Tetrahedron Letters,Vol.24,No.4,pp 335-338,1983 0040-4039/83/040335-04$03.00/0
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3-OXA-5-CARBA ANALOGUES OF β-LACTAM ANTIBIOTICS

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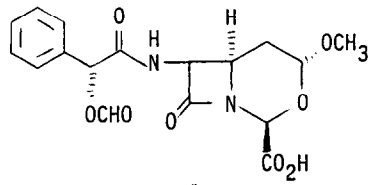
ABSTRACT: The syntheses of some 3-oxa-1-azabicyclo[4.2.0]octan-8-one carboxylic acic salts is described using Hg^{+2}-assisted intramolecular cyclization of an allyl-azetidinone alcohol.

In 1979 Gleason and coworkers[1] reported the synthesis and potent antibacterial activity of 3-oxa-1-azabicyclo[4.2.0]octan-8-one 2-carboxylic acid 1. We would like to report the synthesis and biological activity of the C-4 carbon-substituted system as described by 7.



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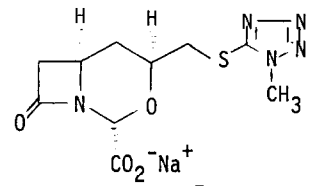
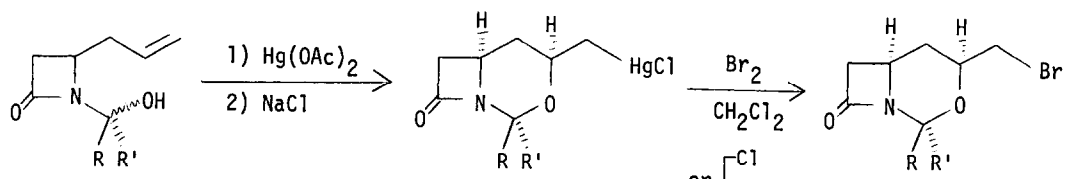


7

We had previously developed a synthesis for this type of β-lactam utilizing Hg^{+2}-assisted ring closure of the known achiral alcohols 2a and 2b.[2]

Thus, treatment of either alcohol with $Hg(OAc)_2$ (1 eq., 4:1 THF/H_2O, 0°, 3 h) generated, after aqueous NaCl treatment, the bicyclic mercuric chloride derivatives 3a and 3b in yields of 25% and 50%, respectively (Scheme I).[3,4]

SCHEME I



2a: R = H, R' = CO_2-p-nitrobenzyl
2b: R = R' = CO_2-p-nitrobenzyl

3a
3b

4a
4b

The relative stereochemistry of 3a was determined by an X-ray crystallographic study[5] which revealed an equatorial C-4 mercuriomethylene group trans to the C-2 ester and cis to the β-lactam. These orientations of substituents at C-2 and C-4 relative to C-6 are opposite to those in Gleason's structure 1. As with 1, however, the β-lactam nitrogen of 3a is not flat, but 0.24 Å above the plane defined by the three attached atoms.[6]

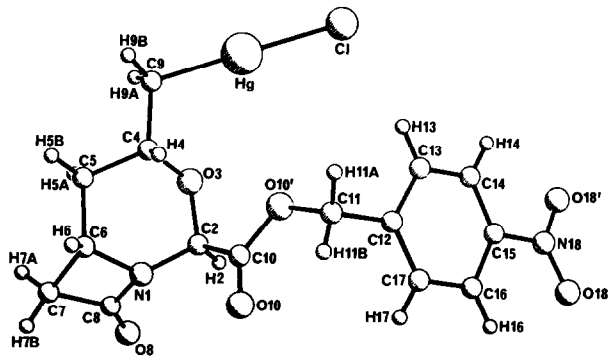
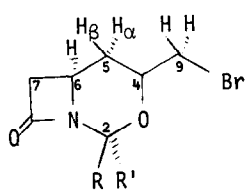


FIGURE 1. ORTEP Plot of 3a

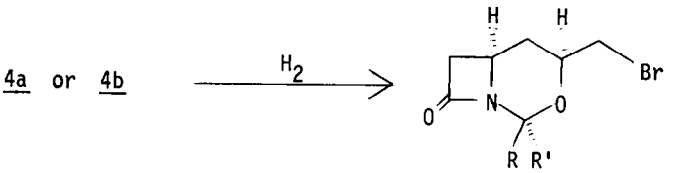
Ring closure of 2b also generated the C-4 equatorial isomer 3b, as evidenced by 360 MHz H'-NMR decoupling experiments (Table 1) on the bromides 4a and 4b.[7]

TABLE 1. Comparison of Coupling Constants (Hz) in d_6-DMSO



	H_{5gem}	H_4–$H_{5\beta}$	H_4–$H_{5\alpha}$	H_6–$H_{5\alpha}$	H_4–H_9
4a	13	11	0	4.5	3.5,6.5
R=H					
R'=CO_2PNB					
4b	13	11	1	4.0	3.7,7
R=R'=CO_2PNB					

Esters 4a and 4b could be converted in high yields to the sodium salts by careful hydrogenolysis (H_2, 10% Pd/C, 40 psi, 15 min, RT) in EtOAc/H_2O containing 2-3 eq $NaHCO_3$.[8] Under these conditions 5b did not decompose or decarboxylate to afford 5a or its isomer.[9]

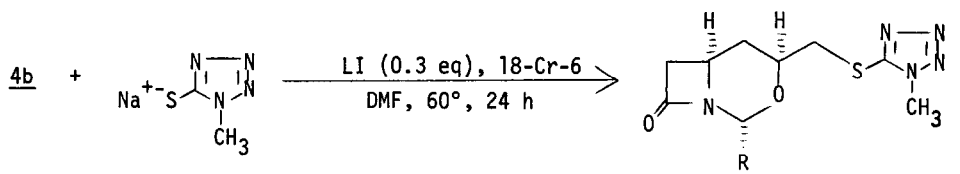


(eq 1)

5a: R = H, R' = $CO_2^-Na^+$

5b: R = R' = $CO_2^-Na^+$

The malonate ester 4b could be transformed into the glyoxate series when allowed to react with LiI/N-methyltetrazolethiolate (sodium salt) in DMF (eq 2). Mild basic hydrogenation afforded 7 in high yield.[10]



(eq 2)

6: R = CO_2PNB

7: R = $CO_2^-Na^+$

The antibacterial activities of carboxylate salts 5a, 5b, and 7 were disappointing.

Acknowledgements. The authors would like to thank Dr. Donald B. Boyd and Mr. Douglas O. Spry for their assistance and Ms. Phylis Hager for her aid in preparing this manuscript.

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2. Allyl azetidinone was prepared from $ClSO_2NCO$ and 1,3-butadiene [E. Moriconi, W. Meyer, Tetrahedron Lett., 3823 (1968)]. Treatment with $HCOCO_2H \cdot xH_2O$ in DMF, followed by esterification with p-$NO_2C_6H_5CH_2Br/K_2CO_3$ afforded 2a, used as a mixture of diastereomers (Eur. Pat. 0-008-514, 1980). Alcohol 2b was synthesized by the method of S. Schmitt, D. Johnston, B. G. Christensen, J. Org. Chem., 45, 1142 (1980).

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4. a) 3a: ir ($CDCl_3$) 1760, 1740 cm^{-1}; H'-NMR ($CDCl_3$) δ 5.8 (H-2,s), m^+=555 (FD).
3b: ir (KBr) 1770, 1750, 1720 cm^{-1}; mp 157-160°.
b) Other recovered products in the ring closure reaction of 2a included the C-2 β-isomer of 3a (4%), starting material (7%) and the isomerized olefin of 2a (2%).

5. X-Ray data: $P2_{1/c}$, 4 molecules/cell, a = 13.926±0.002 Å, b = 14.002±0.003 Å, c = 9.297±0.002 Å, β = 109.23±0.01°, calculated density 2.155 gcm^{-3}, 2458 reflections (CuKα) with no absorption correction), R = 0.096. Supplementary X-ray material has been submitted for deposition at the Cambridge Crystallographic Data Center.

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7. The bromides were synthesized using Br_2 (3 eq) in CH_2Cl_2 (4a) or 1,2-dichloroethane (4b) for 7 h at RT.
4a: ir (KBr) 1768, 1734 cm^{-1}; H'-NMR ($CDCl_3$) δ 5.9 (H-2,s); m^+=399 (FD).
4b: ir (KBr) 1777, 1760, 1750 cm^{-1}; $(m+1)^+$=578, 580 (FD).

8. 5a: ir (KBr) 1740, 1626 cm^{-1}; H'-NMR (d_6-DMSO) δ 5.0 (H-2,s); $(m+1)^+$=264, 266 (FD, NH_4Cl).
5b: ir (KBr) 1757, 1651 cm^{-1}; $(m-CO_2-Br)^+$=184 (FD, NH_4Cl).

9. Compound 5b was stable in D_2O, but decomposed in d_6-DMSO over a period of hours at 20°C.

10. 6: ir (KBr) 1740, 1627 cm^{-1}; H'-NMR (D_2O) δ 5.4 (H-2,s).

(Received in USA 4 October 1982)