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

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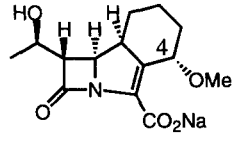
Abstract: The total synthesis of the tricyclic β-lactams, 5α-hydroxyethyl and 5α-methoxyethyl trinems is described and preliminary biological evaluation is reported. © 1997 Elsevier Science Ltd.

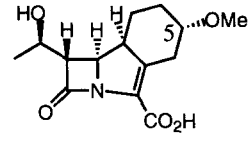
The β-lactams constitute an important class of antibacterial agents,[1] yet the growing number of resistant bacterial strains dictates the need for further development of novel motifs within this area.[2] Recently, the scientists at GlaxoWellcome have reported on a novel class of synthetic tricyclic 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



1
Sanfetrinem



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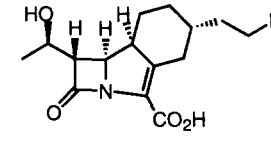

3, R = OH
4, R = OMe

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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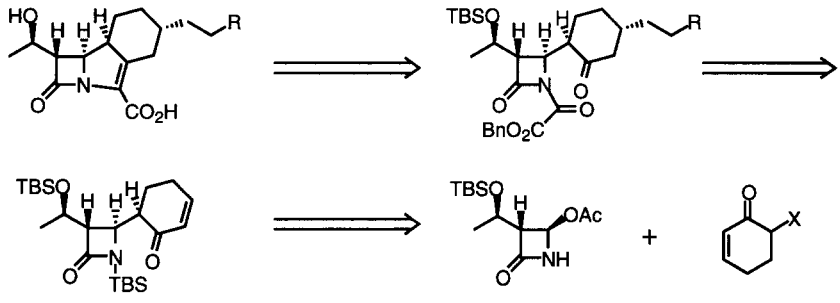
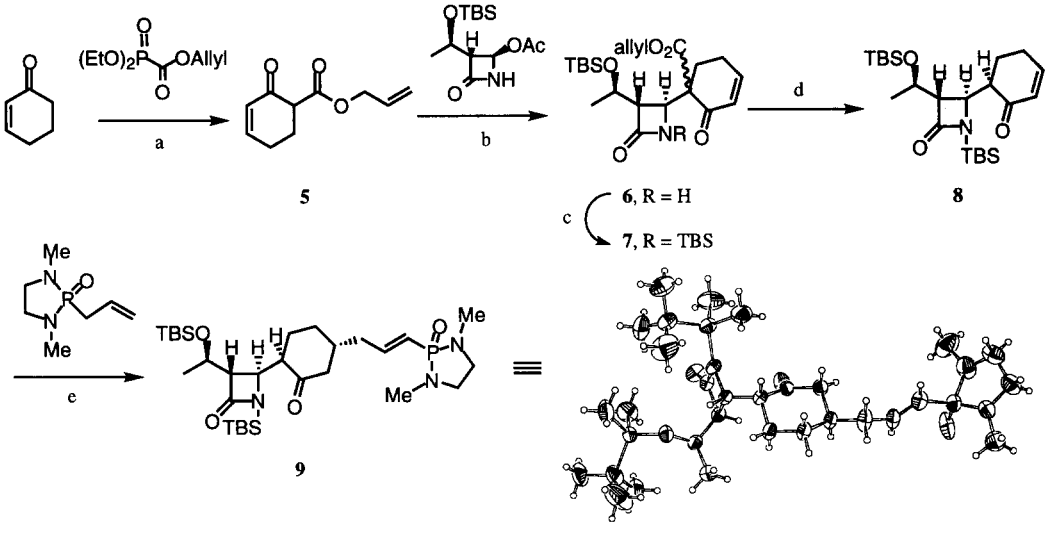
Scheme 1



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 laboratory[4] (Scheme 2). Thus, the lithium salt of cyclohexenone was condensed with allyl diethylphosphonoformate[10] 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

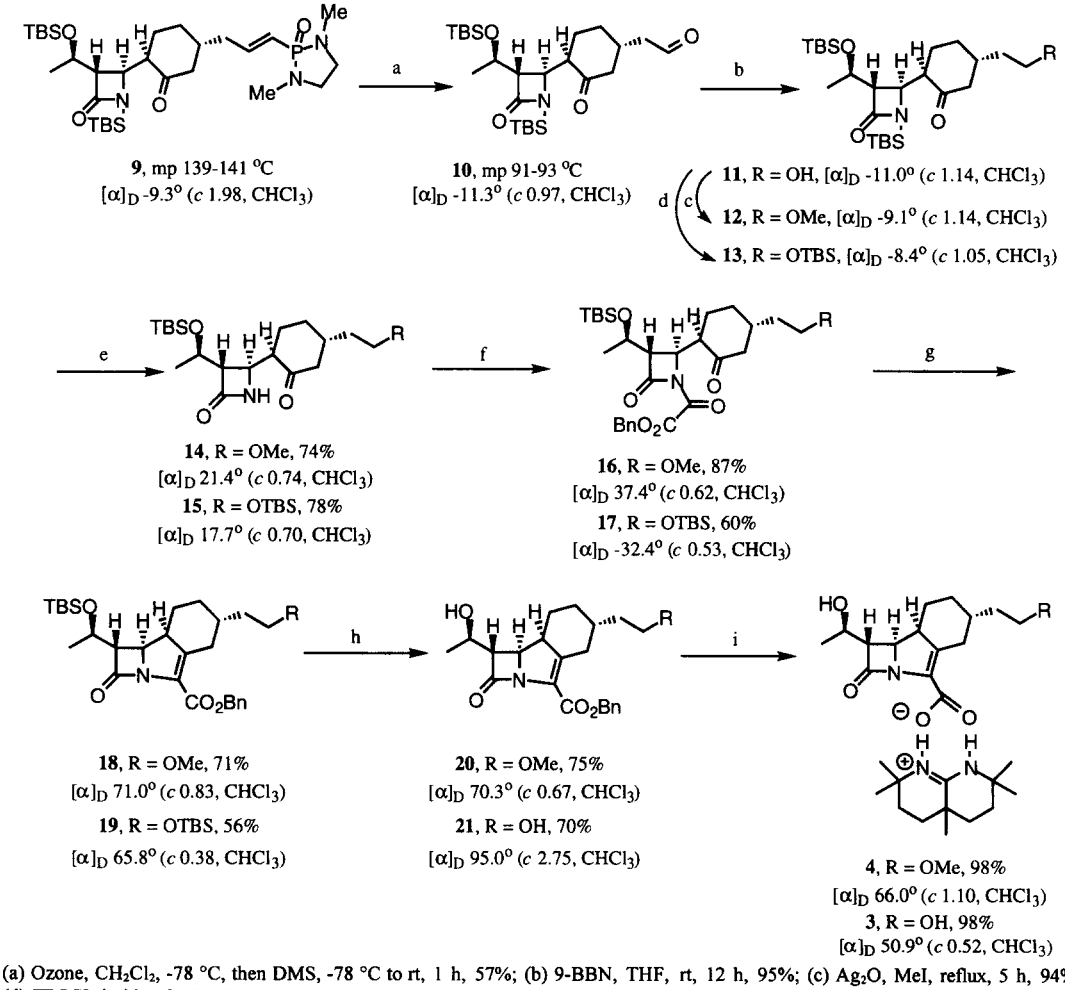


(a) i. LDA, THF, -78 °C, 30 min; ii. add allyl diethylphosphonoformate, -78 °C to rt, 2 h, 61%; (b) i. NaH, THF, -20 °C, 30 min; ii. add (3*S*,4*R*) 4-acetoxy-3-[(1*R*)-1-*tert*-butyldimethylsilyloxyethyl]-2-azetidinone, -20 °C, 2 h; (c) TBSOTf, NEt_3, CH_2Cl_2, 0 °C, 30 min; (d) $Pd(OAc)_2$ (1 mol%), PPh_3 (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%.

The key reaction to install the functionalized two-carbon side-chain at C-5 of the intended target molecules was achieved through a stereoselective conjugate addition of a phosphonamide γ-allyl anion previously reported by us.[11] Thus, deprotonation of 2-allyl-1,3-dimethyl-[1,3,2]-diazaphospholidine with *n*-BuLi followed by the addition of enone **8** afforded the alkylated adduct **9** in 75% yield, as a single isomer, whose absolute stereochemistry was established by single crystal X-ray analysis (Scheme 2). Presumably the stereocontrol in this conjugate addition can be attributed to a sterically less impeded approach of the anionic reagent to the enone.[11]

Elaboration of adduct **9** to 5α-hydroxyethyl trinem **3** and 5α-methoxyethyl trinem **4** is shown in Scheme 3. Oxidative cleavage of **9** by ozonlysis[11] 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



9, mp 139-141 °C
$[\alpha]_D$ -9.3° (*c* 1.98, $CHCl_3$)

10, mp 91-93 °C
$[\alpha]_D$ -11.3° (*c* 0.97, $CHCl_3$)

11, R = OH, $[\alpha]_D$ -11.0° (*c* 1.14, $CHCl_3$)
12, R = OMe, $[\alpha]_D$ -9.1° (*c* 1.14, $CHCl_3$)
13, R = OTBS, $[\alpha]_D$ -8.4° (*c* 1.05, $CHCl_3$)

14, R = OMe, 74%
$[\alpha]_D$ 21.4° (*c* 0.74, $CHCl_3$)
15, R = OTBS, 78%
$[\alpha]_D$ 17.7° (*c* 0.70, $CHCl_3$)

16, R = OMe, 87%
$[\alpha]_D$ 37.4° (*c* 0.62, $CHCl_3$)
17, R = OTBS, 60%
$[\alpha]_D$ -32.4° (*c* 0.53, $CHCl_3$)

18, R = OMe, 71%
$[\alpha]_D$ 71.0° (*c* 0.83, $CHCl_3$)
19, R = OTBS, 56%
$[\alpha]_D$ 65.8° (*c* 0.38, $CHCl_3$)

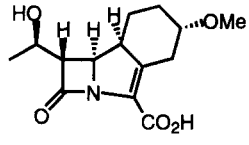
20, R = OMe, 75%
$[\alpha]_D$ 70.3° (*c* 0.67, $CHCl_3$)
21, R = OH, 70%
$[\alpha]_D$ 95.0° (*c* 2.75, $CHCl_3$)

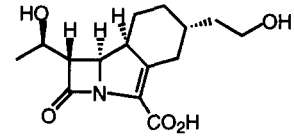
4, R = OMe, 98%
$[\alpha]_D$ 66.0° (*c* 1.10, $CHCl_3$)
3, R = OH, 98%
$[\alpha]_D$ 50.9° (*c* 0.52, $CHCl_3$)

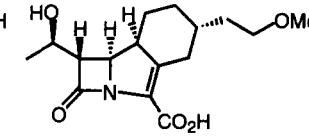
(a) Ozone, CH_2Cl_2, -78 °C, then DMS, -78 °C to rt, 1 h, 57%; (b) 9-BBN, THF, rt, 12 h, 95%; (c) Ag_2O, MeI, reflux, 5 h, 94%; (d) TBSCl, imidazole, DMF, rt, 12 h, 94%; (d) TBAF (1 equiv), AcOH (2 equiv), THF, rt, 30 min; (f) BnOCOCOCl, pyridine, CH_2Cl_2, 0 °C, 2 h; (g) $P(OEt)_3$, *o*-xylene, 140 °C, 7 h; (h) TBAF (3 equiv), AcOH (4 equiv), THF, 4 days; (i) 3,3,6,9,9-pentamethyl-2,10-diazabicyclo[4.4.0]dec-1-ene, H2, Pd(C), dioxane, rt, 1 h.

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

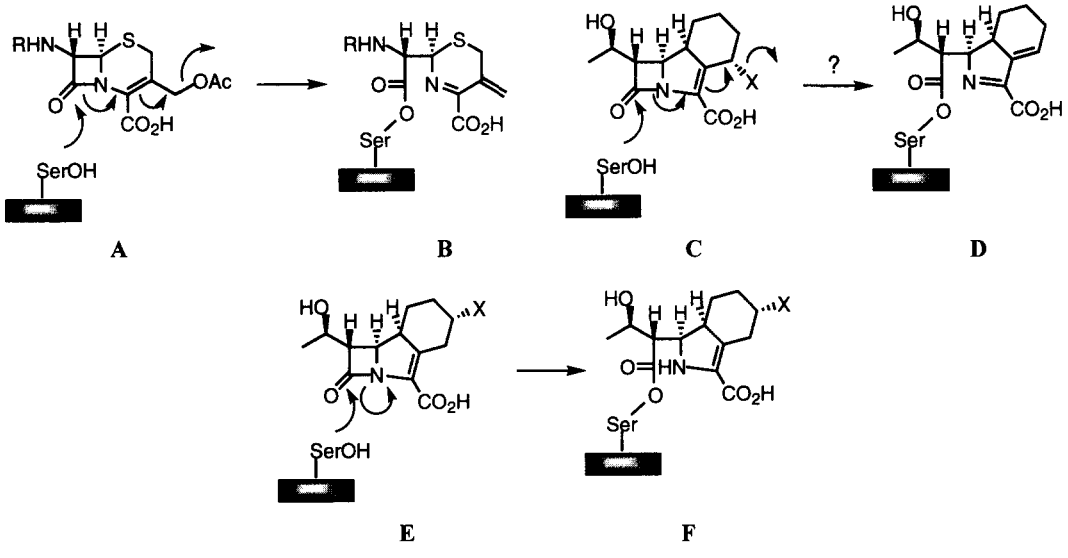
a. Data taken from ref 3b.

The in vitro antibacterial test results,[15] shown in Table 1 on the 5α-(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 5α-methoxy trinem **2** compared to the 5β-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 5α-methoxy trinem **2**, and the related analog **3** (Scheme 4 **E**→**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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