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A STEREOSELECTIVE SYNTHESIS OF N-BENZOYL L-DAUNOSAMINE

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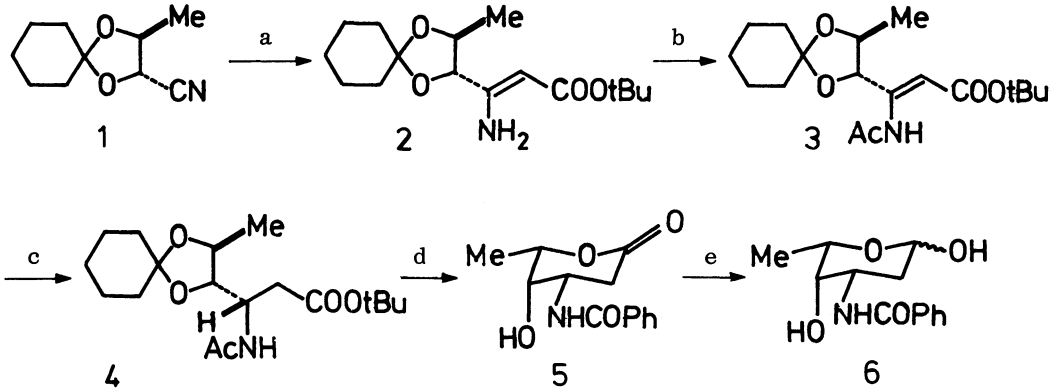
Reaction of (2S,3S)-2,3-(cyclohexylidenedioxy)butanenitrile, derived from L(+)-tartrate or (S)-lactate, with the magnesium enolate of t-butyl acetate gave the corresponding (Z)-β-amino acrylate derivative, which was in turn transformed into N-benzoyl L-daunosamine by acetylation, stereoselective hydrogenation, 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 reaction[4] 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° (c 2.5, CH_2Cl_2); $[\alpha]_D^{24}$ +15.5° (c 8.8, $CHCl_3$)) was prepared from (2R,3S)-2,3-(cyclohexylidenedioxy)butanal[3d,5] by oxime-formation ($NH_2OH \cdot HCl$, pyridine) and dehydration (CCl_4, PPh_3, Et_3N) in 83% yield[6] 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 acetate[4] in ether at 0 °C to give a β-amino acrylate derivative **2**[7] (mp 102-103 °C (hexane), $[\alpha]_D^{26}$ -62.5° (c 5.2, $CHCl_3$)) in 99% yield. Acetylation of **2** gave the corresponding acetamide **3**[7] (59% yield) along with the (E)-isomer (19%).[7]



a: CH_2=C(OtBu)OMgX, ether, 0 °C
b: Ac_2O, Py, 50 °C - 60 °C
c: H_2, PtO_2, 55 kg/cm^2, 70 °C, AcOEt
d: (i) 2 mol/dm^3 HCl, reflux, (ii) PhCOCl, sat aq $NaHCO_3$-acetone (5:2), r.t., (iii) 2 mol/dm^3 HCl
e: iBu_2AlH, THF, -60 °C - -50 °C

Any conventional methods[8] 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/cm^2, 14 h, 1:2, 90%; 5% Rh/C, THF-AcOH (40:1), 55 °C, 60 kg/cm^2, 2.5 d, 2:3, 68%; 5% Pd/Al_2O_3, AcOEt, 55 °C, 60 kg/cm^2, 14 h, 1:2, quantitative; PtO_2, AcOEt, 55 °C, 1 kg/cm^2, 3.5 d, 3:2, 31%; PtO_2, AcOEt, 70 °C, 55 kg/cm^2, 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, $CHCl_3$). 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 ⟶ 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 diisobutylaluminium 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).

References

1) F. Arcamone, "Daunomycin and Related Antibiotics," in "Topics in Antibiotic Chemistry," ed by P. G. Sammes, Ellis Horwood Ltd., Chichester (1978), Vol 2.
2) S. Terashima, J. Synth. Org. Chem. Jpn., 40, 20 (1982).
3) a) G. Fronza, C. Fuganti, and P. Grasselli, J. Chem. Soc., Chem. Commun., 1980, 442; b) P. M. Wovkulich and M. R. Uskokovic, J. Am. Chem. Soc., 103, 3956 (1981) and references cited therein. c) C. Fuganti, P. Grasselli, and G. Pedrocchi-Fantoni, J. Org. Chem., 48, 909 (1983); d) T. Mukaiyama, Y. Goto, and S. Shoda, Chem. Lett., 1983, 671; e) P. DeShong and J. M. Leginus, J. Am. Chem. Soc., 105, 1686 (1983); f) A. Bargiotti, G. Cassinelli, S. Penco, A. Vigevani, and F. Arcamone, Carbohydr. Res., 100, 273 (1982); g) I. Dyong, H. Friege, and T. zu Höne, Chem. Ber., 115, 256 (1982).
4) T. Hiyama and K. Kobayashi, Tetrahedron Lett., 23, 1597 (1982).
5) G. Fronza, C. Fuganti, P. Grasselli, and G. Marioni, Tetrahedron Lett., 1979, 3883; M. Uemura, K. Shimada, T. Tokuyama, and J. W. Daly, ibid., 23, 4369 (1982).
6) T. Hiyama, K. Nishide, and K. Kobayashi, Tetrahedron Lett., in press.
7) The compound was characterized spectrometrically and analytically.
8) M. Slopianka and A. Gossaur, Ann. Chem., 1981, 2258; J. D. Rozzell, Tetrahedron Lett., 23, 1767 (1982); M. Furukawa, T. Okawara, Y. Noguchi, and Y. Terawaki, Chem. Pharm. Bull., 27, 2223 (1979); K. Achiwa and T. Soga, Tetrahedron Lett., 1978, 1119.

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