

A STEREOSELECTIVE SYNTHESIS OF N-BENZOYL L-DAUNOSAMINE

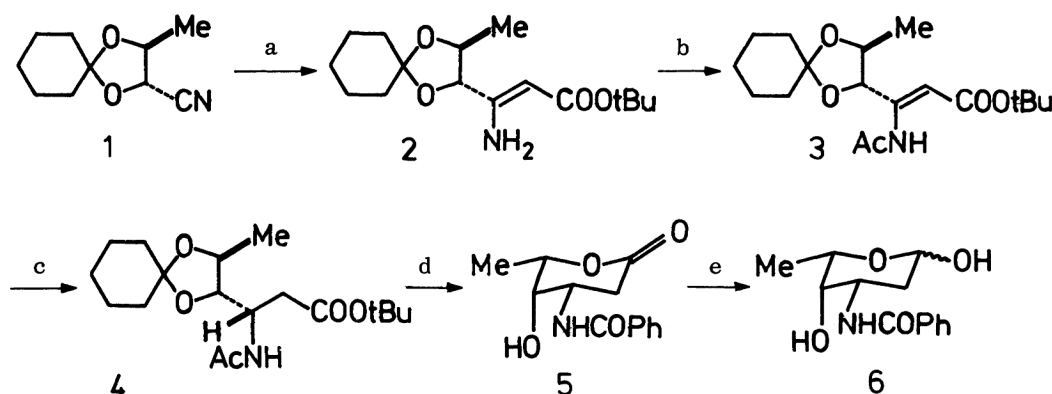
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Reaction of (2S,3S)-2,3-(cyclohexylidenedioxy)butanenitrile, derived from L(+)-tartrate or (S)-lactate, with the magnesium enolate of t-butyl acetate gave the corresponding (Z)- β -amino acrylate derivative, which was in turn transformed into N-benzoyl L-daunosamine by acetylation, stereoselective hydrogenation, acidic hydrolysis, benzoylation, lactonization, and finally by reduction.

Anthracycline antibiotics adriamycin, daunomycin, and carminomycin are highly effective against a wide range of tumors^{1,2)} and contain in common an amino sugar moiety, called L-daunosamine. For the synthesis of this amino sugar, extensive studies are concerned with exploitation of an efficient method recently.³⁾ Herein we add a new chiral synthesis of N-benzoyl L-daunosamine (**6**), employing the magnesium mediated coupling reaction⁴⁾ of t-butyl acetate with (2S,3S)-2,3-(cyclohexylidenedioxy)butanenitrile (**1**) and subsequent stereoselective hydrogenation.

The starting nitrile (**1**, $[\alpha]_D^{22} +11.6^\circ$ (c 2.5, CH₂Cl₂); $[\alpha]_D^{24} +15.5^\circ$ (c 8.8, CHCl₃)) was prepared from (2R,3S)-2,3-(cyclohexylidenedioxy)butanal^{3d,5)} by oxime-formation (NH₂OH·HCl, pyridine) and dehydration (CCl₄, PPh₃, Et₃N) in 83% yield⁶⁾ or, alternatively, by hydrocyanation of (S)-O-ethoxyethyl lactaldehyde followed by acetalization.⁶⁾ The nitrile **1** was allowed to react with the magnesium enolate of t-butyl acetate⁴⁾ in ether at 0 °C to give a β -amino acrylate derivative **2**⁷⁾ (mp 102-103 °C (hexane), $[\alpha]_D^{26} -62.5^\circ$ (c 5.2, CHCl₃)) in 99% yield. Acetylation of **2** gave the corresponding acetamide **3**⁷⁾ (59% yield) along with the (E)-isomer (19%).⁷⁾

a: CH₂=C(OtBu)OMgX, ether, 0 °Cb: Ac₂O, Py, 50 °C - 60 °Cc: H₂, PtO₂, 55 kg/cm², 70 °C, AcOEtd: (i) 2 mol/dm³ HCl, reflux, (ii) PhCOCl, sat aq NaHCO₃-acetone (5:2), r.t., (iii) 2 mol/dm³ HCle: iBu₂AlH, THF, -60 °C - -50 °C

Any conventional methods⁸⁾ for reduction of the β -acetamido-acrylate moiety of **3** turned out unpractical. After extensive studies, we found that catalytic hydrogenation under high pressure was feasible. The catalysts, conditions (solvent, temperature, hydrogen pressure, reaction time), the ratio of (3S)-3-acetamido ester **4** to its 3-epimer, and total yield were as follows: 5% Rh/C, tetrahydrofuran (THF), 55 °C, 60 kg/cm², 14 h, 1:2, 90%; 5% Rh/C, THF-AcOH (40:1), 55 °C, 60 kg/cm², 2.5 d, 2:3, 68%; 5% Pd/Al₂O₃, AcOEt, 55 °C, 60 kg/cm², 14 h, 1:2, quantitative; PtO₂, AcOEt, 55 °C, 1 kg/cm², 3.5 d, 3:2, 31%; PtO₂, AcOEt, 70 °C, 55 kg/cm², 1 d, 5.1:1, 98%. Thus, the reduction of **3** was carried out under the last conditions, and **4**⁷⁾ was separated by TLC as a viscous oil (82% yield), $[\alpha]_D^{20}$ -4.8° (c 1.47, CHCl₃). The C(3) epimer of **4** also was isolated in 16% yield.

Hydrolysis of **4** with hydrochloric acid, benzoylation under Schotten-Baumann conditions, and final lactonization with hydrochloric acid gave the δ -lactone **5**⁷⁾ (mp 138-140 °C, $[\alpha]_D^{20}$ -20.5° (c 0.39, EtOH); lit,^{3a)} mp 125-127 °C, $[\alpha]_D^{20}$ -15.8° (c 1, EtOH)) in 93% yield. The discrepancy of the physical data may be ascribed to a facile γ -lactone $\rightleftharpoons$ δ -lactone transformation. We found that the primary product of the lactonization was the γ -lactone (IR 1780 cm⁻¹) which gradually isomerized to **5** (IR 1740 cm⁻¹). Reduction of **5** with diisobutylaluminum hydride gave N-benzoyl L-daunosamine (**6**) in 94% yield, mp 153-155 °C (ether), $[\alpha]_D^{20}$ -109° (c 0.1, EtOH, after 3 h), consistent with the literature values,^{3c)} mp 152 °C, $[\alpha]_D^{20}$ -108° (c 0.5, EtOH, equilibrium).

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