

New Acyclic Approach to 3-Amino-2,3,6-trideoxy-L-hexoses: a Stereocontrolled Synthesis of *N*-Benzoyl L-Daunosamine

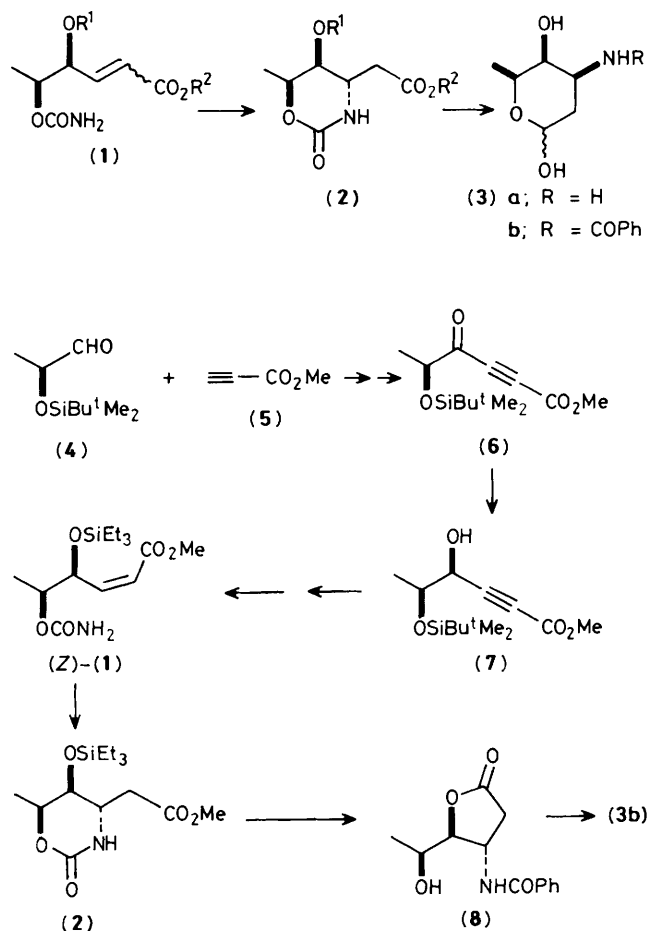
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N-Benzoyl L-daunosamine was synthesized stereoselectively starting from *O*-*t*-butyldimethylsilyl L-lactaldehyde and methyl propiolate; the crucial step, intramolecular conjugate addition of a carbamoyl amino group of methyl *threo*-5-carbamoyloxy-4-triethylsilyloxy-(*Z*)-hex-2-enoate, proceeded with exclusive 1,3-*anti* diastereoselectivity.

Synthesis of daunosamine (**3a**) has been the focus of considerable attention in recent years¹ since it is an essential component of a group of anthracycline antibiotics valuable for their antitumour activity. Recently, we have developed a new carbamate-mediated intramolecular amination methodology² and demonstrated its synthetic utility by the stereoselective

synthesis of all four possible diastereoisomers of racemic *N*-acyl 3-amino-2,3,6-trideoxyhexoses.³ In the synthesis of *N*-benzoyl D,L-daunosamine, however, diastereoselectivity of the crucial amination step [(*E*)-(1)→(2)] was not satisfactorily high, although the desired 1,3-*anti* stereoselection predominated (up to 5 : 1).^{3b} We now describe a synthesis of optically



active *N*-benzoyl daunosamine (**3b**), in which the crucial step proceeded with complete stereocontrol (>100:1).

The favoured conformation of the allylic system in the α,β -unsaturated ester (**1**) with *Z* geometry would be the one in which the allylic C–O bond is perpendicular to the double bond in both ground and transition states,^{4a,b} because of repulsive interactions [*A*(1,3) strain]^{4c} of the ester group with the allylic hydrogen and the OR¹ group. With this conformation an antiperiplanar effect could operate most efficiently in the transition state,^{3b,5} because the LUMO of the unsaturated ester group and σ^* orbital of the allylic C–O bond could overlap most favourably; higher asymmetric induction was therefore anticipated in the amination of (*Z*)-(**1**) than in (*E*)-(**1**).

With this expectation *O*-*t*-butyldimethylsilyl lactaldehyde (**4**)[†] was coupled with the lithium acetylide of methyl propiolate (**5**) [lithium di-isopropylamide (LDA), tetrahydrofuran (THF), –78 °C]⁶ to give a mixture of the *threo* (**7**) and the *erythro* isomer in a ratio of 1:5 (75% yield),[‡] the stereoselection being explicable in terms of a Felkin (Cram)

[†] The aldehyde (**4**) {[α]_D¹⁹ –12° (c 1.5, CHCl₃)} was prepared by a standard procedure from ethyl (*S*)-lactate [i, Bu^tMe₂SiCl, imidazole, dimethylformamide (DMF) (100%); ii, di-isobutylaluminium hydride (DIBAL), CH₂Cl₂, –78 °C (61%)].

[‡] The reaction mixture is poured into a vigorously stirred saturated aqueous solution of NH₄Cl. Otherwise, the yield of the desired products remains less than 50% because of side reactions, such as silyl group migration.

model for a non-chelated transition state.⁷ The mixture was oxidized to ketone (**6**), [α]_D²¹ –22.8° (c 6.8, CHCl₃), with Jones' reagent (acetone, room temperature, 84%) without separating the mixture. Stereoselective reduction of (**6**) was achieved with *L*-Selectride in THF at –78 °C to afford (**7**), [α]_D¹⁸ +18.5° (c 3.6, CHCl₃), in 60% yield (ratio \geq 12:1), while Vitride⁸ showed only moderate selectivity (4.6:1) as well as substantial 1,4-over-reduction. The compound (**7**) was converted without separation into the carbamate (*Z*)-(**1**) (R¹ = SiEt₃, R² = Me; [α]_D²⁰ –10.2° (c 1.4, CHCl₃)) in five steps: (i) protection of the hydroxy group (dihydropyran, H⁺, 84%); (ii) deprotection of silyl ether (Bu₄NF, 74%); (iii) carbamation and simultaneous hydrolysis of tetrahydropyran-2-yl ether (ClSO₂NCO, –78 °C; H₂O, 60 °C, 55%); (iv) re-protection of hydroxy group (Et₃SiCl, DMF, imidazole, 89%); (v) hydrogenation (Lindlar catalyst, H₂, toluene, 71%). At this stage, the contaminating *erythro* derivative was readily separated by recrystallization.[§] Pure (*Z*)-(**1**) thus obtained was subjected to intramolecular conjugate addition (1 equiv. Bu^tOK, THF, 0 °C)^{2,3} to give the 1,3-*anti* cyclic carbamate (**2**) (R¹ = SiEt₃, R² = Me; m.p. 60–61 °C, [α]_D²² –78.2° (c 1.0, CHCl₃)) exclusively (>100:1) in 73% yield. No signal due to the stereoisomer was detected by ¹H n.m.r. (200 MHz) spectroscopy. Thus, a dramatic improvement of diastereoselectivity has been achieved in the conjugate addition of homoallylic carbamate (**1**) by changing the geometry of the double bond from *E*^{3b} to *Z*. Alkaline hydrolysis of (**2**) and subsequent benzoylation^{3b} afforded known *L*-lyxo- γ -lactone (**8**)^{1b,9} {m.p. 143–144 °C; [α]_D²⁶ –19.4° (c 1.0, EtOH), –15.2° (c 0.52, MeOH)}. Reduction of (**8**) with DIBAL (5 mol. equiv., THF, –78 °C) gave *N*-benzoyl *L*-daunosamine (**3b**)⁹ in 53% yield. M.p., t.l.c., ¹H n.m.r., and i.r. spectra and optical rotation of synthetic (**3b**) were identical with those of an authentic sample.

We thank Professor F. M. Hauser, Oregon Graduate Centre, for his gift of a sample of (**3b**).

Received, 11th November 1985; Com. 1586

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[§] Recrystallized readily from diethyl ether–hexane; the melting point is too close to room temperature to measure.