Synthesis of Precursors to L-Ristosamine and L-Daunosamine from L-Lactic Acid

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Condensation of the protected L-lactaldehyde 4 with methyl 3-nitropropionate gave a mixture of nitro alcohols 5, which, in one step, was converted into a 2–5:1 mixture of nitro lactones 6 and 7. Hydrogenation, benzoylation and separation afforded the L-ristosamine precursor 8 and the L-daunosamine precursor 9.

The 3-amino-2,3,6-trideoxy-L-hexoses L-ristosamine (*1*), L-daunosamine (*2*) and L-acosamine are components of naturally occurring glycoside antibiotics. Because of the medical value of some of these glycosides (*e.g.* as cancer chemotherapeutic agents),[1] considerable interest has been focussed on the synthesis of these amino sugars. Thus, derivatives of L-ristosamine have been synthesised from L-arabinose,[2] L-rhamnose,[3–10] D-glucose,[11] (*R,R*)-tartaric acid,[12] or from a chiral building block obtained by reduction with baker's yeast.[13] We now report the use of L-lactic acid as a starting material in the synthesis of carbohydrates. During the course of this work, a similar approach was made by other investigators. L-Daunosamine[14,15] and other sugars,[16–19] but not L-ristosamine, were prepared from L-lactic acid.

The tetrahydropyranyl ether of ethyl L-lactate (*3*) was converted into aldehyde *4*, either by a direct reduction with diisobutylaluminium hydride (50 % yield) or by a reduction-oxidation sequence (LiAlH$_4$–DMSO, oxalyl chloride, 60 %); an 88 % yield of racemic *4* has been obtained from the methyl ester analogue of *3* using the latter procedure.[20]

Several attempts were made to condense *4* with methyl 3-nitropropionate, but only moderate yields of *5* were obtained. The most likely reason for this is the reversible nature of the nitroaldol (Henry) reaction.[21] Most probably, *5* is a mixture of eight stereoisomers (four if the tetrahydropyranyl group is disregarded) and this, in conjunction with its instability, precludes a separation at this stage. However, the number of stereoisomers could be reduced to two by treating crude *5* with pyridinium tosylate in refluxing toluene. This first led to a lactonisation, probably followed by an epimerisation of the nitro group to the *trans* position on the lactone ring, which should be thermodynamically favoured. Finally, this treatment led to a loss of the tetrahydropyranyl group, leaving lactones *6* and *7* as the main

1   *2*
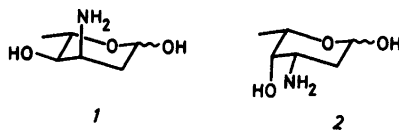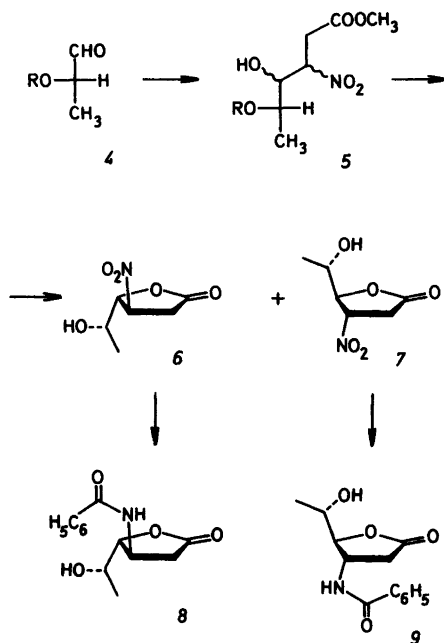
Scheme 1. Synthetic route to the L-ristosamine and L-daunosamine precursors, *8* and *9*, respectively. R=tetrahydropyranyl.

products. The ratio between *6* and *7* was dependent on the method used in the synthesis of *5*. With potassium *tert.* butoxide as base, the ratio 6:7 was *ca.* 2:1 and the combined yield, based on *4*, was 48 %. A reaction between *4*, methyl 3-nitropropionate, KF·2H$_2$O, and tetrabutylammonium chloride [22] (molar ratios 1:1.4:1.5:0.75) in toluene (23 °C, 3 h) gave a ratio of *ca.* 5:1, but the yield of *6* was not raised.

Isomer *6* crystallised from the mixture of *6* and *7*, but the purification of *7* was unsuccessful, also by column chromatography. Hydrogenation over palladium and subsequent benzoylation of *6* afforded the known [12] benzamide *8*, a precursor to L-ristosamine (*1*). Similar treatment of the mixture of *6* and *7*, obtained after crystallisation of *6*, provided *8* and its isomer *9*, the latter being a precursor to L-daunosamine (*2*). The products could be separated by chromatography on silica gel. This four-step conversion of *4* into *8+9* gave total yields of 26 % and 13 % respectively. The benzamide *8* has been reduced to *N*-benzoyl-L-ristosamine with diisobutylaluminium hydride (65 % yield). [12]

Although this synthesis of *8* and *9* involves relatively few steps, the overall yields are low. The ratio between *6* and *7* (2−5:1) is probably determined in the reaction between *4* and methyl 3-nitropropionate. Like in several other nucleophilic additions to α-alkoxy aldehydes, [18,23] the stereochemical outcome can be predicted by applying Felkin's model, regarding the α-alkoxy group as R$_{large}$ ("non-chelation control"). [24] However, because of the possible reversibility of the reaction, this analysis may not apply.

EXPERIMENTAL

Tetrahydrofuran (THF) was distilled over LiAlH$_4$ before use. TLC was run using Kieselgel 60 F$_{254}$ (Merck) plates (0.25 mm). A fused silica capillary column (OV−101, 15 m), mounted in a Hewlett-Packard 5830 A instrument was used for the gas chromatography. Column chromatography was carried out using Kieselgel 60 (230−400 mesh, Merck).

Optical rotations were measured on a Perkin-Elmer 241 polarimeter and IR spectra on a Perkin-Elmer 257 instrument. A JEOL JNM−FX 100 or a JEOL GX 400 instrument was used to record ^{1}H NMR spectra; ^{13}C NMR spectra were recorded on the former instrument. Unless otherwise stated, tetramethylsilane was used as internal reference.

Ethyl 2S-[(tetrahydro-2H-pyran-2(R,S)-yl)oxy]-propanoate (3). A mixture of ethyl L-lactate (59 g, 0.50 mol, Merck-Schuchardt), dihydropyran (63 g, 0.75 mol), methylene chloride (500 ml), and pyridinium p-toluenesulfonate (12.5 g, 0.05 mol) was left for 15 h (23 °C).[25] Methylene chloride and excess dihydropyran were evaporated under reduced pressure and the acetal dissolved in ether. After filtration, washing with aqueous sodium hydrogen carbonate, drying (Na$_2$SO$_4$) and distillation at 52−55 °C (20 Pa), *3* was obtained in a 93 % yield.

2S-[(tetrahydro-2H-pyran-2(R,S)-yl)oxy]-propanal (4). A 1M solution of diisobutylaluminium hydride (0.20 mol, Aldrich) in cyclohexane was added (100 min, N$_2$ atmosphere) to a stirred and cooled (*ca.* −70 °C) solution of *3* (36.3 g, 0.18 mol) in hexane (230 ml). After 15 min, a solution of ammonium chloride (10.7 g) in water (125 ml) was added slowly. The resulting mixture was allowed to reach *ca.* 20 °C, the precipitate was filtered off, and the organic phase separated. The aqueous phase was extracted with ether (2×100 ml) and the combined organic phases washed once with aqueous sodium potassium tartrate. After drying (Na$_2$SO$_4$), concentration and distillation at 52−58 °C (90 Pa), *4* was obtained in a 50 % yield (53:47 ratio of diastereomers, GLC). ^{1}H NMR (CDCl$_3$): δ 9.66 (d with two outer shoulders, 1 H, J 1.5 Hz), 4.8−4.4 (m, 1 H), 4.25 (d of q, 0.5 H, J_1 1.5 Hz, J_2 7.3 Hz), 4.00 (d of q, 0.5 H, J_1 2.4 Hz, J_2 6.8 Hz), 4.0−3.6 (m, 1 H), 3.6−3.2 (m, 1 H), 2.0−1.4 (m, 6 H), 1.37 (d, 3 H, J 7.3 Hz) 1.28 (d, 3 H, J 6.8 Hz).

3-Nitro-2,3,6-trideoxy-L-ribo-hexono-1,4-lactone (6). Methyl 3-nitropropanoate[26] (1.86 g, 14 mmol), dissolved in THF (20 ml) was added (5 min, N$_2$ atmosphere) to a stirred and ice-cooled suspension of potassium *tert.* butoxide (Merck, 1.18 g, 10.5 mmol) in THF (30 ml). After stirring for 10 min, the temperature was lowered to *ca.* −25 °C, and a solution of *4* (1.58 g, 10 mmol) in THF (15 ml) was added (10 min). The reaction flask was stoppered and stored at −20 °C for 18 h. Acetic acid (11 mmol) in THF (5 ml) was added to stop the reaction. The solvent was evaporated, methylene chloride (100 ml) was added and the solution washed once with brine, dried (Na$_2$SO$_4$) and concentrated to a syrup (3.31 g). TLC (methylene chloride-ethyl acetate, 8:1) showed methyl 3-nitropropanoate at R_F 0.81, traces of nitro lactones (R_F 0.70 and 0.65), a little unreacted *4* (R_F 0.61 and 0.55), and nitro alcohols *5* (R_F 0.37, 0.30, 0.24).

The crude condensation product and pyridinium tosylate (0.25 g) were dissolved in toluene (150 ml) and the solvent was slowly (5 h) distilled off, adding portions of toluene (in all 175 ml) to keep the volume roughly constant. After cooling, the solution was decanted and the solvent was evaporated. The nitro lactones were purified on silica gel (70 g) using methylene chloride-ethyl acetate (10:1) as eluent. Compounds *6* and *7* were collected in a single fraction (0.84 g, combined yield, 48 %); ratio 6:7, ca. 2:1 (^{1}H NMR, 400 MHz). On addition of chloroform, isomer *6* crystallised. Recrystallisation from chloroform gave analytically pure *6* (0.32 g); m.p. 77−79 °C); $[\alpha]_D^{24}$ +68° (c 1.0, ethanol); ^{1}H NMR (CDCl$_3$, 400 MHz): δ 5.27 (d of t, H-3, $J_{3,2a}$ 8.9 Hz, $J_{3,2\beta} \approx J_{3,4}$=2.6 Hz), 4.78 (t, H-4, $J_{4,3} \approx J_{4,5}$=2.6 Hz), 4.22 (m, H-5), 3.28 (H-2β) and 3.15 (H-2α) ($J_{2\alpha,2\beta}$ 19.1 Hz, $J_{2\beta,3}$ 2.6 Hz, $J_{2\alpha,3}$ 8.9 Hz), 2.31 (d, OH, J 4.6 Hz), 1.37 (d, H-6, J 6.7 Hz). ^{13}C NMR (CD$_3$CN): 174.2, 86.8, 82.0, 67.8, 34.2, 18.8 ppm (solvent peak at 1.3 ppm as reference); IR (CH$_3$CN): 3480 (m), 1795 (s), 1560 cm^{-1} (s).

The mother liquor contained *6* and *7* in approximately equal amounts; attempted separation on silica gel was unsuccessful.

3-Benzamido-2,3,6-trideoxy-L-ribo-hexono-1,4-lactone (8). Nitro compound *6* (0.28 g, 1.6 mmol) in methanol (35 ml) containing 0.14 ml (1.7 mmol) of conc. hydrochloric acid was hydrogenated over 10 % Pd on C (0.45 g, Merck) at *ca.* 0.4 MPa (24 h). The catalyst was filtered off and the solvents evaporated. Methanol (1.5 ml) and methylene chloride (10 ml) were added, the solution was cooled in an ice-bath, and pyridine (45 mg), triethylamine (0.45 g), and benzoyl chloride (0.31 g, 2.2 mmol) were added. After 2 h at 23 °C, toluene (25 ml) was added and the mixture concentrated. This co-distillation was repeated once, ethyl acetate (100 ml) was added, and the solution was washed with water (10 ml). Drying (Na$_2$SO$_4$). and concentration (finally at *ca.* 10 Pa) gave a residue (0.39 g) from which

crystalline *8* could be obtained by treatment with chloroform. Recrystallisation from ethyl acetate + 2,2,4-trimethylpentane afforded 0.25 g of *8* (63 %). A further 0.07 g of chromatographically pure *8* was obtained from the mother liquors by purification on silica gel (ethyl acetate-toluene, 3:1), total yield, 80 %; m.p. 150−152 °C, lit.[12] m.p. 149 °C; $[\alpha]_D^{25}$ +39° (*c* 0.92, ethanol), lit.[12] value: $[\alpha]_D^{20}$ +37° (*c* 0.95, ethanol); ^{1}H NMR values were the same as those given in Ref. 27.

3-Benzamido-2,3,6-trideoxy-L-*lyxo-hexono-1,4-lactone* (*9*). The material in the mother liquors from the crystallisation of *6* was hydrogenated and benzoylated as above. The mixture of *8* and *9* thus obtained was chromatographed on silica gel (toluene-ethyl acetate, 1:1). Isomer *8* was eluted first (0.26 g), then a mixture ($\approx$1:1) of *8* and *9* (0.09 g), and finally *9* (0.27 g). After recrystallisation of *9* from ethyl acetate-hexane, it showed m.p. 147.5−148 °C (lit.[28] m.p. 147 °C); $[\alpha]_D^{24}$ −20.1° (*c* 1.0, ethanol); ^{1}H NMR values were the same as those given in Ref. 27.

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