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TOTAL SYNTHESIS OF BIOLOGICALLY IMPORTANT AMINO SUGARS VIA THE NITROALDOL REACTION

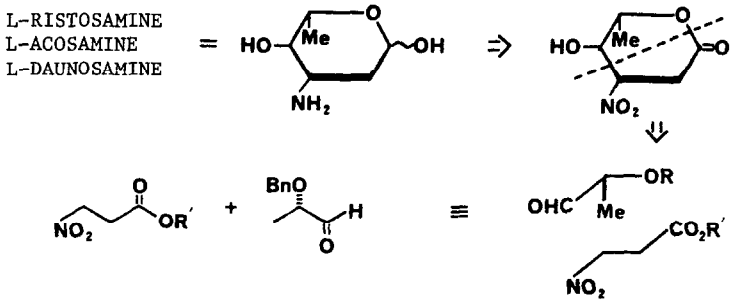
Stephen Hanessian* and John Kloss
Department of Chemistry, Université de Montréal
Montréal, Québec, Canada H3C 3V1

Summary. Aldol condensation between O-benzyl D-or L-lactaldehyde and alkyl 3-nitropropionates in the presence of various catalysts leads to stereoisomeric nitroaldol products which can be transformed into aminodeoxy hexoses in the D- or L-series.

The amino sugars occupy a unique role in natural product chemistry, either as components of antibiotics[1] or biopolymers.[2] The need to develop novel and efficient syntheses of isomeric 3-amino-2,3,6-trideoxy-L-hexoses, which are components of the anthracycline antitumor agents[3] and other natural products is evident, since experience has shown that even minor stereochemical or functional variations can result in dramatic changes in their biological profile.[3,4] Traditionally, most of such syntheses started with carbohydrate precursors and proceeded through the systematic modification of existing functional groups.[5] More recently, imaginative approaches from non-sugar precursors have been reported.[6]

We now describe a versatile and novel route to 3-amino-2,3,6-trideoxy-D- or L-hexoses by a bond-forming strategy which engages a suitably protected D-[7] or L-lactaldehyde[13] and an alkyl 3-nitropropionate in a stereocontrolled nitroaldol reaction[8,9] (Scheme 1). The naturally occurring L-acosamine,[10] L-daunosamine,[3,11] and L-ristosamine[12] are thus accessible by this methodology and by further manipulation of the condensation products.

Scheme 1

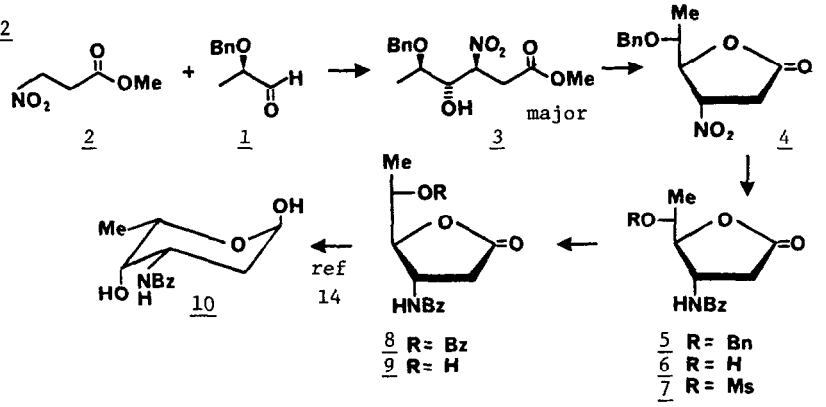


(R)-O-Benzyl ethyl lactate,[7,13] α_D +76.5° (ℓ=1); was carefully reduced (DIBAL, Et_2O, -78°C) to give O-benzyl-D-lactaldehyde 1, α_D +61.5° (ℓ=1). Treatment of 1 with methyl 3-nitropropionate 2 (0.84 equiv.) in the presence of neutral alumina[9] (0.4 g/mmole, 48h), led to a mixture of three nitroaldol products from which the preponderant crystalline D-ribo isomer 3 was isolated by direct crystallization and by subsequent chromatography of the mother liquor (62%); m.p. 108-109°C, $[\alpha]_D$ -33.6° (c1.06, CH_2Cl_2). Interestingly, the

D-ribo isomer was the thermodynamic product in the reaction (ribo:xylo:arabino, 15, 1½, 1), since shorter reaction times gave a lower stereoselection (Scheme 2). Lactonization of 3 (HCl/CH_2Cl_2) gave the desired γ-lactone 4 in quantative yield; $[\alpha]_D$ -40.9° (c1.39, CH_2Cl_2). Reduction of the nitro group (Ra-Ni 500% w/w, Bz_2O, MeOH) with in situ N-benzoylation gave 5 in 71% yield; m.p. 132-133°C, $[\alpha]_D$ -39.4° (c1.08, CH_2Cl_2). Hydrogenolysis (5% Pd/C, MeOH, H^+) gave 6 in quantitative yield; m.p. 145-148°C, $[\alpha]_D$ -43.1° (c1.13, EtOH). The D-ribo lactone 6 was subjected to configurational inversion at C-5 to give the benzoate 8, (NaOBz, DMF, 60%); $[\alpha]_D$ +37.5° (c0.8, CH_2Cl_2) via mesylate 7, (MsCl, pyr, 91%); m.p. 144-146°C, $[\alpha]_D$ -17.7° (c1.05, MeOH). Catalytic debenzoylation (cat. NaOMe/MeOH, H^+, 79%) then gave the known L-lyxo lactone 9[14]; m.p. 138-140°C, $[\alpha]_D$ -24.9° (c1, EtOH) which had been previously converted into N-benzoyl-L-daunosamine 10 by Fuganti and coworkers.[14]

It should be noted that whereas the (R)-D-lactaldehyde 1 gave the D-ribo lactone 6, the (S)-L-lactaldehyde 11 gave the L-ribo lactone 16.

Scheme 2



2 1 3 4

10

8 R= Bz
9 R= H

5 R= Bn
6 R= H
7 R= Ms

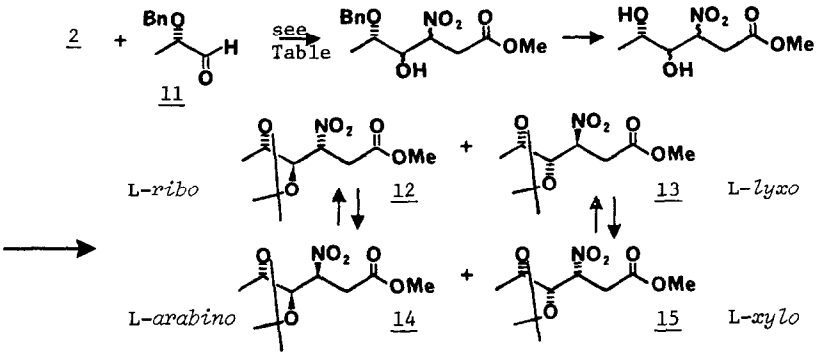
Access to immediate precursors of L-ristosamine and L-acosamine was possible by application of the nitroaldol reaction in the L-series analogously to that as described above, and in the presence of other catalysts. Thus, the mixture of nitroaldol condensation products from O-benzyl-L-lactaldehyde[7] 11, α_D -67.7° (ℓ=1), was debenzylated (5% Pd/C, MeOH, H^+), then subjected to ketalization (acetone/dimethoxypropane, CSA), and chromatography to give the L-ribo acetonide 12 as the major product, (43%, three steps); $[\alpha]_D$ +70.4° (c0.95, CH_2Cl_2). As in the D-series, only minor amounts of the L-xylo, 15 (4.5%, three steps), $[\alpha]_D$ -12.8° (c1.18, CH_2Cl_2); the L-arabino, 14 (2.5%, three steps), $[\alpha]_D$ +58.0° (c0.64, CH_2Cl_2); and the L-lyxo, 13 (trace), $[\alpha]_D$ +6.04° (c1.07, CH_2Cl_2) isomers were formed.

It also was possible to effect equilibration at C-3 of the individual acetonides. Treatment of the L-arabino derivative 14 with tBuOK in THF (0.25 equiv., 24h, 0°C) led to a 3:7 mixture of 14 and the L-ribo isomer 12. Similar treatment of the L-xylo isomer 15 gave a 2:3 mixture of 15 and the L-lyxo isomer 13 (Scheme 3). These could be individually isolated by chromatography.

A nitroaldol condensation also was done in the presence of a catalytic amount of tBuOK (5%, THF, 0°, 2h). In this case, the L-arabino isomer was predominant, but the stereoselection was much lower as compared to alumina (Table 1).

Anticipating the possible influence of the cation on the stereochemistry of the nitroaldol condensation through the intermediacy of metal-coordinated transition states, the reaction was conducted in the presence of various salts of divalent metals. Thus, in the

Scheme 3



presence of tBuOK/$ZnBr_2$ (1 equiv. each, THF, 0°, 2.5h), the L-arabino isomer was favored, whereas with tBuOK/$MgBr_2$ (1 equiv. each, THF, 0°, 2.5h), there was a bias toward the L-xylo isomer.

Table 1

	L-*ribo*	L-*lyxo*	L-*xylo*	L-*arabino*
cat. ^{t}BuOK (0°)	1	trace	1	2
^{t}BuOK (0°)	2	trace	1	1
^{t}BuOK/$MgBr_2$ (0°)	1	trace	3	1
^{t}BuOK/$ZnBr_2$ (0°)	1	trace	1	3
^{t}BuOK/TMSCl/F^- (-78°)	1	0	0	1
neutral alumina	15	trace	1.5	1

In order to test the effect of a chiral auxilliary function, the potassium t-butoxide condensation was done with the d- and ℓ-menthyl 3-nitropropionates,[15] and the reaction mixture processed to the acetonide stage. Surprisingly, with the d-ester, a 1:1:2 ratio (L-ribo:L-xylo:L-arabino) of isomers was obtained; while with the ℓ-ester, the L-ribo and L-xylo isomers predominated (1:3 respectively). Poor stereoselection was observed with the racemic ester, indicating an inherent stereochemical bias with the optically active esters, rather than a purely steric effect. Conversely, condensations on alumina gave exactly the same ratios (1:1:1, ribo:xylo:arabino) when either the d- or the ℓ-menthyl ester was used, which indicates a purely steric effect in this case.

With an effecient protocol to obtain the nitroaldol products in hand, it was possible to gain facile access to the corresponding known N-benzoyl lactones[14] (and hence the free sugars[14]) from the individual acetonides as shown in Scheme 4.

The results described above, particularly with the metal-assisted and alumina catalyzed stereocontrolled reactions, demonstrate a novel approach to the synthesis of aminodeoxy sugars and the corresponding β-amino acids.

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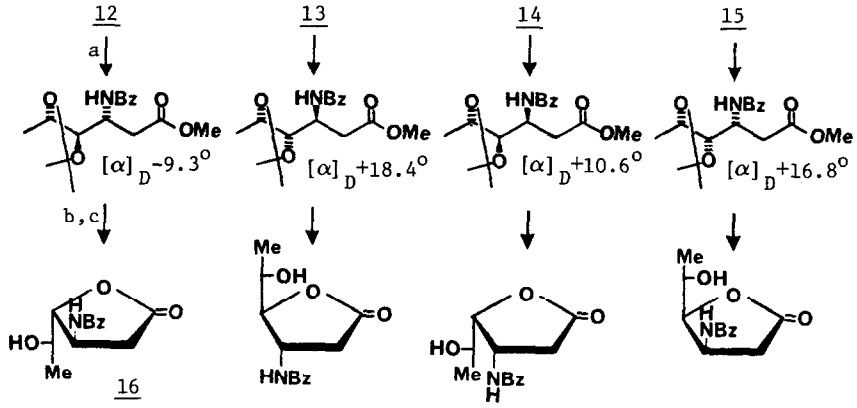
Scheme 4



reagents: a) Ra-Ni, Bz_2O, MeOH, H_2, 65-82%. b) TFA/H_2O 9/1, 0°C. c) HCl/CH_2Cl_2, 71-85%.

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