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A New Approach to L-Daunosamine and L-Acosamine from *t*-Butyl *S*-(+)-3-Hydroxybutanoate

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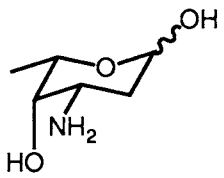
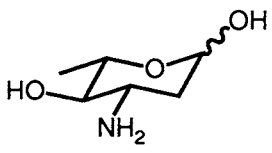
A concise synthesis of the *N*-acyl derivatives of L-daunosamine and L-acosamine is achieved using the highly stereoselective enolate-imine condensation of the lithium dianion of *t*-butyl *S*-(+)-3-hydroxybutanoate with *N*-acylaldimine.

A number of 2,3,6-trideoxy-3-aminopyranoses are found as glycosidic components of biologically active substances. In particular, L-daunosamine (**1**) has attracted considerable attention of synthetic chemists[1] because this is an essential sugar moiety of anthracycline antibiotics such as daunomycin and adriamycin which exhibit a potent antitumor activity against a broad range of tumor.[2] L-Acosamine (**2**) has also been an interesting synthetic target.[1] Replacement of L-daunosamine of the anthracycline antibiotics with L-acosamine resulted in reducing the cardiotoxicity but retaining the anticancer activity.[3] We recently reported that an enolate-imine condensation of the lithium dianion of *R*-(-)-3-hydroxybutanoate with the *N*-acylaldimines proceeded in a highly stereoselective manner with added lithium chloride.[4] We now describe an enantioselective synthesis of L-daunosamine and L-acosamine, via the enolate-imine condensation as a key step.[5]



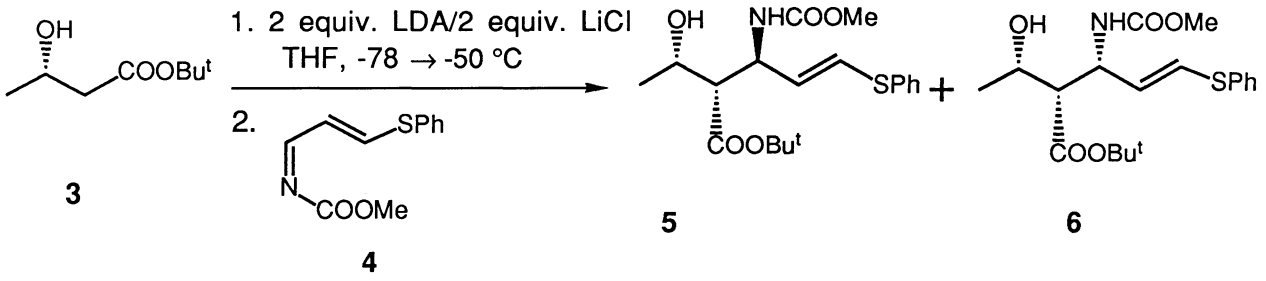
1 Daunosamine



2 Acosamine

t-Butyl *S*-(+)-3-hydroxybutanoate (**3**)[6] was treated with 2 equiv. of LDA in THF in the presence of 2 equiv. of lithium chloride at -78 °C, and, to this solution, a solution of the freshly prepared *N*-methoxycarbonylaldimine **4** in THF was slowly added over 1.5 h to give a mixture of

5[7] and **6** in a ratio of 96:4. The pure (syn, anti) isomer **5** was readily obtained by crystallization from ether-hexane in 85% yield. Treatment of **5** with hydrogen chloride in dichloromethane produced the cyclic hemithioacetal **7** as a 1:1 anomeric mixture in 71% yield, which was converted by treatment with silver nitrate in methanol into the cyclic acetal **8** in 92% yield. The ^{1}H NMR spectrum of **8** provides unambiguous support for stereochemistry of the three continuous chiral centers at the 3, 4, and 5 positions (H4: d 2.79, dd, J=5.1, 3.0 Hz), and for axial orientation of the anomeric methoxy group (H1: d 4.83, dd, J=1.1, 3.5 Hz).



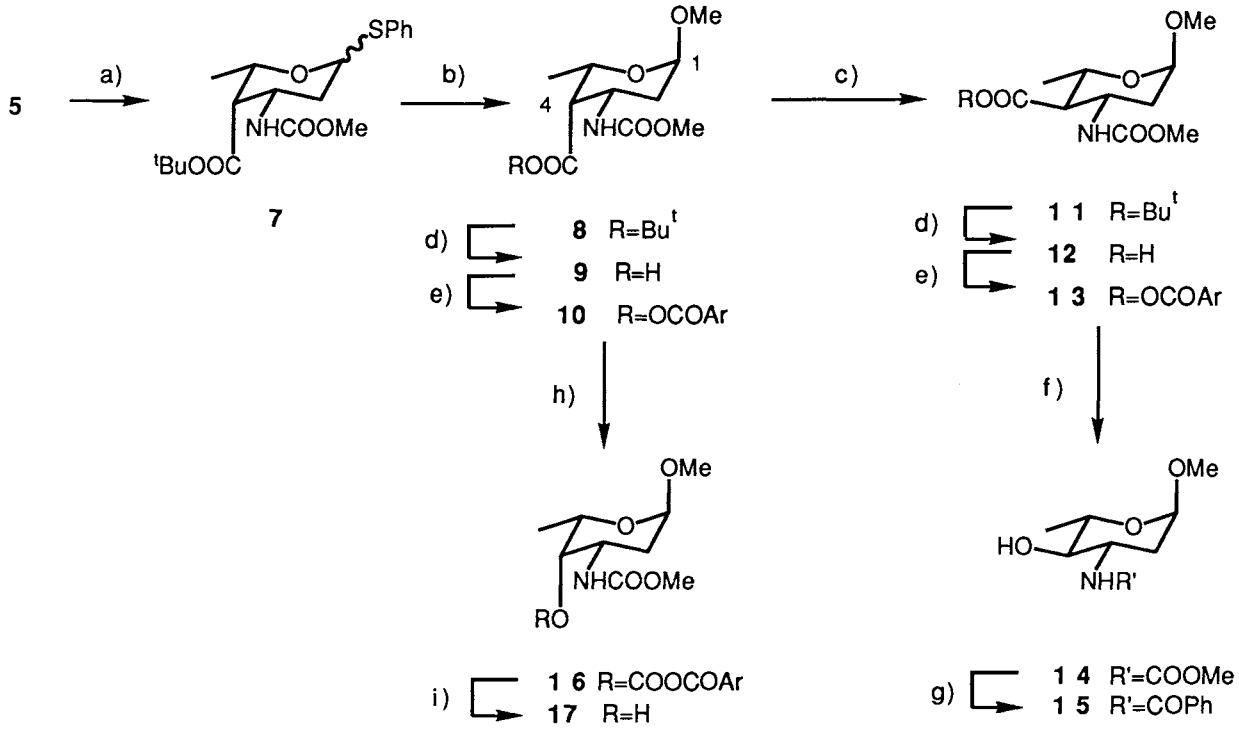
3 **4** **5** **6**

The compound **8** was treated with hydrogen chloride in dry methanol to give the free acid **9**, quantitatively. The C4 epimer **12** was also obtained in 96% yield by the base-induced (LiOH) inversion of the carboxy group of **8** followed by acid treatment.

The remaining step, conversion of the carboxy group into hydroxy functionality with retention of configuration, was established by a carboxy inversion reaction. The compounds **9** and **12** were coupled with *m*-chloroperbenzoic acid using dicyclohexylcarbodiimide in dichloromethane to afford the mixed-peranhydrides **10** and **13**, respectively. Refluxing of **13** in carbon tetrachloride for 3 h produced a mixture of **14** and its *m*-chlorobenzoyl derivative.[8] The mixture was hydrolyzed to give **14** in 37% overall yield from **12**, which could be converted on heating with lithium iodide in collidine followed by treatment with benzoyl chloride into the known methyl *N*-benzoyl-L-acosaminide **15** [$[\alpha]^{25}_D$ -99.4° (c 0.1, MeOH), lit[9] $[\alpha]^{20}_D$ -92° (c 0.53, MeOH)].

Attempt to convert **9** into L-daunosamine derivative under the same conditions was unsuccessful, because the intermediary mixed anhydride **16** was decomposed on prolonged heating to produce a complex mixture. Finally, warming of **10** in CCl4 at 60 °C for 1 h, followed by saponification of **16** furnished the L-daunosamine derivative **17** [mp 146-148 °C, $[\alpha]^{25}_D$ -190.3° (c 0.5, MeOH)] in 36% yield from **9.** The spectral data of **17** were identical with those of methyl *N*-methoxycabonyl-L-daunosaminide [mp 146-148 °C, $[\alpha]^{25}_D$ -199° (c 0.5, MeOH)] prepared from natural daunomycin.[10]

In summary, we have shown a simple route to L-acosamine and L-daunosamine from a common starting material, *t*-butyl *S*-(+)-3-hydroxybutanoate. Although conversion of the carboxy group into the hydroxy group is not so satisfactory in the present stage, the results described



Ar=*m*-chlorophenyl. Reagents: a) 1equiv. HCl, *t*-BuOAc, CH_2Cl_2, 0 °C, 12 h; b) $AgNO_3$, Ag_2O, MeOH, r.t.; c) 3 equiv. LiOH H_2O, MeOH, reflux, 2 d; d) HCl, MeOH, 0 °C, 0.5 h; e) MCPBA, DCC, CH_2Cl_2, r.t.; f) CCl_4, reflux, 3 h; g) LiI, collidine, 150 °C, then PhCOCl, $NaHCO_3$, H_2O; h) CCl_4, 60 °C, 1 h; i) 1 M NaOH, MeOH, 0 °C.

above provide a new efficient access to these amino-sugars because of high stereoselectivity and short steps.

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5) An alternate method for the synthesis of L-daunosamine and L-acosamine starting from *S*-(+)-3-hydroxybutanoate have been reported: D-C. Ha and D. J. Hart, *Tetrahedron Lett.*, **28**, 4489 (1987).
6) t-Butyl *S*-(+)-3-hydroxybutanoate (>99% ee) is commercially available (the Fine Chemical Dept., Chisso Co. Ltd., Tokyo).
7) All new compounds were satisfactorily characterized by microanalytical and/or spectroscopic data. Selected physical data. **5**: mp 86-87.5 °C, $[\alpha]^{25}_{D}$ +17.3° (c 0.5, MeOH). **8**: mp 128-129 °C, $[\alpha]^{25}_{D}$ -223.4° (c 0.5, MeOH), ^{1}H NMR ($CDCl_3$) δ 1.27 (d, J=6,7 Hz, Me), 1.47 (s, *t*-Bu), 1.76 (dd, J=5.1, 12.7 Hz, H2), 2.32 (ddd, J=3.9, 12.6, 12.7 Hz, H2), 2.79 (dd, J=3.1, 5.1 Hz, H4), 3.32 (s, OMe), 3.66 (s, OMe), 4.10 (m, H5), 4.20 (m, H3), 4.83 (d, J=3.5 Hz, H1), and 4.88 (m, NH). **11**: mp 87-88 °C, $[\alpha]^{25}_{D}$ -122.4° (c 0.5, MeOH), ^{1}H NMR ($CDCl_3$) d 1.19 (d, J=6.3 Hz, Me), 1.44 (s, *t*-Bu), 1.55 (m, H2), 2.05 (m, H2), 2.07 (dd, J=10.1, 11.2 Hz, H4), 3.34 (s, OMe), 3.63 (s, OMe), 3.98 (dq, J=9.9, 6.3 Hz, H5), 4.62 (m, NH), 4.75 (dd, J=1.2, 4.6 Hz, H1). **14**: mp 148-150 °C, $[\alpha]^{25}_{D}$ -118.8° (c 0.5 , MeOH), ^{1}H NMR ($CDCl_3$) δ 1.29 (d, J=6.4 Hz, Me), 1.61 (ddd, J=12.5, 12.7, 3.5 Hz, H2), 2.07 (ddd, J=12.7, 4.8, 1.1 Hz, H2), 3.05 (dd, J=8.8, 8.3 Hz, H4), 3.34 (s, OMe), 3.54 (dd, J=6.4, Hz, H5), 3.69 (s, OMe), 3.90 (m, H3), 4.75 (dd, J=3.5, 1.1 Hz, H1).
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10) This sample was prepared by acylation (ClCOOMe, aqueous $NaHCO_3$, r.t.) of methyl β-L-daunosaminide hydrochloride which was derived from natural daunomycin by hydrolysis (0.2 M HCl, 90 °C, 1 h) and subsequent treatment with 0.3 M methanolic hydrogen chloride according to the literature method (Ref. 2).

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