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NEW METHODS AND REAGENTS IN ORGANIC SYNTHESIS. 49.[1] A HIGHLY EFFICIENT STEREOSELECTIVE SYNTHESIS OF L-DAUNOSAMINE THROUGH DIRECT C-ACYLATION USING DIPHENYL PHOSPHORAZIDATE (DPPA)[2]

Yasumasa Hamada,* Akiyoshi Kawai, and Takayuki Shioiri*

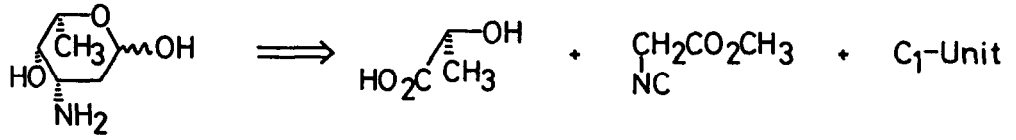
Faculty of Pharmaceutical Sciences, Nagoya City University
Tanabe-dori, Mizuho-ku, Nagoya 467, JAPAN

L-Daunosamine, the carbohydrate component of a group of important anticancer anthracycline antibiotics, has been efficiently prepared from L-lactic acid in a completely stereoselective manner through direct C-acylation using diphenyl phosphorazidate (DPPA).

L-Daunosamine (1, 3-amino-2,3,6-trideoxy-L-lyxo-hexose)[3] is the carbohydrate component of a group of important anticancer anthracycline antibiotics such as adriamycin, daunomycin, and carminomycin. Because of the scarcity of L-daunosamine and the importance of L-daunosamine part on therapeutic activities of natural anthracyclines and their analogs,[3] there has been considerable interest in daunosamine synthesis and a number of research groups have devised ingenious synthetic methods.[3,4,5] However, their efficiency is usually moderate and the practicality seems to be rather small.

Recently, we have found[6] that diphenyl phosphorazidate[1,7] (DPPA, $(PhO)_2P(O)N_3$) can be used efficiently for the direct C-acylation of methyl isocyanoacetate with carboxylic acids to give 4-methoxycarbonyloxazoles, and succeeded[8] a facile synthesis of prumycin, a 2,4-diamino sugar antibiotic, by the use of the direct C-acylation procedure with DPPA. Application of the reaction sequence similar to the prumycin synthesis has now culminated a new highly efficient synthesis of L-daunosamine (1) in a completely stereoselective manner.[9]

Retrosynthetic analysis has revealed that L-daunosamine (1) can be synthesized from L-lactic acid (2), methyl isocyanoacetate (3), and a C_1-unit:



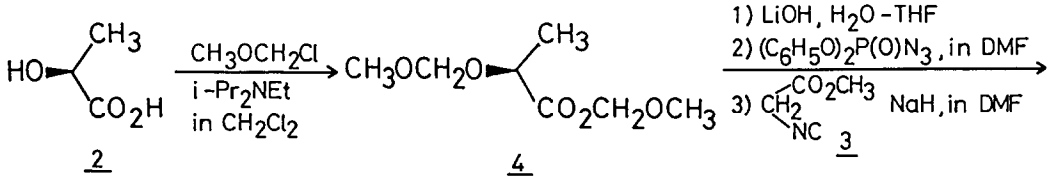
1 2 3

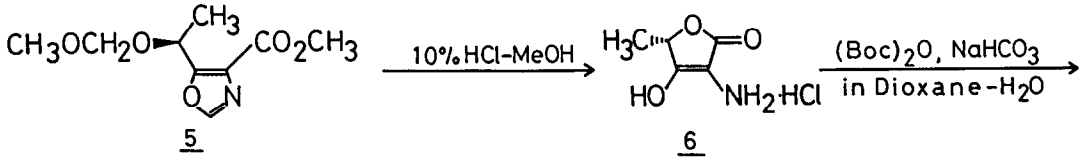
Thus, commercially available L-lactic acid (2) was treated with an excess of chloromethyl methyl ether in the presence of N,N-diisopropylethylamine (CH_2Cl_2; 0°C, 1hr; room temp., 22hr) to give the bis-methoxymethyl derivative **4**[10] in 91% yield as a colorless oil, $[\alpha]_D^{21}$ -77.7° (c=1, MeOH). Alkaline hydrolysis of **4** with lithium hydroxide in tetrahydrofuran-water (2:1) (0°C, 10min; room temp., 40min) quantitatively afforded lithium L-methoxymethyllactate. The crude lithium salt was treated with DPPA in dimethylformamide under argon (0°C, 6hr), followed by the addition of the sodium salt of methyl isocyanoacetate[11] (3) at -10°C. The resulting reaction mixture was stirred at 0°C for 2hr, then at room temp. for 30hr, giving the oxazole **5** in 70% yield as a pale yellow oil, $[\alpha]_D^{21}$ -21.9° (c=1, MeOH). The configurational homogeneity of **5** was ascertained by the NMR spectral study using the chiral shift reagent, Eu(facam)$_3$.

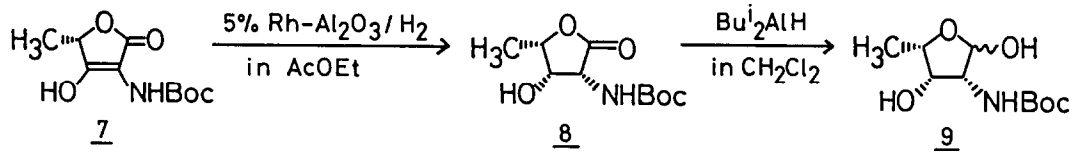
Treatment of **5** with 10% methanolic hydrogen chloride (room temp., 20hr; under argon) quantitatively afforded the amino reductone hydrochloride **6**, which was converted to its tert-butyloxycarbonyl (Boc) derivative **7**, mp 115-116°C, $[\alpha]_D^{21}$ -15.05° (c=1, MeOH), with di-tert-butyl dicarbonate (sodium bicarbonate in water-dioxane (1:1); 0°C, 1hr; room temp., 6hr). Completely stereoselective catalytic hydrogenation of **7** was achieved by the use of 5% rhodium-alumina catalyst in ethyl acetate (room temp., 36hr; 120 kg/cm^2) to give the lyxo-lactone **8**, mp 133.5-134.5°C, $[\alpha]_D^{21}$ -47.7° (c=1, MeOH), in 91% yield. Reduction of **8** with diisobutylaluminumhydride (CH_2Cl_2; -70°C, 6hr; under argon) afforded the lactol **9**, mp 84-85°C, $[\alpha]_D^{25}$ -17.5°→ -41.3° (c=1, MeOH), in 80% yield.

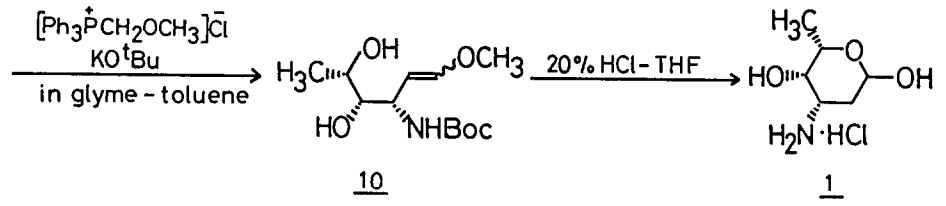
Introduction of the C_1-unit to **9** was carried out by the Wittig reaction of **9** with methoxymethylenetriphenylphosphorane[12] (glyme-toluene; -10°C, 10min; room temp., 40min; under argon), giving the methyl enol ether **10**, a colorless oil, $[\alpha]_D^{25}$ -10.2° (c=1.2, MeOH), in 56% yield. Final construction of L-daunosamine (**1**) was achieved by the treatment of **10** with 20% hydrochloric acid-tetrahydrofuran (1:1.7) (40-50°C, 10hr), giving **1** as its hydrochloride in 90% yield; mp 165-166°C (dec), $[\alpha]_D^{27}$ -68.76° (equil., c=1, 0.1N HCl). Synthetic L-daunosamine hydrochloride was completely identical with a sample, mp 168°C (dec), $[\alpha]_D^{27}$ -68.89° (equil., c=1, 0.1N HCl), derived from natural daunomycin[13] by IR, ^{1}H- and ^{13}C-NMR spectral comparisons.

It should be worthy of note that L-daunosamine can be efficiently and stereoselectively prepared from readily available non-carbohydrate starting material, L-lactic acid, in 9 steps with a good overall yield of 24%. The crucial parts of the above reaction sequence are (1) the direct C-acylation of methyl isocyanoacetate with the lithium salt of **4** using DPPA, (2) the completely stereoselective hydrogenation of **7**, and (3) the introduction of the C_1-unit to **9**. The method will promise the efficient construction of other carbohydrate systems, and its application to a stereoselective synthesis of a derivative of L-vancosamine, a carbohydrate component of antibiotics vancomycin and sporaviridin, will be reported in the following paper.[14]









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References and Notes

1) For Part 48, see Y. Hamada, K. Kohda, and T. Shioiri, *Tetrahedron Lett.*, submitted.

2) Presented in part at the Ninth International Congress of Heterocyclic Chemistry, Tokyo, Aug. 21-26, 1983, *Abstracts* p. 447; A. Kawai, Y. Hamada, and T. Shioiri, *Heterocycles*, 21, 776 (1984).

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5) cf. H. W. Pauls and B. Fraser-Reid, *J. Org. Chem.*, 48, 1392 (1983); T. Hiyama, K. Nishide, and K. Kobayashi, *Tetrahedron Lett.*, 25, 569 (1984).

6) Y. Hamada and T. Shioiri, *Tetrahedron Lett.*, 23, 235, 1226 (1982). cf. Y. Hamada, S. Morita, and T. Shioiri, *Heterocycles*, 17, 321 (1982).

7) For another recent use of DPPA, see S. Mori, T. Aoyama, and T. Shioiri, *Tetrahedron Lett.*, 25, 429 (1984).

8) Y. Hamada and T. Shioiri, *Tetrahedron Lett.*, 23, 1193 (1982).

9) Before the chiral synthesis of L-daunosamine (1), preliminary experiments have been done by the use of the racemic modification and DL- daunosamine has been efficiently prepared by the same reaction sequence.

10) All of the products gave satisfactory elemental and spectral analysis.

11) Prepared separately from methyl isocyanoacetate (3) and sodium hydride in dimethylformamide under argon.

12) Prepared from methoxymethyltriphenylphosphonium chloride with potassium tert-butoxide in glyme-toluene at -15°C under argon.

13) An authentic sample of L-daunosamine was prepared from natural daunomycin by its treatment with 0.2N hydrochloric acid (90-100°C, 1hr). See F. Arcamone, G. Franceschi, P. Orezzi, W. Barbieri, and R. Mondell, *J. Am. Chem. Soc.*, 86, 5334 (1964).

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