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SYNTHESIS OF N-BENZOYL L- AND D-2,3,6-TRIDEOXY-3-AMINO-XYLO-HEXOSE FROM NON-CARBOHYDRATE PRECURSORS

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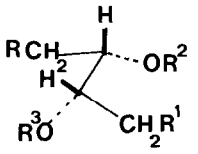
Summary The enantiomeric alcohols (2) and (11), obtained from (2R,3R) tartaric acid and, respectively, L-threonine, have been used to construct the C_6, enantiomeric deoxy amino sugar derivatives (7) and (12)

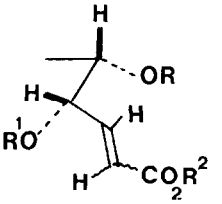
For some years now there has been considerable interest in the synthesis of the enantiomeric forms of the four configurational isomers of 2,3,6-trideoxy-3-aminohexose, because of the biological properties shown by natural products and synthetic analoga of which three of the above amino sugars are a part.[1] The several chiral syntheses reported up to now are, however, all carbohydrate based, and we here describe the obtainment of the N-benzoyl derivative of L- and D-2,3,6-trideoxy-3-amino-xylo-hexopyranose (3-epidaunosamine) through a procedure which uses as chiral sources easily available (2R,3R) tartaric acid and, respectively, L-threonine.

To this end, (2R,3R) tartaric acid was converted according to reported procedures[2,3] into the mono 4-toluenesulfonyl derivative (1), which, upon $LiAlH_4$ reduction in Et_2O, gave in ca. 40% not optimized yield, the (2R,3S) alcohol (2), shown by g.l.c. and comparison with authentic sample to contain ca. 3% of the erythro isomer. Oxidation of (2) with pyridinium chlorochromate in CH_2Cl_2-sodium acetate[4], and treatment of the reaction mixture with $(C_6H_5)_3P{=}CHCO_2Et$ led to the C_6, α,β-unsaturated ester (3), shown by g.l.c. and ^1H-n.m.r. studies to be a 65:35 mixture of E- and Z-isomers, $[\alpha]_D^{20}$ +28.5° (c 1.1, $CHCl_3$), in ca. 30% yield and 45% recovery of the starting alcohol (2). Compound (3) was reacted[5] with dry ammonia in methanol at 0°C for 48 h, and the crude, evaporated material was hydrolysed with 2N HCl to a crystalline lactone hydrochloride, showing in the i.r. ν_{CO} 1780

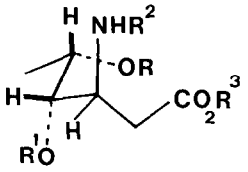
cm^{-1}, with a minor band at 1760 cm^{-1}. This material was benzoylated in pyridine-CH_2Cl_2 with 1 mol. eq. of benzoyl chloride, to give after SiO_2 column chromatography a crystalline δ-lactone, m.p. 230°C, from ethyl acetate-methanol, $[\alpha]_D^{20}$ -25.6° (c 0.5, EtOH), in ca 60% yield from (3). The same compound is obtained when the crude product of addition of ammonia was benzoylated, the crude reaction product separated by SiO_2 column chromatography into a major isomer (4), oil, $[\alpha]_D^{20}$ +30° (c 1.1, EtOH), 75% yield from (3), and into a mixture of (4) and of an isomeric material, 10% from (3), and compound (4) was treated with 2 mol. eq. of NaOH 8 h at room temperature, and subsequently, with aqueous acetic acid. Alternatively, compound (4) gave with aqueous acetic acid the methyl ester (5). The abovementioned δ-lactone was assigned the xylo configuration depicted in (6), on the basis of ^{13}C and ^{1}H-n.m.r. studies (Table). The δ-lactone structure is supported by the presence of a coupling between H-4 and the hydroxyl group and by the value (67.8 ppm) of the ^{13}C chemical shift due to C-4.



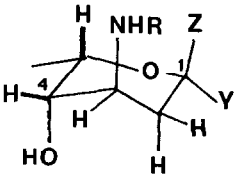
(1) R,R^1 = OH,OTs; R^2,R^3= $>CMe_2$
(2) R,R^1= H,OH; R^2,R^3= $>CMe_2$



(3) R,R^1= $>CMe_2$; R^2= Et



(4) R,R^1= $>CMe_2$; R^2= COC_6H_5; R^3= Me
(5) R=R^1= H; R^2= COC_6H_5; R^3= Me



(6) Z,Y= O; R= COC_6H_5
(7) Z,Y= H,OH; R= COC_6H_5

Furthermore, the values of J(2,3) and J(2',3) point to an axial orientation of the $NHCOC_6H_5$ substituent at C-3, because for an equatorial substituent at the same position we would expect a value for J(2,3)+J(2',3) of about 15-18 Hz. Compound (6) in THF was

TABLE: ^{1}H and ^{13}C n.m.r. parameters (d_6-DMSO sol.; chem. shifts in ppm from int. TMS; J in Hz)

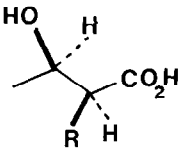
comp.:	(6)			(7)[§]			(6)	
H-1				5.20	J(1,2)	1.5	C-1	171.3
H-2	2.51	J(2,3)	3.6	1.49	J(1,2')	3.7	C-2	31.8
H-2'	2.91	J(2',3)	6.9	2.14	J(2,2')	14.0	C-3	48.9
H-3	4.31	J(2,2')	18.0	~ 4.2	J(2,3)	4.0	C-4	67.8
H-4	3.72	J(3,4)	3.7	3.37	J(2',3)	3.7	C-5	75.4
H-5	4.69	J(4,5)	1.5	~ 4.2	J(3,4)	4.5	C-6	17.1
Me	1.29	J(5,6)	6.7	1.08	J(4,5)	2.0	CONH	167.8
OH-4	5.62	J(4,OH)	4.0	4.98	J(4,OH)	5.2		
OH-1				6.72	J(1,OH)	3.5		
					J(5,6)	6,5		

[§] The signals of (7) are rather broad and the accuracy of J's is ± 0.5 Hz

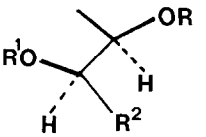
reduced with a toluene solution of diisobutylaluminium hydride at -50°C, in 65% yield, to N-benzoyl 2,3,6-trideoxy-3-amino-L-xylo-hexopyranose (7), m.p. 215-218°C, from ethyl acetate-methanol, $[\alpha]_D^{20}$ -58.5° (c 0.25, EtOH), unchanged after 24 h. The ^{1}H n.m.r. spectrum indicates that in DMSO solution (7) holds an axial orientation of the C-1 hydroxyl group, as shown by the very small J(1,2) and J(1,2') values (Table). Within 1 h the signals of the anomeric form appear reaching about 30%, which remains the equilibrium concentration. The axial orientation of the substituent at C-3 is supported by the J(2,3) and J(2',3) values, typical of axial-equatorial and equatorial-equatorial relationships between the protons in positions 2 and 3. Explorative acid hydrolysis of (7) led to a non-crystalline aminosugar hydrochloride, converted back with C_6H_5COCl and K_2CO_3 in aqueous acetone into (7) in 35% yield.

The D-enantiomer (12) was prepared starting from L-threonine (8) which was deaminated[6] to (2S,3R) dihydroxybutyric acid (9), esterified with methanolic dry HCl, and the methyl ester converted with 2,2-dimethoxypropane and 4-toluenesulfonic acid into the (2S,3R)-ester (10), $[\alpha]_D^{20}$ -18.7° (c 4.1, $CHCl_3$), dist. 90°C at 70 mmHg, shown by glc analysis and comparison with authentic samples to be devoid of the erythro isomer, in ca. 45% yield from (8). Compound (10) was converted in 85% yield upon $LiAlH_4$ reduction into the

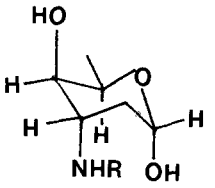
(2S,3R) alcohol (11), the enantiomer of (2). From this compound N-benzoyl 2,3,6-trideoxy-3-amino-D-xylo-hexopyranose (12), identical in every respect to the L-isomer (7), but showing opposite optical rotation (+56.5°), was obtained through the above sequence.



(8) R= NH_2
(9) R= OH



(10) $R,R^1 = >CMe_2$; $R^2 = CO_2Me$
(11) $R,R^1 = >CMe_2$; $R^2 = CH_2OH$



(12) R= COC_6H_5

The high degree of stereospecificity of the β-addition of ammonia onto (3) here observed is in agreement with previous experiments with the D,L-erythro isomer of (3), which yielded, eventually, the N-acetyl D,L-arabino amino sugar (acosamine).[5]

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