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SYNTHESES OF METHYL N-BENZOYLACOSAMINIDE AND METHYL N-(BENZYLOXYOXALYL)-DAUNOSAMINIDE FROM (S)-ETHYL 3-HYDROXYBUTYRATE

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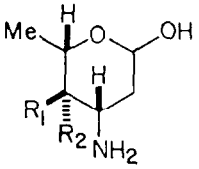
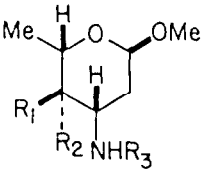
Abstract. A formal total synthesis of acosamine (**1**) and the preparation of N-acylated daunosamine derivative **4** from a common intermediate (**13**) is described.

Acosamine (**1**)[2] and daunosamine (**2**)[3] are 2,3,6-trideoxyaminohexoses found as structural subunits of glycosidic and polysaccharide antibiotics. These aminosaccharides have been the objectives of numerous synthetic studies, largely because of their appearance as components of anthracycline antibiotics and derivatives thereof.[4] This letter describes enantioselective syntheses of methyl N-benzoylacosaminide (**3**) and methyl N-(benzyloxyoxalyl)daunosaminide (**4**) from (S)-ethyl 3-hydroxybutyrate (**5**).





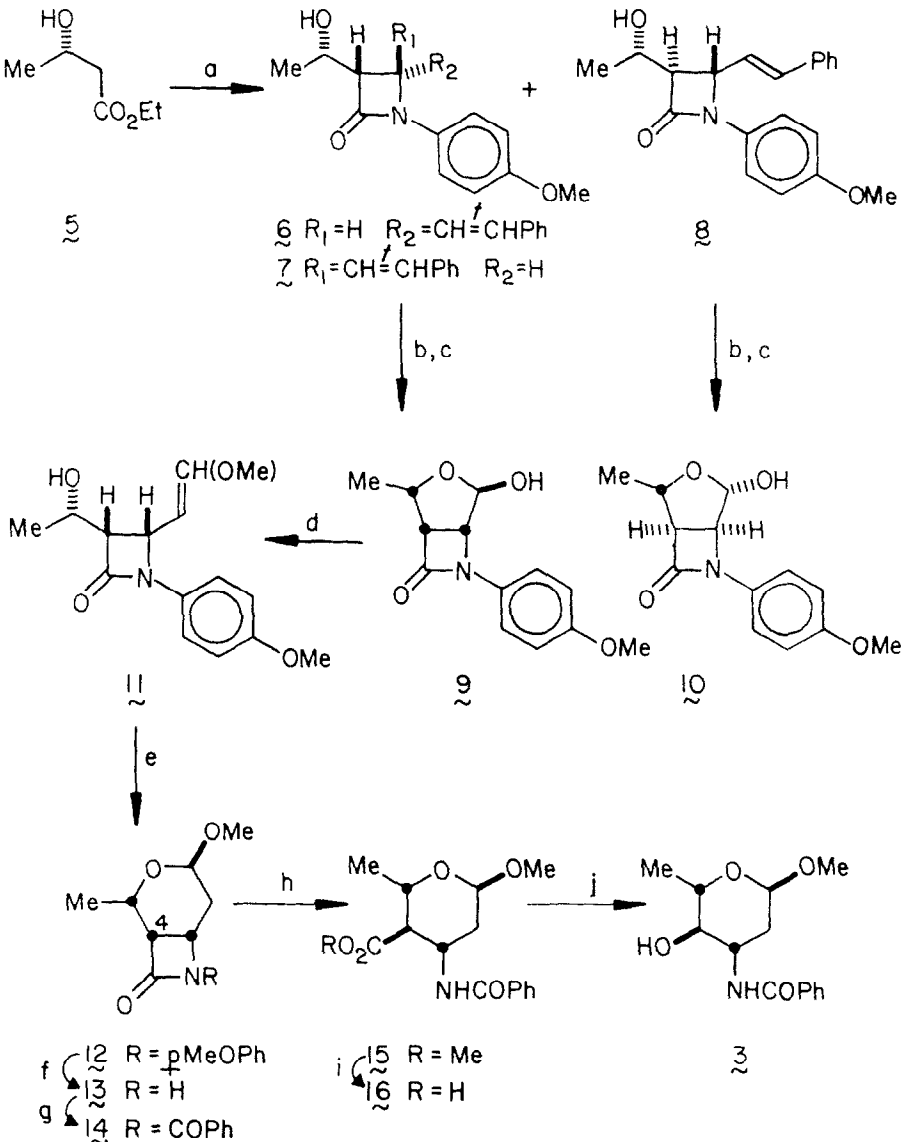
1 R_1 = OH, R_2 = H

2 R_1 = H, R_2 = OH

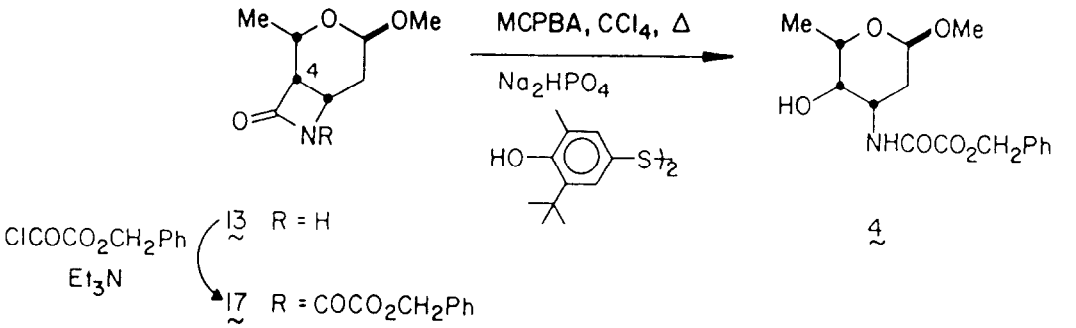
3 R_1 = OH, R_2 = H, R_3 = COPh

4 R_1 = H, R_2 = OH, R_3 = $COCO_2CH_2Ph$

Treatment of the dianion of **5** with N-(p-methoxyphenyl)cinnamaldimine provided a mixture of β-lactams **6-8** in 67% yield as previously reported.[5] Sequential treatment of **6-8** with ozone (CH_2Cl_2, -78°C), dimethylsulfide, and 1,8-diazabicyclo[5.4.0]undecane (0.2 equiv) gave a separable mixture of hemiacetals **9** (68%, mp 174.5-175.5°C) and **10** (6%, mp 171-173°C). Independent experiments showed that ozonolysis of **6** led directly to **9**. On the other hand, ozonolysis of **7** and **8** gave trans aldehydes which isomerized to **9** and **10**, respectively, upon treatment with 1,8-diazabicyclo[5.4.0]undecane. Treatment of **9** with lithium diisopropylamide (1.0 equiv) and excess (methoxymethylidine)triphenylphosphorane (4.0 equiv)[6] gave enol ether **11** (85%, mp 189-190°C) which was converted to tetrahydropyran **12** (98%, mp 128-129°C) upon treatment with acidic Dowex-50 in methanol. Ceric ammonium nitrate oxidation of **12** afforded **13** (mp 137-141°C) in 78% yield.[7]



(a) LDA (2 equiv), THF; PhCH=CHCH=N-⟨⟩-OMe (b) O_3, CH_2Cl_2; Me_2S (c) DBU, CH_2Cl_2, (d) LDA; Ph_3P=CHOMe (e) Dowex-50 ($H^{\oplus}$), MeOH (f) CAN, CH_3CN, H_2O (g) PhCOCl, CH_2Cl_2, Et_3N, 4-DMAP (h) DBU MeOH (i) LiOH, MeOH (j) MCPBA, DCC, CH_2Cl_2; Na_2HPO_4, Δ, CCl_4 ArSH; KOH, MeOH



To complete a synthesis of acosamine derivative **3** from **13**, it was necessary to insert an oxygen into the C_4-acyl bond with inversion of configuration. This was accomplished using a methanolysis-isomerization-carboxyinversion reaction sequence. Thus, acylation of **13** with benzoyl chloride (Et_3N, CH_2Cl_2, 4-DMAP) followed by treatment of the resulting imide **14** (98%, mp 87.5-88.5°C) with 1,8-diazabicyclo[5.4.0]undecane in methanol under reflux gave methyl ester **15** (71%, mp 153-155°C). Treatment of **15** with lithium hydroxide in methanol under reflux gave acid **16** [97%, mp 140 (dec)]. Finally acid **16** was coupled with m-chloroperbenzoic acid (DCC, CH_2Cl_2) and the resulting mixed peranhydride was warmed in carbon tetrachloride (2h, reflux) containing Na_2HPO_4 and 3-tert-butyl-4-hydroxy-5-methylphenyldisulfide[11]. Hydrolysis of the resulting crude material (CH_3OH, KOH) followed by chromatographic purification gave a 34% yield of **3** whose spectral data (IR, ^{1}H-NMR, MS) were consistent with the assigned structure [mp 185-189°C, lit[9] mp 204-206°C; $[\alpha]_D^{20}$ - 87.7° (C 0.69, CH_3OH), lit[9] $[\alpha]_D^{20}$ -92° (C 0.52, CH_3OH)].[10] Since **3** has previously been converted to **1**, this constitutes a total synthesis of acosamine.[9]

To convert **13** into **4** it was necessary to accomplish the formal oxygen insertion sequence with retention of configuration. Thus, acylation of **13** with benzyl chlorooxalate gave imide **17** (98%). Warming **17** with m-chloroperbenzoic acid (1.0 equiv) in carbon tetrachloride containing Na_2HPO_4 and 3-tert-butyl-4-hydroxy-5-methylphenyldisulfide gave daunosamine derivative **4** in 35% yield.[11,12]

The studies described above outline a new protocol for the preparation of 2,3,6-trideoxyaminohexoses from β-lactams. It is notable that intermediates of type **11** are suitably disposed for introduction of oxygen functionality at C(2). It is clear, however, that the procedures for introduction of the C(4)-hydroxyl group are less than satisfactory. Efforts to improve this process as well as alternate routes to the 7-aza-3-oxabicyclo[4.2.0]octan-8-one substructure of **13** will be presented in due course.

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6. For a relevant example see Hamada, Y.; Kawai, A.; Shioiri, T. Tetrahedron Lett. **1984**, 5409. A single geometrical isomer of **11** was obtained ($J_{CH=CH}$ = 10Hz).
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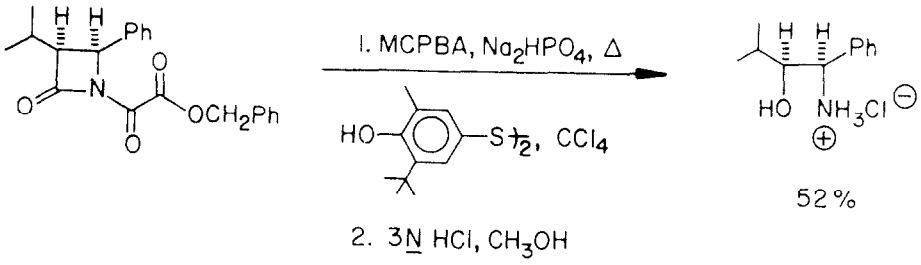
10. Spectral data (IR, MS, 200 MHz ^{1}H-NMR) of this material were in accord with the assigned structure. Recrystallization gave material which exhibited the following properties: mp 205-207°C; $[\alpha]_D^{20}$ -97.9 (C 0.73, CH_3OH).
11. For a similar transformation see Yamamoto, K.; Yoshioka, T.; Kato, Y.; Shibamoto, N.; Shimauchi, Y.; Ishikura, T. J. Antibiotics **1980**, 33, 796.
12. The β-lactam to vicinal aminoalcohol transformation has not been generalized but we can provide one additional example.



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