



TRICYCLIC β -LACTAMS: TOTAL SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF 5α -METHOXYETHYL AND 5α -HYDROXYETHYL TRINEMS

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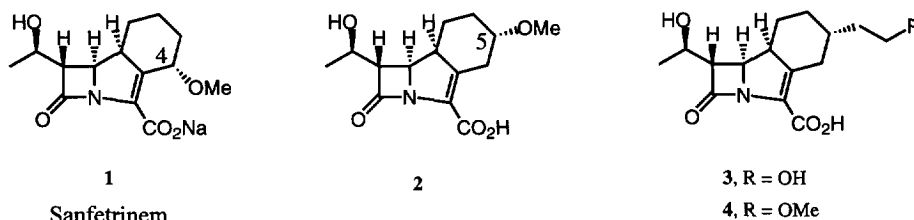
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Abstract: The total synthesis of the tricyclic β -lactams, 5α -hydroxyethyl and 5α -methoxyethyl trinems is described and preliminary biological evaluation is reported. © 1997 Elsevier Science Ltd.

The β -lactams constitute an important class of antibacterial agents,¹ yet the growing number of resistant bacterial strains dictates the need for further development of novel motifs within this area.² Recently, the scientists at GlaxoWellcome have reported on a novel class of synthetic tricyclic β -lactam antibiotics known as 'trinems' (previously known as tribactams).³ 4α -Methoxy trinem **1** (Sanfetrinem) has emerged as a clinically promising drug candidate (Figure 1).

Continuing our studies in the synthesis of novel β -lactam containing molecules,⁴ we have developed an efficient synthesis to 4α -methoxy trinem **1**⁵ as well as structural variants,⁶ including the 5α -methoxy trinem **2**⁷ which exhibited interesting antibacterial activity (Figure 1). We now wish to report in this Letter the synthesis and preliminary biological evaluation of two C-5 chain-extended trinems, the 5α -hydroxyethyl trinem **3** and 5α -methoxyethyl trinem **4** in an effort to probe the functional requirements at this relatively unexplored position.

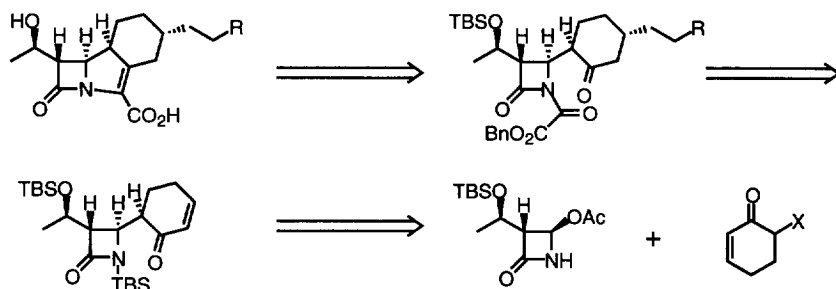
Figure 1



Analysis of our target structure led us to consider installing the C-5 side-chain via a stereoselective conjugate addition of a 2-hydroxyethyl anion equivalent to a suitably protected β -lactam enone **8** (Scheme 1), which in turn could be obtained from the coupling of a commercially available acetoxyazetidinone with a suitable cyclohexenone derivative.

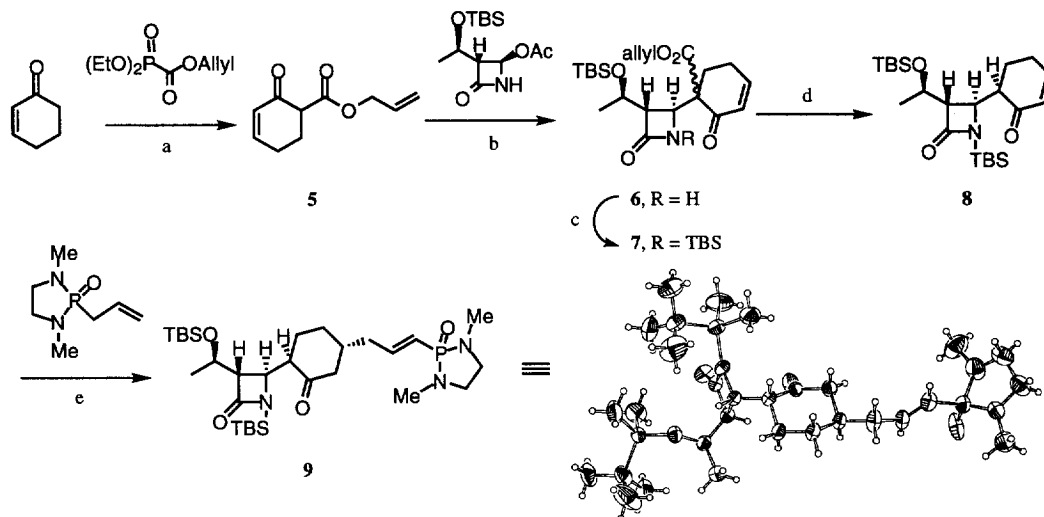
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Scheme 1



The desired enone could be accessible from a stereoselective decarboxylation of a suitable β -ketoester intermediate using methodology originally developed by Miura *et al.*⁸ and Choi *et al.*⁹ and further elaborated by work in this laboratory⁴ (Scheme 2). Thus, the lithium salt of cyclohexenone was condensed with allyl diethylphosphonoformate¹⁰ to afford β -ketoester **5**, which in turn was condensed with commercially available (3*S*,4*R*) 4-acetoxy-3-[(1*R*)-1-*tert*-butyldimethylsilyloxyethyl]-2-azetidinone to yield **6** as a mixture of diastereoisomers. Protection of the nitrogen using TBS triflate followed by treatment with formic acid and catalytic quantities of palladium acetate and triphenylphosphine, provided enone **8** in 67% overall yield from the acetoxyazetidinone.

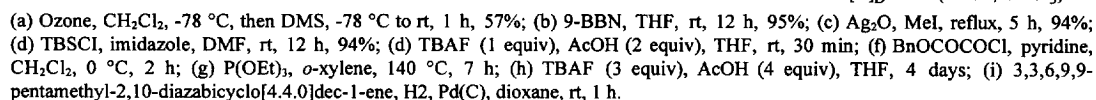
Scheme 2



(a) i. LDA, THF, -78 °C, 30 min; ii. add allyl diethylphosphonoformate, -78 °C to rt, 2 h, 61%; (b) i. NaH, THF, -20 °C, 30 min; ii. add (3*S*,4*R*) 4-acetoxy-3-[(1*R*)-1-*tert*-butyldimethylsilyloxyethyl]-2-azetidinone, -20 °C, 2 h; (c) TBSOTf, NEt₃, CH₂Cl₂, 0 °C, 30 min; (d) Pd(OAc)₂ (1 mol%), PPh₃ (5 mol%), formic acid (3 equiv), EtOAc, reflux, 2 h, 67% over three steps; (e) i. allyl anion formation with *n*-BuLi, THF, -78 °C, 30 min; ii. add **8**, -78 °C, 1 h, 75%.

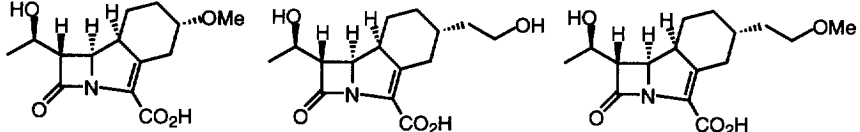
Elaboration of adduct **9** to 5 α -hydroxyethyl trinem **3** and 5 α -methoxyethyl trinem **4** is shown in Scheme 3. Oxidative cleavage of **9** by ozonolysis¹¹ afforded aldehyde **10**, which was selectively reduced to alcohol **11** by 9-BBN.¹² Methylation or protection as a TBS ether under standard chemical conditions then gave **12** and **13**, respectively.

Scheme 3



N-Deprotection using TBAF-AcOH,⁵⁻⁷ followed by acylation with benzyl oxalyl chloride gave oxalimides **16** and **17**, which were ring closed with triethylphosphite^{5,13} in refluxing xylene to yield tricyclic derivatives **18** and **19**. Desilylation with TBAF-AcOH followed by hydrogenolysis in the presence of a bulky amidine^{5,14} gave the desired products **3** and **4** as their amidinium salts.

Table 1



Organism	2	3	4	1, Sanfetrinem ^a	Imipenem
<i>S. aureus</i> 663 PEN-S	0.50	0.25	0.50		0.06
<i>S. aureus</i> 853E PEN-R	1.00	0.50	1.00	0.2	0.06
<i>S. aureus</i> 11311 MET-R	>32.00	>32.00	>32.00		>32.00
<i>E. faecalis</i> 850	8.00	4.00	8.00	1.00	4.00
<i>S. pneumoniae</i> 3512	0.12	0.25	0.12	0.01	<0.01
<i>E. coli</i> 851E	8.00	1.00	8.00		0.50
<i>E. coli</i> 1850E WT	8.00	2.00	8.00	0.50	0.50
<i>E. coli</i> 1852E PM	1.00	2.00	1.00		0.50
<i>E. coli</i> 1919E PM/TEM-1	2.00	2.00	2.00	0.50	0.50
<i>E. cloacae</i> 3647	32.00	4.00	32.00		2.00
<i>K. pneumoniae</i> 3226	4.00	2.00	4.00		0.50
<i>H. influenzae</i> ATCC 49247	4.00	1.00	4.00		1.00
<i>P. mirabilis</i> 3558	8.00	8.00	8.00		8.00
<i>P. aeruginosa</i> 1911E	>32.00	>32.00	>32.00	>32.00	4.00
<i>P. aeruginosa</i> 2032E WT	>32.00	>32.00	>32.00		4.00
<i>P. aeruginosa</i> 2033E PER	16.00	4.00	16.00		0.20
<i>C. perfringens</i> 615E	2.00	4.00	2.00	0.03	0.20
<i>B. fragilis</i> 2017E	16.00	16.00	16.00	0.06	0.20

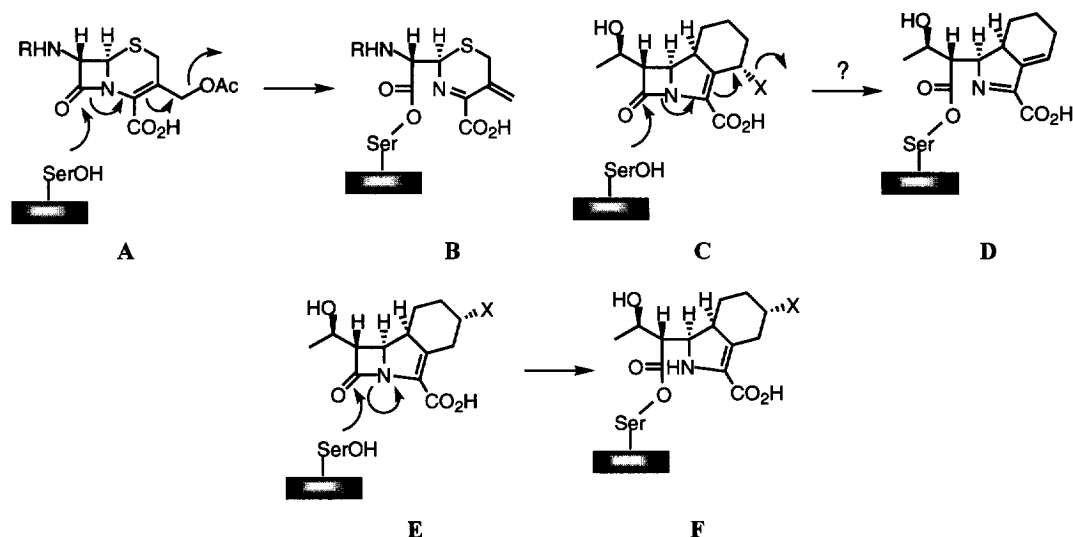
a. Data taken from ref 3b.

The *in vitro* antibacterial test results,¹⁵ shown in Table 1 on the 5 α -(1-hydroxyethyl) derivative **3**, the corresponding methyl ether **4**, and comparisons with **2** are interesting. It is clear that on a relative scale, the 1-hydroxyethyl analog **3**, reported here, is more active against a majority of strains compared with the other two 5-substituted analogs. It is also of interest to note that although weaker than imipenem and **1** in general, compound **3** fared quite favorably in a number of microorganisms.

The β -lactam antibiotics exert their antibacterial activity in part by interacting with penicillin binding proteins, where they are irreversibly attacked by a serine residue. In the case of the venerable cephalosporins, nucleophilic opening of the β -lactam carbonyl group is accompanied by a transposition of the Δ -2 double bond to the exocyclic position with ejection of the acetoxy group as illustrated in Scheme 4 (**A→**B**).¹⁶ It is of interest to speculate whether or not the 4-substituted trinems, in which the substituent is also a potential leaving group, would be subject to the same acylation process (Scheme 4 **C**→**D**). Although the 4-alkyl and the 4-unsubstituted trinems exhibit much weaker antibacterial profiles, compared to the 4-methoxy trinem **1**, these results do not in themselves validate the leaving group hypothesis shown in Scheme 4 (**C**→**D**). There also appears to be a**

stereochemical preference for the α -orientated 4-alkoxy substituent. The significant antibacterial profile of the 5 α -methoxy trinem **2** compared to the 5 β -isomer,⁷ has already lent support to a stereochemical dependence at that position. It also showed that appropriate substitution at C-5 was a viable alternative for antibacterial activity in vitro. Obviously, detailed kinetic experiments are needed to demonstrate the nature of the acylated intermediate in the case of Sanfetrinem **1**, the 5 α -methoxy trinem **2**, and the related analog **3** (Scheme 4 E \rightarrow F).

Scheme 4



This work has demonstrated that there is considerable room for functional modification at the C-5 position of the trinems, with polar groups being better tolerated. Based on other data in the literature,¹⁷ it is highly probable that the presence of a basic site at the extremity of the two-carbon chain would also be an interesting analog. Clearly a major challenge in this area of research still remains the discovery of novel entities that exhibit promising activity against resistant strains.

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