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SYNTHESIS OF THE N-BENZOYL DERIVATIVES OF L-ARABINO,L-XYLO AND L-LYXO (L-VANCOSAMINE) ISOMERS OF 2,3,6-TRIDEOXY-3-C-METHYL-3-AMINOHEXOSE FROM A NON-CARBOHYDRATE PRECURSOR †

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The synthesis of the N-benzoyl derivatives of L-arabino (10),L-xylo (13) and L-lyxo (L-vancosamine) (12) 2,3,6-trideoxy-3-C-methyl-3-aminohexose from the (2S,3R) diol (1) prepared in fermenting bakers' yeast from α-methylcinnamaldehyde and acetaldehyde is reported

The 3-C-methyl branched amino sugars L-vancosamine (12,R= H) and its L-xylo isomer (13,R= H) occur as glycoside components in the glycopeptide antibiotics vancomycin[1] and A35512B[2]. In our interest in non-carbohydrate synthesis of deoxy-[3] and deoxy-amino sugars,[4] which are present in biologically active substances,we refer now on the synthesis of the N-benzoyl derivatives of the above mentioned amino-sugars and of the L-arabino isomer (10), using as source of chirality the (2S,3R) methyl diol (1) prepared from α-methyl cinnamaldehyde and acetaldehyde in commercial bakers' yeast[5].

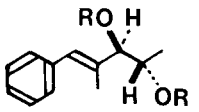
The synthetic scheme is based on the preparation of the C_5 methyl ketone (3) from a protected form of (1),of the sulfenimine (4) and on the C_7-N adduct (6),formed by threo, stereoselective addition of $BrMgCH_2CH{=}CH_2$ onto (4). Cleavage with O_3 of the terminal methylene group of (6) yields the L-arabino-3-C-methyl branched deoxy sugar derivative (10). Inversion of configuration at C-4 of a derivative of (10) gives rise,eventually,to N-benzoyl-L-vancosamine (12). The threo sulfenimine (5) which accompanies (4) yields similarly the isomeric adduct (7),converted,in turn,into the L-xylo isomer (13).

Thus,the diol (1) was quantitatively converted into (2) ($Me_2C(OMe)_2$,TsOH,benzene), ozonised,in turn,at -20 °C in CH_2Cl_2,to give,after treatment with 1 mol. eq. of $(C_6H_5)_3P$, the C_5 methyl ketone (3) and benzaldehyde,separated by fractional distillation,in 60-70% yield. A sample of (3) (dist. 80-85°C at 25-30 mm/Hg),obtained by preparative g.l.c. showed $[\alpha]_D^{20}$ -52° (c 1.6,EtOH). The ketone (3) was reacted with NH_3,$C_6H_5SSC_6H_5$ and $AgNO_3$ in MeOH[6] to give the sulfenimines(4)+(5) (see below),in ca. 65% yield. The above mixture,showing a single spot in different t.l.c. systems,upon treatment with an excess of allylmagnesium bromide at -78°C in THF (75%),followed by acid hydrolysis (10% HCl in aqueous ethanol) and bezoylation of the acid soluble material(s) (benzoyl chloride, K_2CO_3,aqueous acetone) gave

rise in ca. 50% yield to the C_7-N adducts (6), $[\alpha]_D^{20}$ -22° (c 0.5,$CHCl_3$),and (7),showing a small negative rotation,separated by SiO_2 column chromatography,in 7:3 ratio. The two compounds resulted epimeric at position 4,since (6) upon HIO_4 oxidation in dry THF gave the aldehyde (8), $[\alpha]_D^{20}$ -14° (c 1.1,EtOH),whereas (7) afforded the enantiomer (9), $[\alpha]_D^{20}$ 13.5 (c i,EtOH).

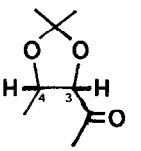
Upon ozonolysis at -20°C in MeOH,and subsequent Me_2S treatment,the C_7-N adduct (6) gave the N-benzoyl deoxyhexose (10),oil,which solidified on standing, $[\alpha]_D^{20}$ -5.1° (c 0.5,MeOH), in ca. 80% yield,showing in DMSO-d_6 the following ^{1}H-n.m.r.data: δ 4.82 (J(1,2a) 2.0),H-1; δ 2.27 (J(1,2b) 9.7),H-2a; δ 2.00 (J(2a,2b) 13.0),H-2b; δ 3.67 (J(4,5) 9.4),H-4; δ 3.45 (J(5,Me) 6.0),H-5; δ 1.4,3-C-Me; δ 1.20,Me-5; δ 6.44 (J(OH-1,H-1) 6.0),OH-1; δ 5.63 (J(OH-4,H-4) 3.4),OH-4. Similarly,compound (7) gave the aminosugar derivative (13),m.p. 230-233°C (from ethyl acetate hexane), $[\alpha]_D^{20}$ -61.3° (c 0.5,MeOH),in 85% yield. Its ^{1}H-n.m.r. data (DMSO-d_6) are the following: δ 5.20 (J(1,2a) 1.0),H-1; δ 1.58 (J(1,2b) 3.5), H-2a; δ 1.90 (J(2a,2b) 13.5),H-2b; δ 3.81 (J(4,5) 1.3),H-4; δ 4.21 (J(5,Me) 6.5),H-5; δ 1.52,3-C-Me; δ 1.70,Me-5; δ 6.84 (J(OH-1,H-1) 3.2),OH-1; δ 4.86 (J(OH-4,H-4) 7.0, OH-4; δ 8.28,NH. These data indicate that compound (13) hold a threo relative configuration for positions 4 and 5,whereas in (10) there is an erythro configuration at the same positions. The L-xylo configuration depicted in (13) is assigned to the synthetic amino deoxy sugar obtained from (7) because of its conversion into the derivative (14),m.p. 177°C, $[\alpha]_D^{20}$ -188° (c 1,MeOH),these physical properties being in good agreement with those reported[2] for the L-xylo compound isolated from antibiotic A35512B. Considering together the results of the degradative work which indicated that (10) and (13) must hold opposite stereochemistry at position 3 and the information on the stereochemistry at position 4 and 5 arising from ^{1}H-n.m.r. studies on (10),we can assume as established the L-arabino configuration depicted in structural formula (10) for the synthetic deoxy amino sugar arising from (6). It follows that the two synthetic amino sugars (10) and (13) show,respectively,an erythro and threo relati configuration for positions 4 and 5,which should originate from positions 3 and 4 of the starting ketone (3),but an identical relative stereochemistry for the substituents at positions 3 and 4. These results can be most economically explained assuming that: (i) some α-epimerization had occurred in the original C_5 erythro framework under the basic conditions used in the preparation of the sulfenimine,which caused the formation of some of the threo isomer (5),in addition to the erythro derivative (4),and (ii) the addition of the allyl magnesium bromide onto the epimeric products (4) and (5) takes place with a very high degree of stereocontrol,with formation of the threo adducts (6) and (7),in agreement wiyh the metal-chelation controlled addition model[7].

The stereochemistry at position 4 of the L-arabino product (10) was inverted by sequential

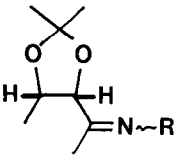


(1) R = R^1 = H

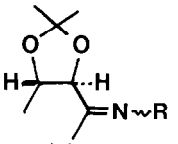
(2) R, R^1 = $>CMe_2$



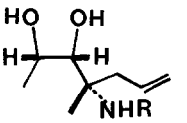
(3)



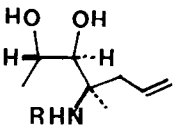
(4) R= SC_6H_5



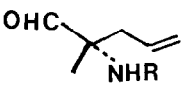
(5) R= SC_6H_5



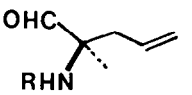
(6) R= COC_6H_5



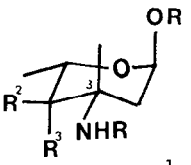
(7) R= COC_6H_5



(8) R= COC_6H_5



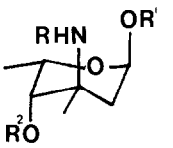
(9) R= COC_6H_5



(10) R= COC_6H_5; R^1= R^3= H; R^2= OH

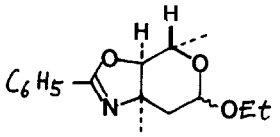
(11) R= COC_6H_5; R^1= Me; R^2= OMs; R^3= H

(12) R= COC_6H_5; R^1= R^2= H; R^3= OH



(13) R= COC_6H_5; R^1= R^2= H

(14) R= COC_6H_5= R^2; R^1= Me



(15)

treatment with: (i) MeOH, H_3O^+; (ii) $MeSO_2Cl$, Et_3N in CH_2Cl_2; (iii) boiling aqueous sodium acetate, and, (iv) dil. HCl, to give, in moderate yields, N-benzoyl-L-vancosamine (12), m. 155°C, $[\alpha]_D^{20}$ -85° (c 0.5, MeOH) after 5', showing the following ^{1}H-n.m.r. data (DMSO-d_6): δ 5.14 (J(1,2a)+J(1,2b) 5.0), H-1; δ 2.0‡, H-2a; δ 2.0‡, H-2b; δ 3.5 (J(4,5) 1), H-4; δ 4.2 (J(5,Me) 6.3), H-5; δ 1.68, 3-C-Me; δ 1.10, Me-5; δ 6.02 (J(OH-1,H-1) 3.3), OH-1; δ 4.84

(J(OH-4,H-4) 7.0),OH-4; δ 7.38,NH. An exoploratory experiment designed to prepare the L-ribo isomer by repeating the above sequence on compounds of the L-xylo series,gave,in the work-up of the mesylate,the product (15),which decomposed under the acidic conditions we used in the attempt to convert it into the required N-benzoyl-L-ribo amino sugar derivative.

The above results have shown that compound (1),easily available in quantities by yeast transformation,can be converted through unexceptional steps into the N-benzoyl derivatives of three of the four configurational isomers of the biologically important 2,3,6-trideoxy-3-C-methyl-3-amino-hexose,the fourth,hopefully,being accessible too. However,further work is needed to settle the synthetic problem completely,since in the present procedure from the erythro ketone (3) the two α-epimeric sulfenimines (4) and (5) were obtained. We have been able to convert (3) into its α-threo epimer at an extent of 90%,and we hope to be able to prepare from the two C_5 ketones,in separate experiments,the two sulfenimines (4) and (5). In this way,one should be able to direct the synthetic sequence either in the L-arabino-→L-lyxo or in the L-xylo-→L-ribo series,depending on the stereochemistry of the starting ketone. Finally,we must mention that an attempt to obtain the above mentioned products along the scheme followed in the synthesis of N-trifluoroacetyl-L-acosamine and L-daunosamine[4],from the (2S,3R) diol prepared from cinnamaldehyde and bakers' yeast,failed, because the C_6 α,β -unsaturated ester obtained from (3) did not add ammonia across the trisubstituted double bond under the conditions we explored.

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•J in Hz ¶Compounds (12) and (13),just after the dissolution in DMSO,are stable in the α-pyranose form,while (10) gives rise immediately to a mixture in which the β-pyranose isomer is the most abundant. ‡Overlapped signals. §X part of a deceptively simple ABX system.

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