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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 4-AMINO TRINEMS

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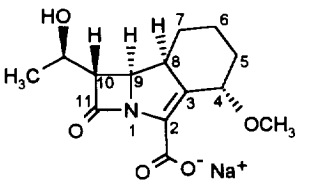
Abstract

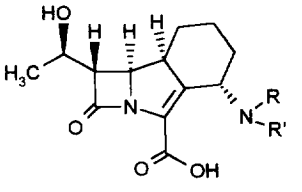
This article deals with the study carried out on the synthesis of 4-amino substituted trinems **1** starting from the key-intermediate (3S, 4R)-3-[(R)-1-(t-butyldimethylsilyloxy)ethyl]-4-[(1'R, 2'S, 3'R)-1',2'-epoxycyclohex-3'-yl]azetidin-2-one **2**. In particular, epoxide opening with various amines and subsequent cyclization to the corresponding trinems were explored. Their synthesis and antimicrobial activity are reported.

β-Lactams are the most widely used antibiotic class in the world due to their excellent therapeutic profile; however, an increasingly large number of bacterial strains is resistant to these antibiotics. In order to overcome this problem, a new class of β-lactam compounds, the trinems (formely referred to as tribactams), containing a tricyclic nucleus has recently been discovered in our laboratories.[1,2] Amongst them, the 4-methoxy derivative GV104326 (**Figure 1**), shows a broad spectrum of activity, is endowed with a good enzymatic stability[3] and has been selected as a candidate for development. In addition to the 4-alkoxy derivatives, the substitution with 4-amino groups has also been explored (**1a-d**).

FIGURE 1



GV104326



1a-d

a R = R' = H

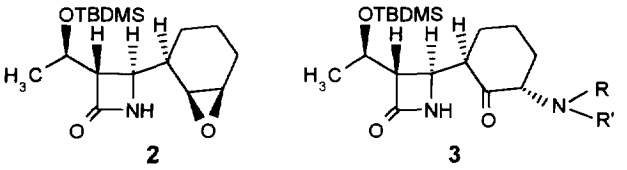
b R = CH_3 R' = H

c R = cyclopentyl R' = H

d R = R' = CH_3

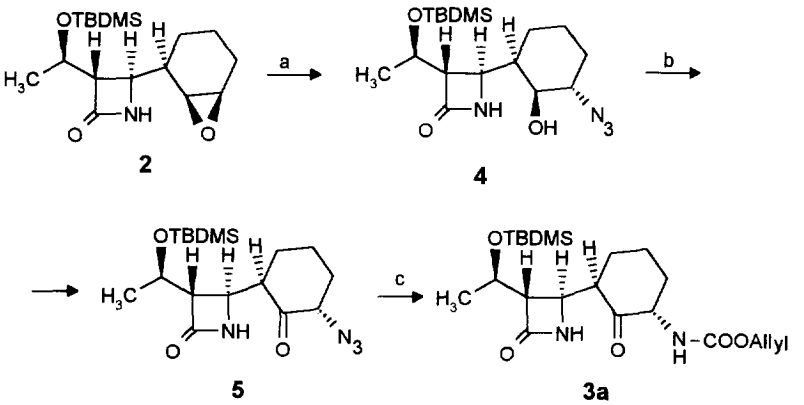
Considering that the relative configuration 4α, 8β represents the best compromise in terms of activity and biological stability at least for compounds studied to date, a synthetic route which permitted the stereoselective introduction of substituents at C-4 was sought. Thus, the epoxide **2** (**Figure 2**), synthesized by known procedures[4], proved to be a suitable intermediate for the synthesis of the key-derivatives **3** (**Figure 2**).

FIGURE 2



In particular, in order to obtain the final compound **1a**, sodium azide[5] was used for the epoxide opening reaction. The reaction can be performed (**Scheme 1**) in the presence of either ammonium chloride[6] or magnesium sulfate to give the azidoalcohol **4** in comparable yield (70%). Oxidation of the alcohol with pyridinium chlorochromate[7] (70%), followed by reduction of the azido group[6] to its corresponding amine and immediate protection with allyl chloroformate gave compound **3a** (43%).

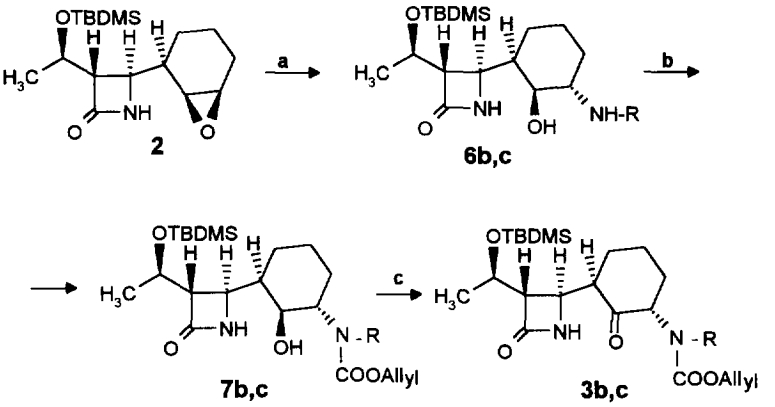
SCHEME 1



a: $NaN_3/MgSO_47H_2O$, MeOH, reflux, 20h , 70% or NaN_3/NH_4Cl, $EtOH/H_2O$, reflux, 20h, 73%
b: PCC, CH_2Cl_2, 22°C, 18h, 70%
c: 1) H_2, Pd/C10%, AcOEt, 22°C, 3 atm., 5h 2) $ClCOOCH_2CH{=}CH_2$, TEA, CH_2Cl_2, 0°C, 10min, 43%

The introduction of a secondary amino group was achieved by ring opening of epoxide **2** with primary amines as nucleophiles (**Scheme 2**) using ammonium chloride as catalyst. The amino alcohols **6b,c**, were obtained in moderate to good yield, depending on the bulk of the nucleophile (from 100% for **6b** to 45% for **6c**). Sequential protection as allylcarbamates (57-75%) and oxidation with pyridinium chlorochromate (80-90%) led to compounds **3b,c**.

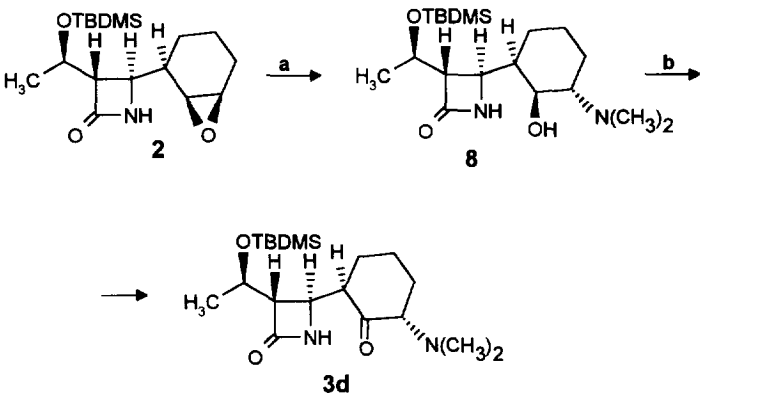
SCHEME 2



a: R-NH_2, NH_4Cl, $EtOH/H_2O$, reflux, 24h (R=Me quant.; R=cC_5H_9 45%)
b: $ClCOOCH_2CH{=}CH_2$, 2,2,6,6-tetramethylpiperidine, CH_2Cl_2, 0°C, 10min (R=Me 75%; R=cC_5H_9 57%)
c: PCC, CH_2Cl_2, 22°C, 9h, Y=80-90%

The same reaction conditions were also used with secondary amines (**Scheme 3**), such as dimethylamine. In this case a Swern oxidation[8] was performed to give **3d** in 90% yield.

SCHEME 3



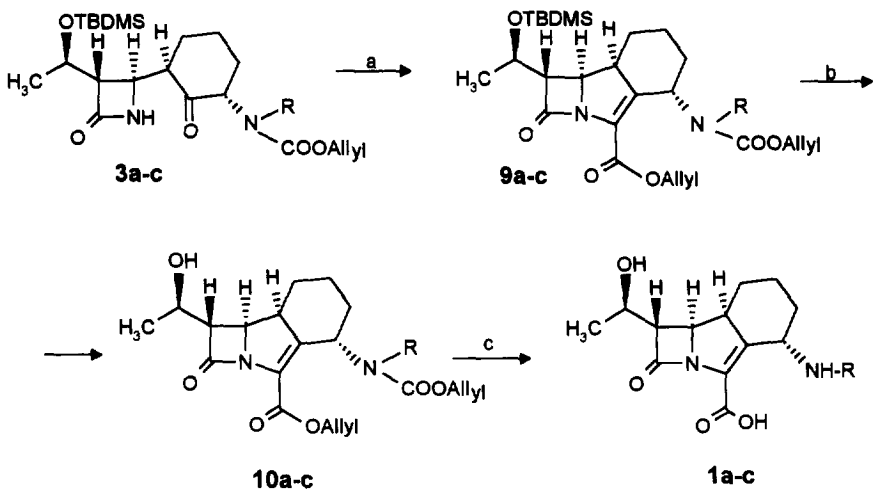
a: $(CH_3)_2NH$, NH_4Cl, $EtOH/H_2O$, reflux, 3h, 55%
b: $(COCl)_2$/DMSO, DIPEA, , CH_2Cl_2, -55° to 22°C, 30min, 90%

Conversion of the aminoketones **3a-c** into the trinem nucleus was achieved *via* N-1 acylation with allyloxalyl chloride followed by treatment with triethylphosphite to give a Wittig-type cyclization[9] (**Scheme 4**). It is worth noting that cyclization yields decreased with increasing steric hindrance of the substituents at

the 4 position (82% in the case of **9a**, 16% for **9c**). Unfortunately, under the conditions used, the 4-dimethylamino trinem was not isolated unstead many degradation compounds were recovered.

Deprotection of the hydroxyethyl side-chain using tetrabutylammonium fluoride and acetic acid in tetrahydrofuran afforded compounds **10a-c** (50-60%), which were deprotected under standard conditions[10] to give the final derivatives **1a-c** (75-85%).

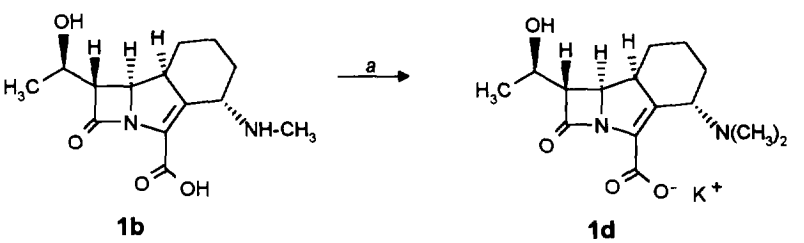
SCHEME 4



a: 1) $ClCOCOOCH_2CH{=}CH_2$, K_2CO_3, TEA, CH_2Cl_2, 22°C, 45min 2) $P(OEt)_3$, xylene, reflux , for **9a** reflux 2h and 82%, for **9b** reflux=7h and 70%, for **9c** reflux=20h and 16%
b: TBAF $3H_2O$, AcOH, THF, 22°C, 15h, 50-60%
c: $Pd(PPh_3)_4$, dimedone, THF, 22°C, 1h, 75-85%

Compound **1d** was prepared *via* methylation of the 4-methylamino substituted trinem **1b** in 30% yield (**Scheme 5**).

SCHEME 5



a: Me_2SO_4, phosphate buffer pH 8.5, THF, 22°C , 4h, 30%

Antibacterial activity was evaluated against a series of Gram positive and Gram negative bacterial strains. **Table 1** reports the *in vitro* antibacterial activity[11] (MIC μg/ml) of compounds **1a-d** in comparison with GV104326, as determined by the microtiter broth dilution test (MIC values). All the compounds were active against both Gram positive and Gram negative bacteria, with improved activity against *Pseudomonas aeruginosa* with respect to GV104326. Furthermore, these compounds showed good stability both to β-lactamases and to renal human dihydropeptidase.

TABLE 1

Compound	S. a. 663	S.a. 853	E.faecalis 850	E. coli 1850	E. coli 1919	P.aeruginosa 1911
GV104326	0.25	0.25	1.00	0.50	0.50	>32.00
1a	0.25	0.25	16.00	1.00	0.50	4.00
1b	0.25	0.50	16.00	2.00	0.50	4.00
1c	8.00	4.00	32.00	8.00	32.00	32.00
1d	0.25	0.25	>32.00	2.00	1.00	8.00

In conclusion, the stereoselective synthesis of the 4-amino trinems was successfully achieved starting from the homochiral epoxy derivative **2**. The epoxide ring opening occurred in satisfactory overall yield. The next critical step was the cyclization of the key-interemediates **3** to trinems, which was dependent on the steric hindrance of the substituent at the 4 position. Cyclization of compound **3d** using this route failed, nevertheless, the synthetic problems were overcome by preparing **1d** by direct methylation of **1b**.
All these compounds show good activity against both Gram positive and Gram negative strains; in particular, compounds **1a** and **1b** show increased antibacterial activity versus *Pseudomonas aeruginosa*.

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References and notes

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11. Minimum Inhibitory Concentrations (MIC) determined in Mueller Hinton broth: Anaerobes Schadler broth Inoculum = $5x10^5$ CFU/ml **S. a. 663**= *Staphylococcus aureus* 663E ; **S. a. 853**= *Staphylococcus aureus 853*E β-Lactamases producing strains, ***E.* faecalis 850** = *Enterobacter faecalis* 850 ; **E. coli 1850**= *Escherichia coli* 1850E; **E. coli 1919** = *Escherichia coli* 1919E β-Lactamases producing strains; **P. aeruginosa 1911** = *Pseudomonas aeruginosa* 1911E.

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