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5- AND 7-OXA TRINEMS: THEIR SYNTHESIS AND BIOLOGICAL EVALUATION

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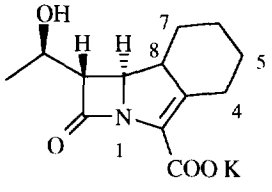
Abstract. Introduction of the methoxy group at the allylic C-4 position of trinem **1** has mainly resulted in a remarkable enhancement of antimicrobial activity. A successful attempt in terms of antibacterial activity was made by introduction of an oxygen atom alternatively at the allylic position 5 and 7 of **1** In particular compounds **3** and **4** resulted of relevant interest. Copyright © 1996 Elsevier Science Ltd

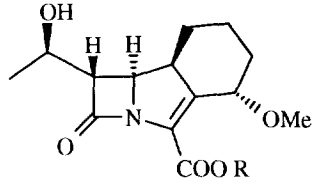
Compound **1** (Fig. 1) was the first member of a new class of tricyclic β-lactam antibiotics, known as trinems[1] (formerly referred to as tribactams) showing an interesting antimicrobial activity. Introduction of a methoxy group at the C-4 position of **1** led to the synthesis of Sanfetrinem, which has been shown to be a potent and broad spectrum antibacterial agent active against aerobic and anaerobic Gram-positive and Gram-negative bacteria[2] and stable to β-lactamases and renal dehydropeptidases.[3] Sanfetrinem and the corresponding metabolically labile ester, GV 118819 are currently in phase II clinical trials.

Fig.1

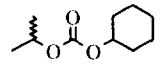


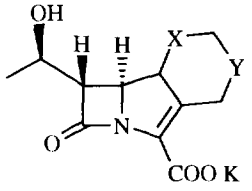
1 (C-8 = **S**)

2 (C-8 = **R**)



Sanfetrinem, R = H

GV 118819, R = 



3 (X = O, Y = CH_2, C-8 = **S**)
4 (X = CH_2, Y = O, C-8 = **S**)
5 (X = O, Y = CH_2, C-8 = **R**)
6 (X = CH_2, Y = O, C-8 = **R**)

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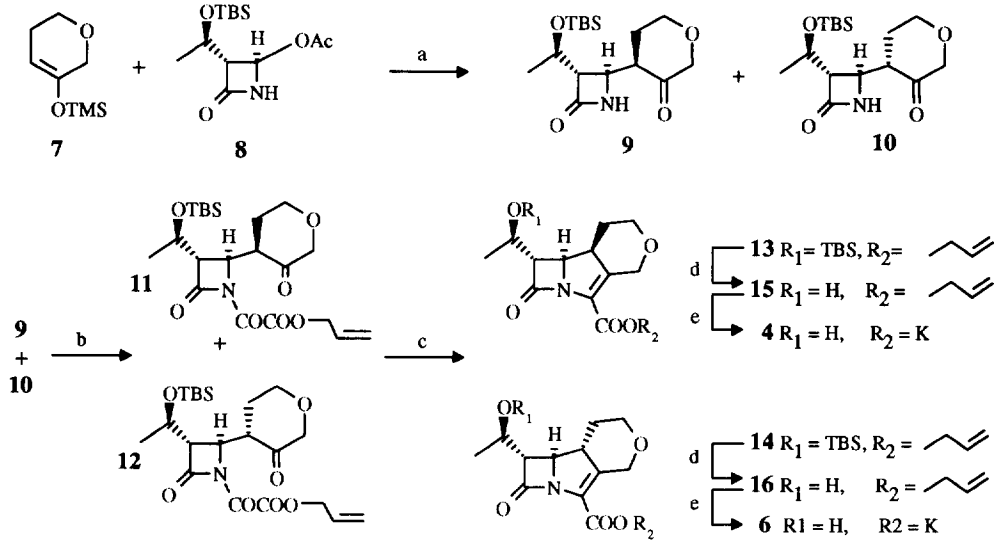
We have tentatively attributed the microbiological profile of Sanfetrinem to the pseudoperiplanar orientation of the methoxy group with respect to the double bond which should enhance both the chemical reactivity of the β-lactam and the antibacterial activity.[4] Among the possible isomers of Sanfetrinem bearing the methoxy group on one of the chemically accessible allylic positions,[5] Sanfetrinem exhibited a superior antimicrobial potency and breadth of spectrum. In order to further investigate this class of compounds, our interest was stimulated by the possibility of including the alkoxy group *inside* the six membered ring, hence synthesis of the 5 and 7-oxa trinems **3**, **4**, **5** and **6** (Fig. 1) they are characterised by the presence of an allylether motif differently oriented in space, was undertaken.

In this paper we report the synthesis and biological activity of 5 and 7-oxa derivatives **3**, **4**, **5** and **6** in comparison with Sanfetrinem and unsubstituted trinems **1** and **2**. The synthesis of **4** and **6** are reported in scheme 1.

Scheme 1



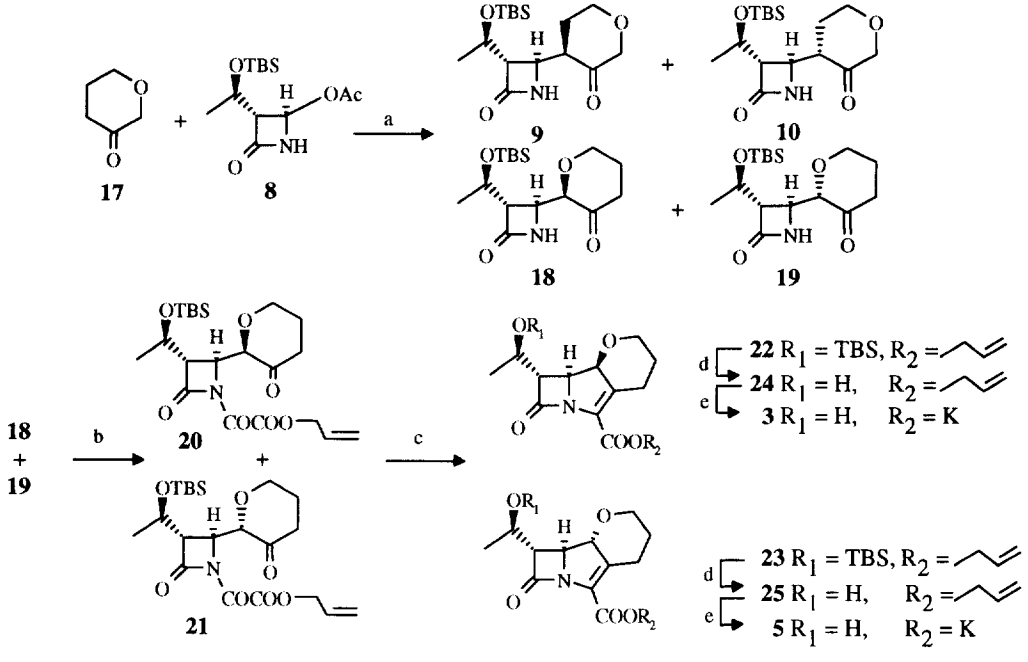
a) TMSOTf, CH_2Cl_2, 0°C, b) $COClCOOCH_2CH{=}CH_2$, TEA, CH_2Cl_2, c) $P(OEt)_3$, xylene, 120-130°C, d) TBAF, AcOH, THF, e) $Pd(Ph_3P)_4$, potassium 2-ethylhexanoate, THF

Treatment of pyran-3-one **17** with trimethylsilyl chloride and triethylamine in anhydrous dimethylformamide at 60° C, gave the silylenolether **7** which was isolated in 60 % yield after distillation in agreement with the literature.[6]

Azetidinones **9** and **10** were obtained by adding a dichloromethane solution of the commercially available (+)-(3*R*,4*R*,1'*R*)-4-Acetoxy-3-[1'-(*tert*-butyldimethylsilyl)oxy]-ethyl]-2-azetidinone (**8**)[7] and the silylenolether **7** to a solution of trimethylsilyltriflate in anhydrous dichloromethane at 0° C to give, after work-up and purification by flash chromatography, the desired isomers as a non separable 3 : 7 mixture in 62 % overall yield.

The mixture of these compounds was converted to the corresponding fully protected trinems, **13** and **14** (again as an inseparable mixture), according to a well established protocol.[8] After removal of the silylether protecting group using TBAF/AcOH in tetrahydrofuran, the desired trinems **15** and **16** were separated by flash chromatography, in 10 and 12 % overall yields respectively, from the mixture of azetidinones **9** and **10**. Finally, the target compounds **4** and **6** were obtained in 45 and 60 % yields respectively by removing the allyl ester group using $Pd(Ph_3P)_4$ and potassium 2-ethylhexanoate.

Scheme 2

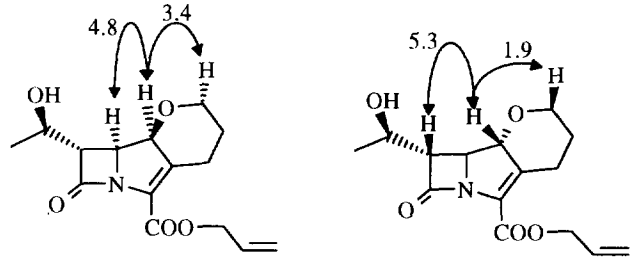


a) LTMP, THF, b) $COClCOOCH_2CH{=}CH_2$, TEA, CH_2Cl_2, c) $P(OEt)_3$, xylene, 120-130°C, d) TBAF, AcOH, THF, e) $Pd(Ph_3P)_4$, potassium 2-ethylhexanoate, THF

The most direct route to the 7-oxa isomers **3** and **5** was by addition of the lithium enolate of the ketone **17** (LTMP in tetrahydrofuran at -78°C) to the azetidinone **8** as shown in scheme 2. As expected, this reaction, after flash chromatography, gave a complex mixture of four azetidinones **9**, **10**, **18** and **19** in 65 % overall yield. Only after a second flash chromatography was it possible to isolate enriched fractions of the desired key azetidinones **18** and **19**, which were then converted into the final compounds **3** and **5** by using the same procedure as above.

In order to determine the key stereochemical features for compounds **15-16** and **24-25**, NMR experiments were performed; in particular the skeletons of the four isomers were defined by 1D and 2D-NMR. It has to be noted that the H-8 signals in the two pairs of compounds are quite different: in compounds **15-16** they appear as a multiplet (at 3.15 and 3.20 ppm) while in compounds **24-25** they appear as a doublet (at 4.4 and 4.68 ppm).
In addition, Figure 2 shows the n.O.e. results for compounds **24** and **25** confirming the stereochemistries, 8-*S* in the first case and 8-*R* in the second, and giving information on the preferred conformation in solution. Similar findings were also found for compounds **15** and **16**. For compounds **3**, **4**, **5** and **6** ^{1}H-NMR assignments together with their corresponding FT-IR data are reported below.[9]

Fig. 2



24 **25**

The antimicrobial activities of compounds **3**, **4**, **5** and **6** in comparison with Sanfetrinem and the carbocyclic unsubstituted tricyclic β-lactam **1** are reported in Tab.1

Table 1. *In vitro* antibacterial activity of trinems **3**, **4**, **5**, and **6** compared to Sanfetrinem, trinems **1** and **2** (MIC, μg/ml)

	S.aureus 853	*S.pneumoniae* 3512	*E.faecalis* 850	*E.coli* 1850	*E.coli* 1852	*C.perfringens* 615	*B.fragilis* 2017
Sanfetrinem	**0.2**	**<=0.01**	**1**	**0.5**	**0.5**	**0.03**	**0.06**
1	**1**	**0.06**	**8**	**1**	**1**	**0.1**	**1**
2	**1**	**0.5**	**16**	**2**	**2**	**1**	**0.5**
3	**0.5**	**0.06**	**1**	**1**	**1**	**0.06**	**0.1**
4	**0.5**	**0.06**	**8**	**0.5**	**0.5**	**0.5**	**0.2**
5	**1**	**0.2**	**16**	**2**	**4**	**1**	**0.2**
6	**2**	**0.1**	**32**	**2**	**4**	**2**	**0.1**

***S. aureus* 853** = *Staphylococcus aureus* 853E, Penicillinase (PC1) producing strain; ***S. pneumoniae* 3512** = *Streptococcus pneumoniae 3512*; ***E. faecalis* 850** = *Enterobacter faecalis* 850; ***E. coli* 1850** = *Escherichia coli* 1850E; ***E. coli* 1852** = *Escherichia coli* 1919, with permeable outer membrane; ***C. perfringens* 615** = *Clostridium perfrigens*615E; ***B. fragilis* 2017** = *Bacteroides fragilis* 2017

Compounds **3** and **4**, which are characterised by an *S* stereogenic centre at the C-8 position (Fig.1), were the most active compounds among the 5 and 7-oxa trinems herein reported. In particular, the antimicrobial activity

enhancement observed for compounds **3** and **4** with respect to the carbocyclic trinem **1** would support the idea that the oxygen can really exert a positive influence on the biological profile, even if their overall antibacterial potencies are still lower than Sanfetrinem. On the contrary, for compounds **5** and **6** the presence of the oxygen, at the position C-5 or C-7 respectively, did not result in a significant enhancement of the biological profile compared to that of the corresponding carbocyclic compound **2**. All of the oxa-trinems mentioned herein were tested against *Pseudomonas* spp. and were found to be inactive at 32 μg/ml. Furthermore, their stability to mammalian DHP-I was found to be comparable at Imipenem.

In conclusion, the data presented here appear to support the importance played by an oxygen at the allylic position inside the six membered ring of trinems particularly if that is combined with a suitable stereochemistry at the C-8 position of trinem. Further studies of this class of compounds are ongoing, with particular attention to the effect of a substituent on the 6-membered ring.

Acknowledgements

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7) (+)-(3*R*,4*R*,1'*R*)-4-Acetoxy-3-[1'-(*tert*-butyldimethylsilyl)oxy]-ethyl]-2-azetidinone (**10**) is commercially available from Aldrich Chemical Company Inc, Milwaukee, WI.

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9) ^{1}H-NMR assignment and FT- IR stretching of the final compounds.

3: ^{1}H-NMR (300 MHz, D_2O) δ 4.42 (d, J=9.0 Hz, 1H), 4.12 (m, 1H), 4.00 (dd, J= 3.3, 8.4 Hz, 1H), 3.92 (m, 1H), 3.62 (m, 1H), 3.37 (m, 1H), 3.05 (m,1H), 2.25 (m, 1H), 1.73-1.3 (m, 1H), 1.10 (d, J= 6.3 Hz, 3H); IR (nujol mull) ν_{max} 1765, 1591

4: ^{1}H-NMR (300 MHz, D_2O) δ 5.01 (m,1H), 4.3-3.3 (m, 6H), 3.30 (dd, J= 3.5, 5.8 Hz, 1H), 3.1 (m,1H), 1.80-1.3 (m, 2H), 1.12 (d, J= 6.0 Hz, 3H); IR (nujol mull) ν_{max} 1751, 1655, 1580

5: ^{1}H-NMR (300 MHz, D_2O) δ 4.75 (d, J=5.1 Hz, 1H), 4.08 (m, 1H), 3.88 (m, 1H), 3.72 (dd, J= 3.3, 5.4 Hz, 1H), 3.52 (m, 1H), 3.32 (dd, J=3.3, 5.4 Hz, 1H), 2.96 (m, 1H), 2.15 (m,1H), 1.73-1.4 (m, 2H), 1.11 (d, J= 6.6 Hz,3H); IR (nujol mull) ν_{max} 1774, 1600

6: ^{1}H-NMR (300 MHz, D_2O) δ 4.91 (d, J= 13.8 Hz,1H), 4.07 (m, 1H), 3.94 (m, 1H), 3.86 (m, 1H), 3.67 (dd, J= 2.7, 8.10 Hz, 1H), 3.39 (m, 1H), 3.27 (dd, J= 2.7, 5.7 Hz), 1H), 3.17 (m, 1H), 2.06 (m, 1H), 1.56 (m, 1H), 1.13 (d, J= 6.6 Hz, 3H); IR (nujol mull) ν_{max} 1761, 1599

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