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STEREOSELECTIVE SYNTHESIS OF L-DAUNOSAMINE

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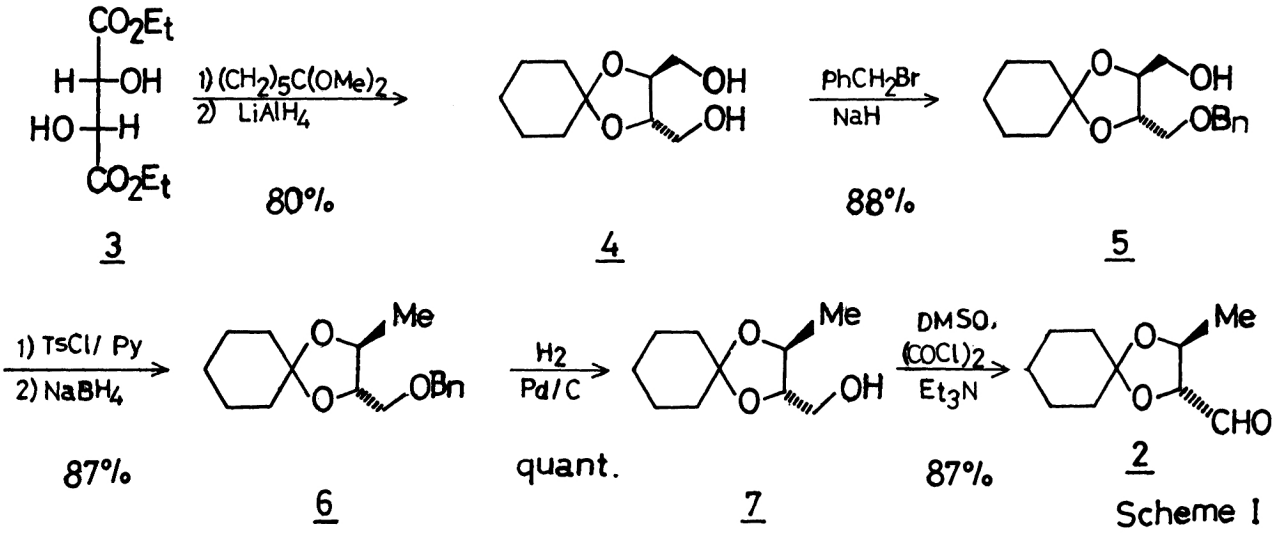
L-Daunosamine was conveniently synthesized from β-amino amide 1 obtained by the stereoselective addition of α-lithio N,N-dimethylacetamide to the imine of 2,3-O-cyclohexylidene-4-deoxy-L-threose in the presennce of zinc halide.

3-Amino-3-deoxy-hexoses have been widely mentioned as sugar moieties of biologically active substances. L-Daunosamine (3-amino-2,3,6-trideoxy-L-lyxo-hexose) in particular is important as the carbohydrate constituent of the anthracycline antibiotics such as daunorubicin and adriamycin having strong antitumor activity. Of several methods developed[1] for the syntheses of L-daunosamine, almost all of the chiral syntheses are based on conversion of natural carbohydrates such as D-mannose and L-rhamnose and D-glucose through multistep sequences.

In this communication, we wish to describe a chiral and efficient synthesis of L-daunosamine from 2,3-O-cyclohexylidene-4-deoxy-L-threose (2), a building block for the synthesis of L-sugars, prepared by a similar procedure previously shown in the case of 4-O-benzyl-2,3-O-isopropylidene-L-threose[2] from a non-carbohydrate starting material L-tartaric acid. The key step of the total sequence is a new stereoselective carbon-carbon bond forming reaction between α-lithio N,N-dimethylacetamide and the imine of 2,3-O-cyclohexylidene-4-deoxy-L-threose (2), prepared in 53% yield from diethyl L-(+)-tartrate (3) shown in Scheme I.

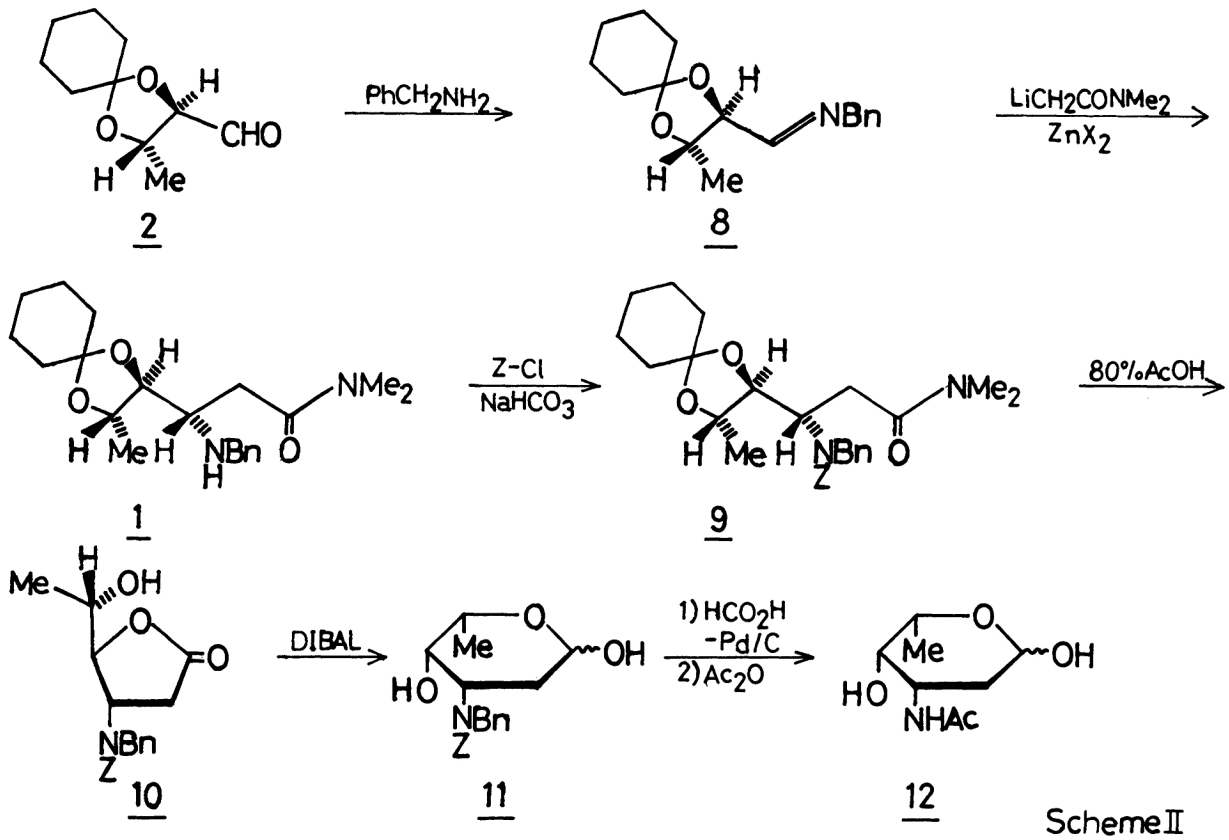


Scheme I

In the first place, the addition of α-lithio N,N-dimethylacetamide to the imine 8 was tried and it was found that the effective addition took place to afford a mixture of two diastereomers of β-amino amide 1 in good yield: the reaction of α-lithio N,N-dimethylacetamide with the imine 8 in THF at 0°C, followed by the benzyloxycarbonylation of the amino group afforded the corresponding β-amino amide in 72% yield. In this reaction, the amide 9[6] of lyxo configuration was isolated as a minor product[3] (diastereomer ratio 1 : 2).

Further, it was found that the coexistance of metal salt causes a significant change in the stereoselectivity. That is, when the same reaction was carried out in the prensence of zinc halide, the reaction proceeded stereoselectively to afford the amide 9 predominantly. Especially in the presence of $ZnBr_2$ almost pure 9 was obtained.

The pure amide 9 was converted to N-acetyl-L-daunosamine 12 by the following procedure. First, 9 was treated with 80% acetic acid-water to afford the lactone 10, which in turn was reduced to the hemiacetal 11 by diisobutylaluminiumhydride (DIBAL). This amino sugar 11 was converted to N-acetyl-L-daunosamine 12 according to the conventional procedure, and L-daunosamine was identified by NMR spectra and specific rotation.



Scheme II

A typical procedure for the preparation of N-acetyl daunosamine is as follows: To a solution of benzylamine (4.41 mmol) in ether at 0°C was added ethereal solution of the aldehyde 2 (4.33 mmol), and the reaction mixture was stirred for 30 min. Then the solvent was evaporated to dryness and the resulting residue, the

crude imine 8, was used in the next step without purification. To a THF solution of α-lithio N,N-dimethylacetamide (4.76 mmol) prepared by conventional manner was added well dried zinc bromide (4.76 mmol) at 0°C and the resulting solution was stirred for 10 min. Then, to this solution was added the THF solution of imine 8 and the reaction mixture was kept standing for 2.5 h at 0°C. The reaction was quenched by the addition of a 5% $NaHCO_3$ solution, followed by subsequent extraction, and the organic layer was concentrated in vacuo to give 1 as a sticky oil, which was in turn treated with benzyloxycarbonyl chloride (4.83 mmol) and $NaHCO_3$ (5.24 mmol) in ether-water (3 : 1) for 30 min at 0°C. The subsequent extractive work-up and the purification by the flash column chromatography (silica gel, ethyl acetate : hexane, 1 : 1) afforded the pure 9 in 50% yield based on 2.

A solution of 9 (1.46 mmol) in acetic acid (8 ml) and water (2 ml) was refluxed for 8 h. After the solution had been cooled, satd. $NaHCO_3$ (140 ml) was added and extracted with dichloromethane. The extract was dried and evaporated, and the residue was purified by the flash column chromatography (silica gel, ethyl acetate: hexane, 1 : 2) to give the lactone 10 in 90% yield. The lactone 10 was reduced by DIBAL[4] to give the amino sugar 11 in 67% yield. The benzyloxycarbonyl group and benzyl group of 11 were removed by catalytic transfer hydrogenation and the resulting compound was acetylated to afford N-acetyl-L-daunosamine 12 [mp 137-139°C; $[\alpha]_D^{21}$-103° (equil., c 1.01, H_2O)/lit.[1b] $[\alpha]_D^{23}$-100° (equil., c 0.55, H_2O)] in 70% yield from 11.[5]

It should be noted that, according to the present method, L-daunosamine is conveniently prepared from the intermediate β-amino amide 1 by stereoselective nucleophilic addition of α-lithio N,N-dimethylacetamide to the imine of 2 in the presence of zinc halide.

We wish to express our hearty thanks to Sumitomo Chemical Co., Ltd. for the kind gift of the authentic sample of N-trifluoroacetyl-L-daunosamine, and to Dr. T. Hiyama for the NMR data of methyl N-acetyl-α-L-daunosaminide.

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2) T. Mukaiyama, K. Suzuki, and T. Yamada, Chem. Lett., 1982, 929.
3) The other product was determined to be a diastereomer of the amide 9 by ^1H-

and ^{13}C-NMR spectra.

4) T. Mukaiyama, T. Miwa, and T. Nakatsuka, Chem. Lett., 1982, 145.

5) N-Trifluoroacetyl-L-daunosamine similarly converted from 11 was also identified with an authentic sample by ^{1}H- and ^{13}C-NMR spectra.

6) Physical data of 9 is as follows.
^{1}H-NMR ($CDCl_3$) δ 1.02 (d, J = 6 Hz, 3 H), 1.47 (s, 10 H), 2.4-3.0 (m, 2 H), 2.8 (s, 6 H), 3.2-4.9 (m, 5 H), 5.18 (s, 2 H), 6.7-7.3 (m, 10 H);
^{13}C-NMR ($CDCl_3$) δ 18.4, 23.8, 24.0, 25.2, 33.3, 35.4, 36.4, 36.8, 37.0, 50.6, 67.4, 74.7, 82.1, 108.6, 127.3, 128.1, 128.3, 128.4, 136.6, 138.7, 152.4, 170.5; IR(neat) 1641, 1692 cm^{-1}.

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