl derivative **2**, having the side chain of the natural antibiotic thienamycin, a different approach was chosen. This strategy, starting from commercially available, **optically active** "Azetidon-Kaneka" **3**, has been successfully applied in the synthesis of 6-hydroxyethyl-2-isopropyloxapenemcarboxylic acid by Japanese chemists.[7]

Due to its increased stability, as compared to earlier oxapenems, **2** showed excellent in vitro activity against penicillin- and methicillin-resistant bacteria when compared to common antibiotics (**Fig. 1** and **Table 1**). Its activity against anaerobic and various aerobic gram-positive and gram-negative bacteria is shown in **Table 2** and **3**).

**Fig. 1.** Antibacterial activity of **2** and other antibiotics against methicillin resistant Staph. aureus 25768. Difco nutrient agar.

| Strain: Staph. aureus | Oxa-cillin | Methi-cillin | Mezlo-cillin | Ampi-cillin | Cipro-floxacin | Cefoxi-tin | 2 |
|---|---|---|---|---|---|---|---|
| 13N München | >100 | 50 | 50 | 50 | 1.56 | >100 | 1.56 |
| 48N München | ≤0.78 | 6.25 | 12.5 | 50 | 12.5 | 6.25 | ≤0.78 |
| 90 Innsbruck | >100 | 50 | >100 | 50 | 12.5 | 100 | ≤0.78 |
| 77 Innsbruck | 100 | 50 | 100 | 50 | >100 | 25 | ≤0.78 |
| 4978 Israel | ≤0.78 | ≤0.78 | 3.12 | 1.56 | ≤0.78 | 1.56 | ≤0.78 |
| 17N München | 1.56 | 3.12 | 12.5 | 25 | 12.5 | 12.5 | 1.56 |
| 79B Innsbruck | 50 | 25 | 50 | 50 | 100 | 25 | ≤0.78 |
| 86 Innsbruck | 100 | 25 | 50 | 50 | 100 | 12.5 | ≤0.78 |
| 41h Belgium | >100 | >100 | 3.12 | 50 | 100 | 1.56 | 12.5 |
| 21b Belgium | >100 | >100 | 50 | >100 | 50 | ≤0.78 | 12.5 |
| 1756 | 50 | 50 | 50 | 50 | ≤0.78 | 50 | 1.56 |
| 25464 | >100 | >100 | 100 | 50 | ≤0.78 | 50 | 3.12 |
| 25697 | 1.56 | 6.25 | 25 | 25 | 12.5 | 12.5 | 1.56 |
| 25768 | 6.25 | 6.25 | 25 | 50 | 100 | 12.5 | ≤0.78 |
| 25463 | 1.56 | 1.56 | 12.5 | 50 | 1.56 | 1.56 | 1.56 |
| 25470 | 100 | >100 | 25 | 50 | ≤0.78 | >100 | 50 |
| 25085 | 3.12 | 6.25 | 50 | 50 | ≤0.78 | 12.5 | 1.56 |

**Table 1.** Antibacterial activity (MIC, µg/ml) of various antibiotics and oxapenem **2** against clinical isolates of Staph. aureus. Bouillon dilution method, Isosensitest broth, inoculum: overnight culture, dilution 1 : 10000.

| | Cefo-taxim | Nor-floxacin | 2 |
|---|---|---|---|
| B. fragilis ES 25 | 4 | >16 | 2 |
| B. fragilis 06688 | 2 | >16 | 2 |
| B. fragilis DSM 2151 | 4 | >16 | 1 |
| B. fragilis L 1168 Italien | 4 | >16 | 2 |
| B. fragilis Kr 1 TV | 1 | >16 | 2 |
| B. fragilis 1560 I/82 | 2 | >16 | 2 |
| B. fragilis 010848 | 16 | >16 | 2 |
| B. fragilis Kr II | 2 | >16 | 2 |
| B. fragilis GA I - 0558 Japan | 8 | >16 | 2 |
| B. fragilis 2034/35 Kr43 | >128 | >16 | 2 |
| B. fragilis 4891/91 Kr | 4 | >16 | 2 |
| B. fragilis 4661 Kr | 4 | >16 | 2 |
| B. thetaiotaomicron DSM 2079 | 128 | >16 | 1 |
| B. thetaiotaomicron 235 München | 128 | >16 | 4 |
| B. melaninogenicus Kr | 2 | 16 | 0.5 |
| B. melaninogenicus Heidelberg | 2 | >16 | 4 |
| B. ovatus Heidelberg 32 | | >16 | 2 |
| B. distasonis Heidelberg | 2 | >16 | 8 |
| B. distasonis Kr | 2 | >16 | 1 |
| B. vulgatus Kr III | 2 | >16 | 1 |
| Fusobacterium nucleatum DSM 20482 | 0.5 | 16 | 0.5 |
| Sphaerophorus necrophorus Kr | 1 | 2 | 1 |
| Clostr. perfringens 1024027 | ≤0.25 | 2 | 1 |
| Clostr. perfringens DSM 756 | ≤0.25 | >16 | 1 |
| Clostr. perfringens 24071 | 2 | 4 | 0.5 |
| Clostr. perfringens 24072 | 0.5 | 4 | 0.5 |
| Clostr. ramosum DSM 1402 | 2 | >16 | 1 |
| Clostr. septicum | 128 | 16 | 2 |
| Clostr. butyricum | 1 | 16 | 2 |
| Clostr. sporogenes | 0.5 | 16 | 0.5 |
| Peptostrept. anaer. DSM 20357 | 16 | >16 | 1 |
| Peptostrept. anaer. Kr I | 32 | >16 | 2 |
| Peptostrept. anaer. Kr II | ≤0.25 | 2 | 0.25 |
| Peptostrept. anaer. 222 I/82 | 0.5 | >16 | 2 |
| Peptococcus prevotii DSM 20548 | 8 | >16 | 2 |
| Peptococcus asacchar. DSM 20463 | ≤0.25 | 4 | 0.5 |

**Table 2.** Antibacterial activity (MIC, µg/ml) of selected antibiotics and oxapenem 2 against anaerobes. Agar dilution method using a multipoint inoculator, Wilkins-Chalgren agar, inoculum: overnight culture, dilution 1 : 100.

| | | |
|---|---|---|
| Escherichia coli | T7 | 2 |
| Escherichia coli | A 261 | 2 |
| Escherichia coli | Neumann | 2 |
| Escherichia coli | 183/58 | 1 |
| Escherichia coli | F14 | 16 |
| Escherichia coli | C 165 | 8 |
| Escherichia coli | 4322 | 2 |
| Klebsiella | 57 USA | 4 |
| Klebsiella | 63 | 4 |
| Klebsiella | 1852 | 16 |
| Klebsiella | 6097 | 16 |
| Serratia | 16001 | 64 |
| Serratia | 16002 | 64 |
| Providentia | 12012 | 4 |
| Proteus morganii | 932 | 2 |
| Proteus vulgaris | 9023 | 1 |
| Proteus vulgaris | 1017 | 1 |
| Proteus vulgaris | N6 | 1 |
| Proteus rettgeri | 1007 | 2 |
| Proteus mirabilis | 1235 | 4 |
| Staph. aureus | 1756 | 2 |
| Staph. aureus | 133 | 0.12 |
| Staph. aureus | 25455 | 0.12 |
| Staph. E | 25185 | ≤0.06 |
| Strept. pneumoniae | 4959 | 0.25 |
| Strept. faecalis | 27101 | 2 |
| Strept. faecalis | 113 | 16 |
| Enterococcus | 9790 | 2 |
| Enterococcus | 27158 | 16 |
| Pseudomonas aerug. | F41 | >128 |
| Pseudomonas aerug. | Walter | >128 |
| Pseudomonas aerug. | 7053 | >128 |
| Pseudomonas aerug. | 7451 | >128 |
| Enterobacter cloacae | 56 US | 16 |
| Enterobacter cloacae | 5744 | 32 |
| Micrococcus luteus | | ≤0.06 |

**Table 3.** Antibacterial activity (MIC, µg/ml) of oxapenem **2** against aerobic bacteria. Agar dilution method using a multipoint inoculator, Isosensitest agar, inoculum: overnight culture, dilution 1 : 500.

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8. All reported compounds **4** - **7** and **9** gave correct elemental analyses. Physical data of **2**: White non-crystalline powder. TLC ($C_{18}$, reversed phase silica gel): $R_f$ 0.2 ($CH_3CN/H_2O$ 1 : 3). $[\alpha]_D^{20}$ 184 °, c = 0.4). UV-spectrum in $H_2O$: $\lambda_{max}$ 260 nm (ε = 4500). $^1H$-NMR-spectrum in $D_2O$/ $Me_3SiCD_2CO_2Na$: δ (ppm) = 1.25 (s, 9H, t-Bu), 1.33 (d, 3H, J = 6.5 Hz, $H_3C$-CH-OH), 3.80 (dd, 1H, J = 0.7 Hz, J = 5.2 Hz, C-CH-CO-N), 4.25 (dq, 1H, J = 5.2 Hz, J = 6.5 Hz, $H_3C$-CH-OH), 5.81 (d, 1H, J = 0.7 Hz, N-CH-O).