BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 52 (9), 2731—2732 (1979)

A Stereoselective Total Synthesis of Methyl α-DL-Daunosaminide

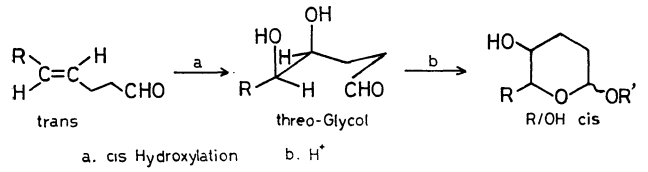
Isao IWATAKI, Yasuo NAKAMURA, Koji TAKAHASHI, and Takeshi MATSUMOTO*

Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo 060

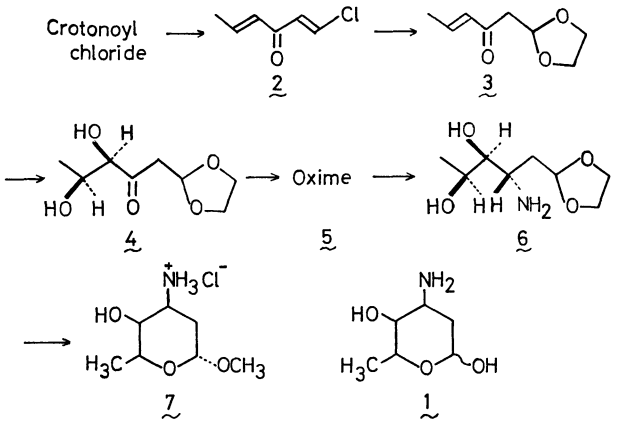
(Received December 4, 1978)

Synopsis. Starting from crotonoyl chloride, methyl α-DL-daunosaminide was synthesized through the *cis* hydroxylation of a key intermediate, 1,1-ethylenedioxy-4-hexen-3-one, followed by oximation, catalytic hydrogenation (Pt, AcOH), and treatment with MeOH/HCl.

Daunosamine (**1**) is the amino sugar moiety of the two antibiotics daunomycin[1] and adriamycin.[2] Both of these antibiotics, but adriamycin in particular, have attracted attention as promising anticancer agents. A number of syntheses of daunosamine have previously been described.[3-7] However, all these syntheses were carried out, starting from naturally occurring hexoses, through rather lengthy routes. In previous papers[8] we reported the synthesis of some deoxyhexoses from unnatural compounds through 2-ethoxy-6-methyl-3,4-2*H*-dihydropyran as a key intermediate. We wish to report here a new route to daunosamine as racemic methyl glycoside hydrochloride, starting from crotonoyl chloride and vinyl chloride.[9] The success of the present synthesis suggests the possibility of extending the new route as a general synthetic method for 2,6-dideoxyhexoses.



First, crotonoyl chloride was converted, by means of the Friedel-Crafts reaction with vinyl chloride, to 1-chloro-1,4-hexadien-3-one (**2**). α-Keto acetal, **3**, was obtained by the reaction of **2** with 1,2-ethanediol in the presence of potassium carbonate at −10 °C. The *cis* hydroxylation ($KMnO_4$, acetone, −40 °C) of **3** afforded dihydroxy derivative, **4**, which was transformed to the oxime, **5**, and was then hydrogenated over a Pt catalyst under acidic conditions (AcOH), according to the Roth method.[10] The amino diol, **6**, thus obtained was treated with methanolic hydrogen chloride to give methyl pyranoside, **7**. The 3-epimer of **7** was not isolated. The following NMR data (pyridine-d_5) indicate the **7** stereostructure. The signals around δ 2.45 ppm (q, 2H, J=9 and 3 Hz) are attributable to the C_2 protons. They are practically magnetically equivalent (the AA′ part of the AA′XY system) and couple to the anomeric proton H_1 (δ 4.78, t) with J=3 Hz. This establishes the equatorial configuration of H_1, therefore, **7** is the α-anomer. The coupling constant $(J_{2a,3a}+J_{2e,3a})/2=9$ Hz[11] was confirmed by the double-resonance technique, showing the presence of the axial proton at C_3. The broad triplet (1H, J=3 Hz) at δ 4.43 indicates the equatorial configuration of H_4, and $J_{4,5}$=3 Hz was acertained by the spin decoupling. Since the C_4–C_5 moiety has the *threo* configuration, the methyl group at C_5 is equatorial.



Experimental

All the melting points and boiling points are uncorrected. The IR spectra were recorded on a JASCO IR-S spectrophotometer. The NMR spectra were measured on a Varian A-60 instrument. For column chromatography, Merck silica gel (0.08 mm) was used, while for TLC, Wakogel B-5 was utilized. The starting material, 1-chloro-1,4-hexadien-3-one (**2**), was prepared by a modification of the Kochetkov method,[12] using vinyl chloride instead of acetylene, in a yield of 53%.

*1,1-Ethylenedioxy-4-hexen-3-one (**3**).* Into a suspension of potassium carbonate (65 g, 0.47 mol) in a mixture of water (20 cm³) and 1,2-ethanediol (100 cm³, 1.8 mol), a solution of **2** (50 g, 0.38 mol) in tetrahydrofuran (50 cm³) was stirred at −10 °C. The mixture was stirred for a further 3 h at this temperature and then for 24 h at room temperature. The reaction mixture was poured into water and extracted with petroleum ether, and the extract was dried (Na_2SO_4). The subsequent evaporation of the solvent and distillation (78—82 °C/2 mmHg**) of the residue gave **3** as a colorless liquid (8.5 g, 14%); 2,4-dinitrophenylhydrazone mp 121 °C. Found: C, 61.42; H, 7.71%. Calcd for $C_8H_{12}O_3$: C, 61.53; H, 7.69%.

*1,1-Ethylenedioxy-4,5-dihydroxyhexan-3-one (**4**).* The acetal **3** (10 g, 0.064 mol) in acetone (100 cm³) was cooled to −40 °C, and then, to the solution a cold solution of potassium permanganate (12 g, 0.075 mol) in water (400 cm³) and acetone (200 cm³) was added. After the manganese dioxide formed had been filtered off, the solvent was distilled off, the residue was poured into water and extracted with ethyl acetate, and the organic phase was dried. The removal of the solvent *in vacuo* gave a colorless oil, which was subsequently purified by column chromatography on silica gel (150 g), with ethyl acetate–benzene (1 : 1) as an eluent, to give **4** (4.3 g, 35%). Found: C, 50.52; H, 7.38%. Calcd for $C_8H_{14}O_5$: C, 50.50; H, 7.73%. NMR ($CDCl_3$) δ=1.2 (3H, d, J=7 Hz), 3.2 (2H, d, J=5 Hz), 3.6 (4H, m), 4.2—4.44 (2H, m),

** 1 mmHg≈133.322 Pa.

5.4 (1H, t, J=5 Hz) and 5.9 ppm (2H, s); IR (neat) 3440 (OH) and 1718 cm^{-1} (C=O).

*1,1-Ethylenedioxy-3-hydroxyimino-4,5-hexanediol (**5**).* To a mixture of sodium ethoxide (0.5 g, 0.0073 mol) and hydroxylamine hydrochloride (0.7 g, 0.01 mol) in 50 cm^3 of ethanol, **4** (2.3 g, 0.012 mol) was added at room temperature, after which the soln was stirred for 24 h. After the solvent had been removed *in vacuo*, the oxime, **5**, was extracted with ether and the solvent was evaporated to give a colorless oil (1.4 g, 56%). This was used in the subsequent reaction without purification. IR (neat) 3120 and 1030 cm^{-1} (N–OH).

*1,1-Erhylenedioxy-3-amino-4,5-hexanediol (**6**).* The oxime, **5** (2 g, 0.0098 mol), was hydrogenated over the Adams catalyst (0.2 g of PtO_2) in 30 cm^3 of acetic acid at atmospheric pressure for 12 h at room temperature.[9] Then the catalyst was filtered off, and the solvent was removed *in vacuo*. The residue was dissolved in a mixed solvent of water (1.2 dm^3) and methanol (400 cm^3), and the solution was passed through Amberlite IR-400 to remove the residual acetic acid. The subsequent evaporation of the solvent under reduced pressure left 1.5 g (81%) of crystalline **6**, which was recrystallized from 1-propanol–ether as colorless crystals. Mp 111—112 °C. Found: C, 50.06; H, 8.75; N, 7.63%. Calcd for $C_8H_{17}NO_4$: C, 50.25; H, 8.96; N, 7.35%. IR (Nujol) 1705 (NH) and 1135 cm^{-1} (acetal).

*Methyl α-DL-Daunosaminide Hydrochloride (**7**).* The amine, **6** (0.3 g, 0.016 mol), was dissolved in 2%-methanolic hydrogen chloride (9 cm^3), after which the soln was stirred for 24 h at 40 °C under a N_2 stream. The reaction mixture was then cooled, and the excess hydrochloric acid was neutralized with sodium hydrogen carbonate. After the evaporation of the filtered solution *in vacuo*, the residue was extracted with ethanol. The solvent was distilled off, and the residual solid was recrystallized from 1-propanol to afford 0.28 g (84%) of colorless crystals. Mp 161—163 °C. Found: C, 42.80; N, 7.84; N, 7.14%. Calcd for $C_7H_{16}NO_3Cl$: C, 42.53; H, 8.10; N, 7.09%. NMR (pyridine-d_5) δ=4.78 (1H, t, J=3 Hz), 4.43 (1H, br s), 4.32 (1H, m), 3.87 (1H, dq, J=1.5 and 6 Hz), 3.20 (3H, s), 2.45 (2H, q, J=9 and 3 Hz) and 1.39 (3H, d, J=6 Hz); IR (Nujol) 3300 (OH), 1620, 1580, 1510 (NH_3^+), 1200, 1130, 1080, 1060, and 980 cm^{-1}.

References

1) E. Arcamone, G. Cassinelli, P. Orezzi, G. Franceschi, and R. Mondelli, *J. Am. Chem. Soc.*, **86**, 5335 (1964).

2) F. Arcamone, G. Franceschi, S. Penco, and A. Selva, *Tetrahedron Lett.*, **1969**, 1007.

3) A. C. Richardson, *Carbohydr. Res.*, **4**, 422 (1967); *J. Chem. Soc., Chem. Commun.*, **1965**, 627.

4) H. H. Baer, K. Capek, and M. C. Cook, *Can. J. Chem.*, **47**, 89 (1969).

5) J. P. Marsh, C. W. Mosher, E. M. Acton, and L. Goodman, *Chem. Commun.*, **1967**, 973.

6) D. Horton and W. Weckerie, *Carbohydr. Res.*, **44**, 227 (1975).

7) T. E. Walker and R. Baker, *Carbohydr. Res.*, **64**, 266 (1978).

8) S. Yasuda, T. Ogasawara, S. Kawabata, I. Iwataki, and T. Matsumoto, *Tetrahedron*, **29**, 4087 (1973).

9) A similar principle of synthesis was applied to the total synthesis of the mushroom toxin muscarine: T. Matsumoto, A Ichihara, and N. Ito, *Tetrahedron*, **25**, 5889 (1969). A 6-step total synthesis of a DL-daunosamine derivative from 3-buten-2-ol has recently been reported: I. Dyong and R. Wiemann, *Angew. Chem.*, **90**, 682 (1978).

10) W. Roth, W. Pigman, and I. Danishefsky, *Tetrahedron*, **20**, 1675 (1964).

11) $J_{2a,e}$=13 Hz and $J_{2e,3}$=5 Hz are shown for a compound related to daunosamine. See Ref. 6. Practically identical NMR data (100 MHz, pyridine-d_5) have been reported for **7**: F. Arcamone, G. Cassenelli, G. Franceschi, R. Mondelli, P. Orezzi, and S. Penco, *Gazz. Chim. Ital.*, **100**, 949 (1970).

12) N. K. Kochetkov, A. Ya. Khorlin, B. P. Gottikh, and A. N. Nesmeyanov, *Izv. Akad. Nauk SSSR Otdel. Khim. Nauk*, **1956**, 1053.