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NUCLEAR ANALOGS OF β-LACTAM ANTIBIOTICS 8.

STEREOSPECIFIC SYNTHESIS OF A C-3 METHOXYLATED MONOCYCLIC β-LACTAM[1]

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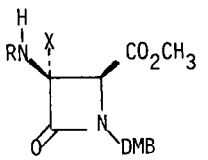
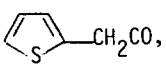
Methoxylation of 1(R = $PhOCH_2CO$) occurred stereospecifically from the α-face as determined by x-ray crystallography to provide 2 which was converted to 4 whose *in vitro* antimicrobial activity was determined.

The 7-α-methoxy cephalosporins were discovered independently by two groups in the early 1970's as naturally occurring fermentation products from Streptomyces.[2,3] Extensive studies on semisynthetic cephamycins derived from them showed that these antibiotics often demonstrated an expanded spectrum of activity against certain Gram-negative organisms as well as an increased stability to β-lactamase relative to their unmethoxylated counterparts.[4,5,6] Recently, there has been a large amount of research which has resulted in the total synthesis of various β-lactam nuclear analogs.[1] The isolation of an α-methoxy β-lactam monocycle from a bacterial fermentation[7] has also been reported within the last year. In light of the improved biological properties conferred on some β-lactam antibiotics by an α-methoxy group, we decided to investigate the synthesis of an α-methoxy nuclear analog of a totally synthetic biologically active β-lactam monocycle.

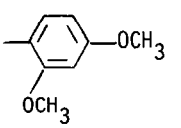
The cis-amido-β- lactam 1[8] is a key intermediate in the synthesis of some biologically active penicillin and cephalosporin analogs. Monocycles such as 3 exhibit *in vitro* activity against Gram-negative bacteria comparable to thienylpenicillin.[1] In this communication, we report the stereospecific synthesis of the α-methoxy β-lactam 2 and its conversion to 4.

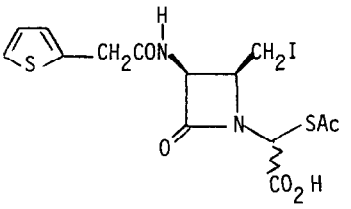


1

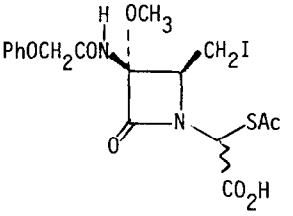
1 R = $PhOCH_2CO$ or  CH_2CO, X = H

2 R = $PhOCH_2CO$, X = OCH_3

DMB = 



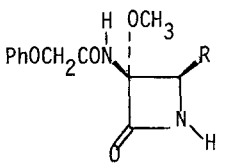
3

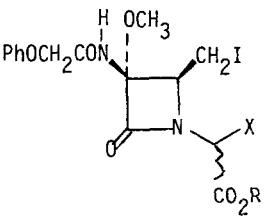


4

The cis-azetidinone 1 (R = $PhOCH_2CO$) was treated with 3.5 equiv. of lithium methoxide in tetrahydrofuran at -40° for 5 min. followed by 1 equiv. of tert-butyl hypochlorite. After stirring for 60 min. and quenching with acetic acid, it afforded α-methoxy- β-lactam 2 as a gum.[9] Without intermediate purification, the β-lactam nitrogen of 2 was deblocked oxidatively with buffered persulfate[10] to afford after chromatography on silica 5 (29% from 1). Selective reduction of the ester with 10 equiv. of sodium borohydride in methanol gave alcohol 6, (79%).[11]

Analogy to the methoxylated cephalosporins which have been prepared in a similar fashion would suggest that the acylimine of 1 (R = $PhOCH_2CO$) should undergo Micheal addition of methanol from the α-face if the steric effects of the 4- β-carbomethoxy and 1-aryl substituents are as great as those of the fused dihydrothiazine ring of cephalosporins. Nuclear Overhauser studies performed on 5 were not conclusive as to the stereochemistry at C-3. An x-ray crystallographic study on 6 was performed.[12]





5 R = CO_2CH_3

6. R = CH_2OH

7. R = CH_2OTS

8 R = CH_2I

9 R = $CH(Ph)_2$, X = OH

10 R = $CH(Ph)_2$, X = $SCOCH_3$

The crystallographic data indicated that the methoxylation had occurred from the α-face. Figure 1 shows a computer generated ORTEP stereoview of 6.

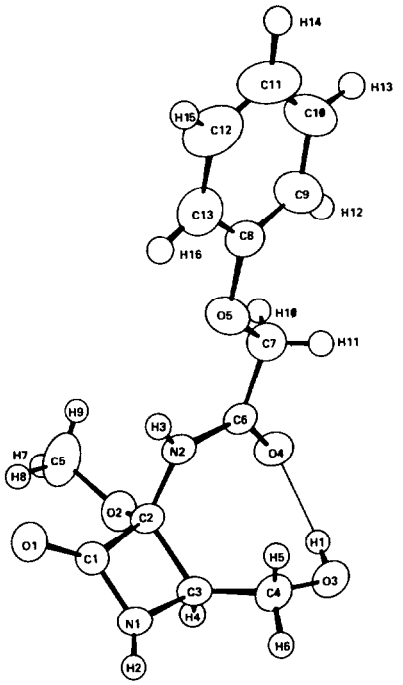


FIGURE 1

Treatment of the alcohol 6 with 1.1 equiv.tosyl chloride in dry pyridine at 0^0 for 4 h afforded 7 as a slightly unstable oil which was immediately converted with dry sodium iodide in refluxing acetone for 6h to iodide 8 (45%). The iodide 8 was treated with 1 equiv. of benzhydrylglyoxylate and triethylamine in dioxane over 4Å molecular sieves for 4 h to provide hydroxy iodide 9 (44%) as a mixture of carboxylate epimers. This mixture was converted with 1.5 equiv. of thionyl chloride and 1.5 equiv. N,N-diethylaniline in dry methylene chloride at -10^0 to an unstable chloride which was treated *in situ* with 5 equi. of potassium thioacetate in DMF at -10^0 for 5h to provide after preparative TLC, thioacetate 10 as a mixture of epimers (11% from 9) IR ($CHCl_3$) 5.60 (β-lactam), 5.72 (ester), 5.86 (thioacetate), 5.93 nm (amide), NMR ($CDCl_3$) δ2.43, 2.44 (3H,2s,$SCOCH_3$),3.55 (3H,s,OCH_3), 4.00-4.17 (1H,m,C-4 H), 4.54, 4.55 (2H,2s,$PhOCH_2CO$), 6.13, 6.37 (1H,2s,$CHCO_2$) 6.84, 6.85 (1H,2s,CO_2CHPh_2), 6.90-7.38 (15H,m), m/e 689 $(M+H)^+$, 560. The thioacetate ester was converted to 4 with cold trifluoracetic acid (40%) IR (CH_2Cl_2) 5.67 (β-lactam), 5.73 (acid), 5.89 (thioacetate), 6.07 nm (amide) NMR ($CDCl_3$) δ2.32 (3H,s,$SCOCH_3$), 3.45 (3H,s,OCH_3), 4.00-4.20 (1H,m,C-4H), 4.65 (2H,s,$PhOCH_2CO$), 5.96 (1H,s,$CHCO_2H$), 6.65-7.40 (1H,s,CHO), m/e 394 $(M-HI)^+$.

Compounds 4 and 10 were tested for *in vitro* antimicrobial activity. Both α-methoxy β-lactam acid and ester had activities lower than those found for the corresponding compounds unsubstituted at C-3.

ACKNOWLEDGEMENT We are grateful to J. Guarini for the *in vitro* testing and D. Staiger for the Nuclear Overhauser study.

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11. Satisfactory combustion analyses were obtained for compounds 5 and 6. Compound 10 displayed a parent ion at m/e 688 that was too weak for an exact mass measurement. However, m/e 560 corresponding to $(M-HI)^+$ gave 560.1658 (calc'd for $C_{30}H_{28}N_2O_7S$ 560.1617).
12. The crystal structure was performed by Molecular Structure Corporation, College Station, Texas. Supplementary x-ray material has been submitted for deposition at the Cambridge Crystallographic Data Center.

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