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β-LACTAM SYNTHESIS: CHEMOSPECIFIC SULFONATION AND CYCLIZATION OF THE β-HYDROXYVALINE NUCLEUS

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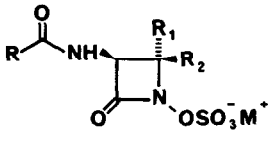
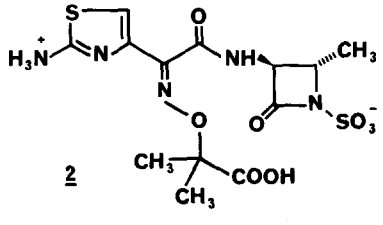
Abstract: The intramolecular cyclization of "hydroxamate" 3 using Mitsunobu conditions was inefficient for the formation and isolation of the C-4 dimethyl monobactam 4. However, chemospecific O-sulfonation of 3 and subsequent cyclization with base provides a useful method for β-lactam synthesis from a sterically hindered β-hydroxy amino acid. Competitive rearrangement of 3 also occurs during cyclization providing isomeric β-lactam 5.

Azetidinone-1-sulfates 1[1] (monosulfactams) are members of a new and potent class of monocyclic β-lactams antibiotics known as monobactams. The C-4 unsubstituted and monomethyl substituted monosulfactams possess high intrinsic antibacterial activity, yet they display both chemical and β-lactamase instability[2] in marked contrast to azetidinone-1-sulfonates such as aztreonam (2).[3,4] Although 4,4-dimethyl substitution in azetidinone-1-sulfonates resulted in decreased intrinsic antibacterial activity,[5] it was hoped that dimethyl substitution at C-4 in the more activated monosulfactam series would result in improved chemical and β-lactamase stability while maintaining high antibacterial activity.



1 R_1, R_2 = H or CH_3



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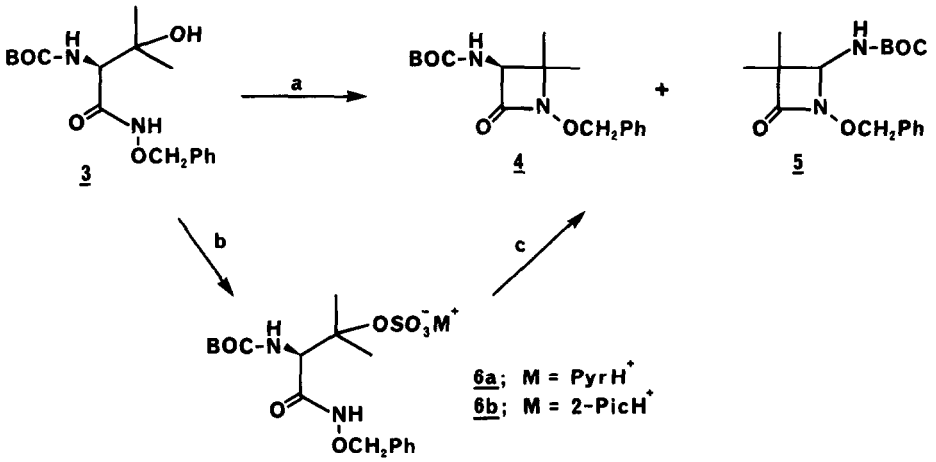
The availability of 3-hydroxyvaline[6] and the successful use of acyclic amino acid precursors in the synthesis of 1-hydroxyazetidinones[7] made hydroxamate 3 an attractive intermediate in the synthesis of 4,4-dimethyl substituted monosulfactams. Condensation of (S)-N-BOC-3-hydroxyvaline[8] with O-benzylhydroxylamine (DCC/HOBT in EtOAc) provided (S)-hydroxamate 3.[9] Cyclization of 3 using Mitsunobu conditions ($Ph_3P/CCl_4/Et_3N$ in CH_3CN or Ph_3P/DEAD (diethylazodicarboxylate) in THF) afforded two isomeric products,[10] the desired β-lactam (S)-4 and an unprecedented rearrangement product 5,[11] contrary to the recent report by Yoshida *et al.*[12] Azetidinone 4 could be isolated only in 20-25% yield after repeated chromatography on silica gel using CH_2Cl_2-EtOAc (10:1) to separate it from isomer 5. The modest yield of 4 and the presence of an isomeric β-lactam component contrasts with the efficient cyclization of hydroxamates derived from primary and secondary hydroxy amino acids such as serine, threonine, and allothreonine.[7,13]

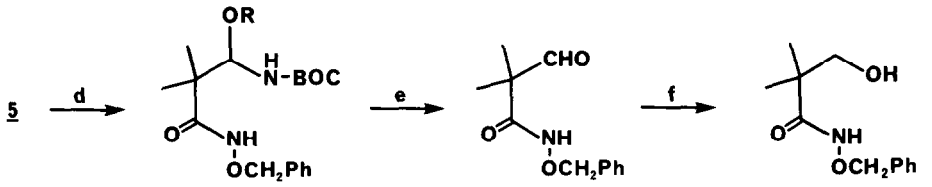


(a) Ph_3P, CCl_4, Et_3N, CH_3CN or Ph_3P, DEAD, THF; (b) pyridine · SO_3, pyridine or 2-picoline · SO_3, MIBK; (c) K_2CO_3, H_2O, EtOAc, 70°C; or $K_2B_4O_7$, KOH, H_2O, MIBK, pH 8.6-9.0, 70°C.

Clearly an improved method of cyclization was desirable. Cyclization via mesylate displacement[13] was not applied, since mesylation (CH_3SO_2Cl, pyridine or Et_3N) of the tertiary alcohol in 3 was nonselective due to steric hindrance. Sulfonation was considered as an alternative for selectively converting the tertiary hydroxyl group in 3 to an effective leaving group. Conceivably, kinetic sulfonation might occur competitively at the hydroxamate, carbamate, and tertiary alcohol centers; however, if under the reaction conditions sulfonation of the amide linkages is reversible, sulfate 6 should be the thermodynamically favored product. Indeed, sulfonation of chiral (S)-3 with pyridine · SO_3 complex (1.35 equiv.) in pyridine (55°C, 3h) proceeded to yield crude 6a[14] (quantitative yield) after removal of pyridine. Refluxing (2h) crude 6a with K_2CO_3 (6 equiv.) in aqueous EtOAc gave (S)-4 in 50% yield after passage through a pad of silica gel using EtOAc-hexane (3:2) and crystallization from diisopropyl ether. More conveniently, (S)-3 was sulfonated with 2-picoline · SO_3 complex[15] (1.2 equiv.) in methyl isobutyl ketone (MIBK) at ambient temperature (1-2h) to give 6b. Addition of water and $K_2B_4O_7$ (4 equiv.), followed by warming to 70°C and subsequent addition of aqueous KOH (2 equiv.) over 45 min, afforded (S)-4[16] in 58% yield after

evaporation of the organic phase and crystallization from diisopropyl ether. Although azetidinone 4 is the major product formed in the cyclization of sulfates 6, a substantial amount of the isomeric β-lactam 5 is found in the mother liquors, and we estimate that under these conditions 4 and 5 are formed in approximately a 2:1 ratio.[17]

Whereas stereochemistry is conserved in the formation of 4 from (S)-3, azetidinone 5 was obtained in racemic form from (S)-3 in the redox reaction with $Ph_3P/CCl_4/Et_3N$ or the sulfonation-cyclization ($KOH/K_2B_4O_7$) sequence. Structure 5 was assigned on the basis of crystallographic analyses, spectral data, and chemical degradation. Although the complete crystal structure of 5 was not solved[18a], an analysis based on a pronounced supercell of X-ray intensities revealed all 23 non-hydrogen atoms of the rearranged molecular skeleton, thereby providing the rationale for the following degradation sequence. Mild acid hydrolysis of 5 afforded a product, formulated as hemiaminal 7a, which was converted to 7b (CH_3OH, p-TsOH), the structure of which was confirmed through X-ray analysis.[18b] Further acid hydrolysis of 7a gave aldehyde 8 which was then reduced to known alcohol 9.[7,19] Interestingly, hemiaminal 7a and aldehyde 8 are detected in the cyclization of sulfonates 6, presumably as the result of the decomposition of 5.



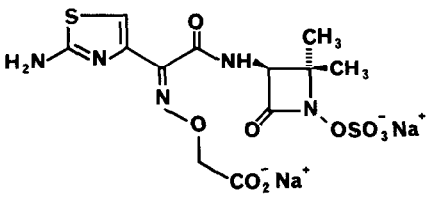
7a; R = H
7b; R = CH_3

8

9

(d) 1N HCl, EtOAc; (e) conc. HCl, H_2O, CH_3CN; (f) $NaBH_4$, H_2O, THF.

The availability of intermediate 4, using the above route, allowed the preparation of a variety of potent antibiotics having activity against gram-negative bacteria. These compounds are stable to both chemical and β-lactamase-mediated hydrolysis. A member of this series, SQ 30,213 (10), is highly orally-absorbed in a variety of animal models and is currently undergoing preclinical evaluation.[20]



SQ 30,213 (10)

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8. (S)-N-BOC-3-hydroxyvaline (mp 120-121°C; $[\alpha]_D$ = +7.81° (c = 2.16, EtOAc), >99% optical purity) was obtained from *d,l*-3-hydroxyvaline and $(BOC)_2O$ in *t*-butanol/water at pH 10.0 followed by resolution as its S-(-)-α-methylbenzylamine salt.

9. SELECTED DATA: 3, mp 104-105°C; $[\alpha]_D$ = +7.2° (c = 2.0, EtOAc); 4, mp 121-122°C; R_f 0.39 (silica gel, CH_2Cl_2:THF, 94:6); IR ($CHCl_3$) 1770, 1713 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.10 (s, 3 H), 1.32 (s, 3 H), 1.44 (s, 9 H), 4.29 (br s, 1 H), 4.97 (s, 2H), 5.03 (br s, 1 H), 7.39 (s, 5 H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 162.30, 155.55, 135.28, 129.23, 129.00, 128.55, 80.45, 78.92, 67.87, 62.66, 28.17, 23.26, 19.49; 5, mp 109-111°C; R_f 0.43 (silica gel, CH_2Cl_2:THF, 94:6); IR ($CHCl_3$) 1778, 1719 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.07 (s, 3 H), 1.22 (s, 3 H), 1.47 (s, 9 H), 4.32 (br s, 1 H), 4.94, 4.96 (AB q, J_{AB} = 11 Hz, 2 H), 5.04 (br s, 1 H), 7.41 (s, 5 H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 169.48, 154.39, 135.17, 129.53, 129.14, 128.64, 80.65, 77.75, 72.56, 49.91, 28.20, 20.35, 17.26.

10. We obtained 4 and 5, using $Ph_3P/CCl_4/Et_3N$ conditions, as a crystalline mixture (1:1) in 76% yield after silica gel chromatography (benzene:EtOAc, 85:15). The identical reaction is reported to give amorphous 4 in 64% yield after chromatography (reference 12).

11. For the mechanism of the formation of 5 see, J. D. Godfrey, Jr., R. H. Mueller, and D. J. Von Langen, following paper in this issue.

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14. ^{13}C NMR (CD_3CN) spectral comparisons showed the expected shift of the quaternary C-3 valine carbon from 72.41 δ in 3 to 83.52 δ in 6a.

15. The 2-picoline · SO_3 complex was prepared from chlorosulfonic acid and 2-picoline (2.5 equiv.) at -78°C in MIBK followed by warming to room temperature.

16. No racemization occurred on cyclization of (S)-3 using this route or the procedure involving sequential treatment with pyridine · SO_3 and aqueous K_2CO_3/EtOAc as ascertained by chiral shift studies using $Eu(hfbc)_3$. (S)-4: $[\alpha]_D$ = +21.88° (c = 2.50, CH_2Cl_2). Similarly, no racemization occurred on cyclization of (S)-3 using $Ph_3P/CCl_4/Et_3N$ or Ph_3P/DEAD.

17. The estimation of the ratio of 4 to 5 is based upon the actual isolated yield of 4 and TLC analysis of the mother liquors. The chemical instability of 5 under the reaction conditions (*vide infra*) precludes a more accurate determination of the product distribution (*e. g.*, by ^1H HMR spectral analysis).

18. (a) a = 18.09, b = 19.29, c = 10.55 Å, β = 95.6° (Z = 8); all *l*-odd reflections were ignored and a subcell was chosen with c' = c/2, space group $P2_1/n$, Z = 4; (b) a = 11.557 (5), b = 19.101 (8), c = 9.910 (3) Å, β = 115.37 (3)°, space group $P2_1/c$, Z = 4, R = 0.06 for 1349 observed intensities.

19. The methyl resonance in the ^1H NMR of compound 37 (our structure 9) reported in reference 7 should be corrected from 1.3 to 1.13 δ (M. J. Miller, private communication).

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