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

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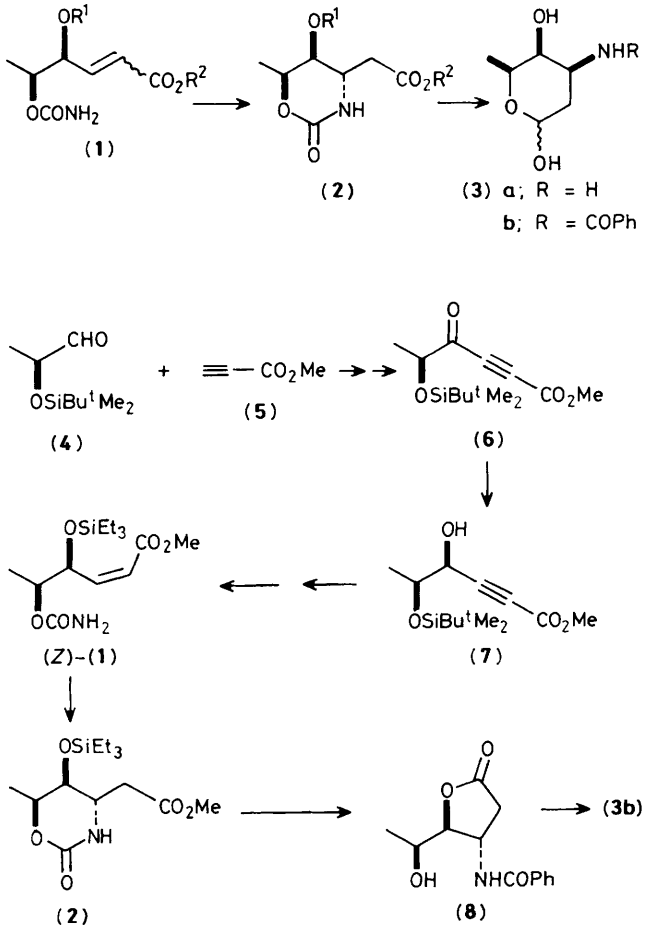
N-Benzoyl L-daunosamine was synthesized stereoselectively starting from *O*-t-butyldimethylsilyl L-lactaldehyde and methyl propiolate; the crucial step, intramolecular conjugate addition of a carbamoyl amino group of methyl *threo*-5-carbamoyloxy-4-triethylsilyloxy-(*Z*)-hex-2-enoate, proceeded with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

Synthesis of daunosamine (**3a**) has been the focus of considerable attention in recent years[1] 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 methodology[2] 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 OR^1 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) model for a non-chelated transition state.[7] The mixture was oxidized to ketone (**6**), $[\alpha]_D^{21}$ −22.8° (*c* 6.8, $CHCl_3$), 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**), $[\alpha]_D^{18}$ +18.5° (*c* 3.6, $CHCl_3$), in 60% yield (ratio ≥12 : 1), while Vitride[8] 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**){R^1 = $SiEt_3$, R^2 = Me; $[\alpha]_D^{20}$ −10.2° (*c* 1.4, $CHCl_3$)} in five steps: (i) protection of the hydroxy group (dihydropyran, H^+, 84%); (ii) deprotection of silyl ether (Bu_4NF, 74%); (iii) carbamation and simultaneous hydrolysis of tetrahydropyran-2-yl ether ($ClSO_2NCO$, −78 °C; H_2O, 60 °C, 55%); (iv) reprotection of hydroxy group (Et_3SiCl, DMF, imidazole, 89%); (v) hydrogenation (Lindlar catalyst, H_2, 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**) {R^1 = $SiEt_3$, R^2 = Me; m.p. 60—61 °C, $[\alpha]_D^{22}$ −78.2° (*c* 1.0, $CHCl_3$)} 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; $[\alpha]_D^{26}$ −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.

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† The aldehyde (**4**) {$[\alpha]_D^{19}$ −12° (*c* 1.5, $CHCl_3$)} was prepared by a standard procedure from ethyl (*S*)-lactate [i, Bu^tMe_2SiCl, imidazole, dimethylformamide (DMF) (100%); ii, di-isobutylaluminium hydride (DIBAL), CH_2Cl_2, −78 °C (61%)].

‡ The reaction mixture is poured into a vigorously stirred saturated aqueous solution of NH_4Cl. Otherwise, the yield of the desired products remains less than 50% because of side reactions, such as silyl group migration.

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