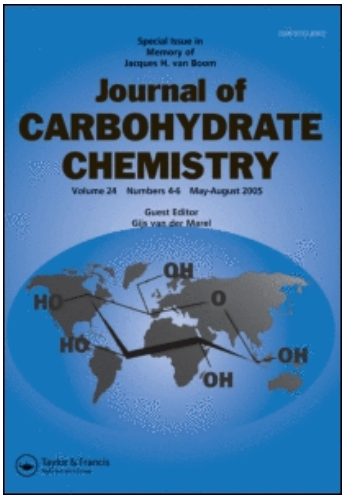

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Synthesis of *N*-Trifluoroacetyl Derivatives of Enantiomeric 2,5,6-Trideoxy-5-Amino Hexoses from Non-Carbohydrate Precursors

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SYNTHESIS OF N-TRIFLUOROACETYL DERIVATIVES OF ENANTIOMERIC 2,5,6-TRIDEOXY-5-AMINO HEXOSES FROM NON-CARBOHYDRATE PRECURSORS

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ABSTRACT

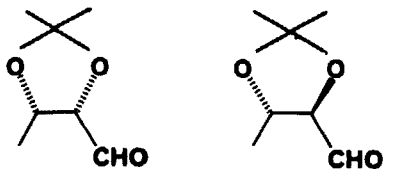
The **D**-lyxo and **D**-ribo methyl-N-trifluoroacetyl-2,5,6-trideoxy-5-amino hexofuranosides (**13**) and (**14**) are accessible from carbohydrate-like acyclic C_7 products **3** and **5**, whereas the 3-C-methyl analog of **13** is prepared in similar way from **15**. Azide treatment of the toluensulphonate ester at position 4 of methyl-2,6-dideoxy-3-C-methyl-**L**-ribo hexopyranoside (**21**), using hexamethylphosphoric acid triamide as co-solvent, gives rise to a mixture of azido derivatives in which prevails the arabino material (**24**), formed from **21** via inversion of configuration at positions 4 and 5.Product **24** gives rise to the 5-amino sugar derivative **28**. The enantiomers of **13** and **14** are accessible from **D**-allo threonine and **L**-threonine, respectively.

INTRODUCTION

There has been in recent years a considerable interest in the synthesis of the configurational isomers of 2,3,6-trideoxy-3-amino-**L**-lyxo hexose due to the relevant biological properties shown by the natural and synthetic glycosides of which they are a part.[1]

Current approaches to this class of compounds are based on the use, as starting materials, of both hexoses of the **L** and **D**-series or

of relatively small, highly functionalized, optically active materials, components of the "pool of chirality" or produced by enzymic transformation of non-conventional substrates.[2] In the latter instance, the stereoselective elaboration of the C_6 framework of the target aminodeoxy sugar often occurs through addition of carbon nucleophiles onto α (and β) oxygen substituted carbonyl compounds. Along this line, starting from the (2S,3S) aldehyde (**1**)[3] and its α-epimer (**2**),[4] we prepared, via addition of allyl metals,[5] the two sets of C_7 compounds **3-4** and **5-6**, respectively, used, inter alia, as intermediates in the synthesis of N-protected derivative of 2,3,6-trideoxy-3-amino-L-lyxo hexose (**7**) (**L**-daunosamine)[4] and 2,4,6-trideoxy-4-amino-L-lyxo hexose (**8**) (L-isodaunosamine).[6]



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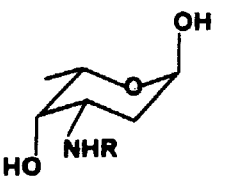
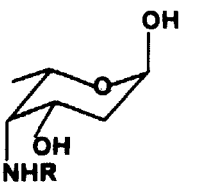




R = $COCF_3$ or COC_6H_5

7 **8**

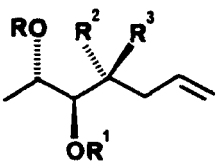
The outstanding biological properties of the glycoside derived from **8** and adriamycinone[7] induced us to extend further the synthetic applications of products like **3-6** to the preparation of enantiomeric forms of configurational isomers of 2,5,6-trideoxy-5-amino hexose with the aim of submitting to pharmacological study the derived anthracycline glycosides. Here we report on the results obtained.

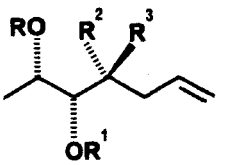
RESULTS AND DISCUSSION

Inspection of the **L**-ribo and **L**-lyxo carbohydrate-like products **3** and **5**, obtained as almost the only diastereoisomers in the reaction of **1** and **2** with diallyl zinc,[5] indicates that the conversion into the **D**-lyxo and **D**-ribo isomers of the target 2,5,6-trideoxy-5-aminohexose only requires introduction, at some stage of the sequence, of a nitrogen function at position 2 with inversion of configuration. To this end products **3** and **5** were O-benzylated to **3a** and **5a** and subsequently hydrolyzed to the diols (**3b**) and (**5b**). These materials, on treatment with 1 molar equivalent of 4-toluenesulphonyl chloride in CH_2Cl_2 in

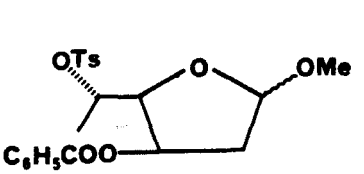
the presence of pyridine afforded, as the only products, the 2-tosylates (3c) and (5c). The structure of these materials is supported by ^1H NMR studies and by their conversion, by ozonolysis and Me_2S treatment, into the methyl glycosides (9) and (10). During the ozonolysis, in some runs, we observed oxidation of the benzyl group to the benzoate (the synthetic sequence is described for the benzoate derivatives). The tosylate esters (9) and (10), on treatment with NaN_3 in DMF and basic hydrolysis, afforded the azides (11) and (12). Conversion of the latter into the required methyl glycosides (13) and (14) required catalytic hydrogenation, treatment with trifluoroacetic anhydride and controlled hydrolysis of the O-trifluoroacetate esters.

The synthesis of the L-enantiomers of 13 and 14 was achieved starting from the enatiomers of 1 and 2 available from D-allo threonin and L-threonin, respectively.[3]





3	$R,R^1 = CMe_2$; R^2=OH; R^3= H	5	$R,R^1 = CMe_2$; R^2=H; R^3= OH
3a	$R,R^1 = CMe_2$; R^2= OBzl; R^3= H	5a	$R,R^1 = CMe_2$; R^2=H; R^3= OBzl
3b	R,R^1,R^3 = H; R^2= OBzl;	5b	R,R^1,R^2 = H; R^3= OBzl
3c	R = Ts; R^1,R^3 = H; R^2= OBzl	5c	R = Ts; R^1,R^2= H; R^3= OBzl
4	$R,R^1 = CMe_2$; R^2= H; R^3= OH	6	$R,R^1 = CMe_2$; R^2= OH; R^3= H



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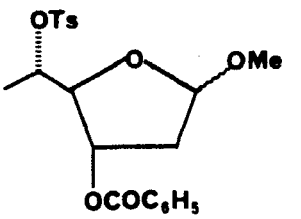

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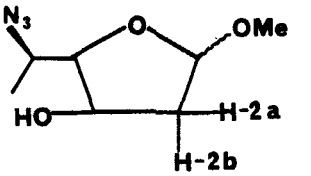

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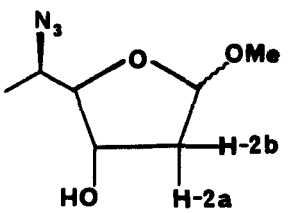

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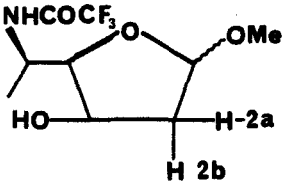

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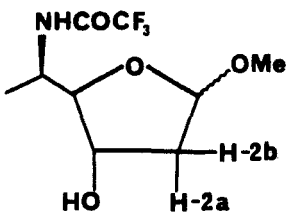


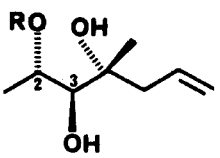
14

The 3-C-methyl analog of **13** seemed available from the ribo adduct **15**, prepared[5] from the methyl ketone analog of **1** and allylmagnesium bromide. Thus, product **15** was converted into the monotosylate (**16**), yielding, upon ozonolysis, as above, the methyl glycoside (**17**). The latter upon azide displacement afforded the D-lyxo azide (**18**), from which the N-trifluoroacetyl derivative (**19**) was eventually obtained.

Subsequently, we thought to be able to have access from the L-ribo adduct **15** to the products isomeric with **19** via the L-ribo methyl glycoside (**20**) and its 4-toluensulphonate (**21**). Current studies[8a,c] on product distribution and steric course of the reaction with different nucleophiles of 4-sulphonate esters of hindered and unhindered 6-deoxy glycopyranosides, indicate the prevalent formation of glycofuranosides with inversion at position 4, the incoming nucleophile being introduced at position 5 with prevalent retention of configuration.

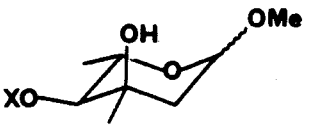
According to this observation, we submitted the 4-tosylate (**21**) to azide treatment in DMF at 150 °C for 16 h, without observing noticeable transformation products. However, when 10% hexamethylphosphoric acid triamide was added to the reaction mixture, under the same conditions, a rapid conversion of **21** into an inseparable mixture of products **22**, **23** and **24** took place in ca. 70% yield. The ratio of the above mentioned products in the mixture was determined by ^{1}H NMR studies (see below) and were found to be ca. 15 : 20 : 65. Whereas the assignment of the xylo structure **22** to the minor transformation product was straightforward, the identification of product **23** and **24** by spectroscopic means required unambiguous synthesis of one of the components of the mixture and direct comparison. To this end, the D,L-arabino γ-lactone (**25**), intermediate in the synthesis of D,L-mycarose,[9] was converted into the 5-tosylate (**26**), yielding upon azide displacement in DMF the xylo material **27**, converted, in turn, upon DIBAH reduction, into a material identical with **23**. The inversion of configuration in the azide displacement is expected from analogies: i.e, the conversion of the brosylate of methyl 5,6-dideoxy-2,3-isopropylidene-α-L-allofuranoside into the D-talo-5-azide upon azide treatment.[8b] Furthermore, since it appeared from the ^{1}H NMR studies that the two ring contraction products have the same relative stereochemistry at positions 3 and 4, it follows that the major isomer obtained

in the reaction described above has the D-arabino configuration depicted in **24**. The mixture **22-24** was submitted to catalytic hydrogenation yielding, after N-trifluoroacetylation, the D-arabino methyl glycoside (**28**).



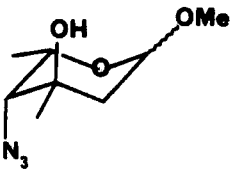
15 R = H

16 R = Ts



20 X = H

21 X = Ts



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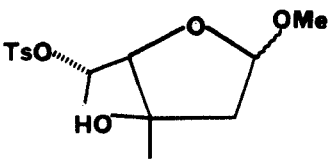
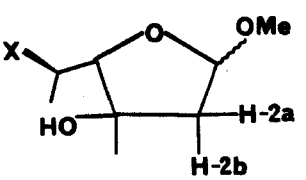
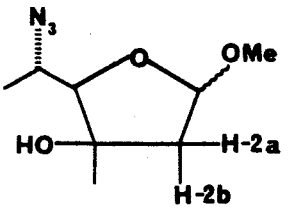


17



18 X= N_3

19 X=NHCOCF_3



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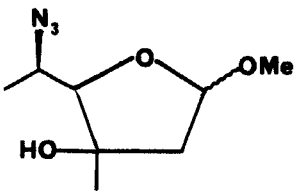

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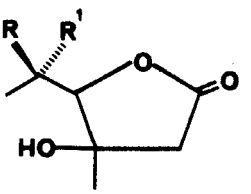
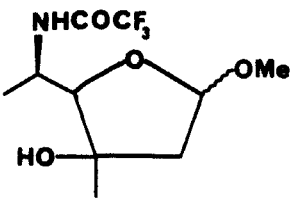


25 R= OH ; R^1= H

26 R= OTs; R^1= H

27 R= H ; R^1= N_3



28

The relative stereochemistry of the ring carbons for the above mentioned 5-aminohexoses was deduced from the NMR data. Compounds, **14**, **18**, **19** and **28** have been isolated as α and β anomers. The ^{1}H chemical shifts and coupling constants are collected in Table 1 and Table 2 respectively, while the ^{13}C chemical shifts of the 3-C-methyl derivatives are reported in Table 3. Values of the vicinal coupling constants lower than 4 Hz in furanose rings are generally associated with neighbouring trans hydrogens.[10] Within the series of compounds **11-14** the value of J(3,4) of 1.9-3.4 Hz for **11**β, **12**α, **13**β and **14**α indicates a trans relationship between the protons H-3 and H-4. Most probably an intramolecular hydrogen bonding between OH-3 and OMe groups may contribute to the stabilization of a ring conformation for these anomers with the H-3 and H-4 protons in a pseudoequatorial orientation. This conclusion is supported by the observation that OH-3 resonates at lower fields with respect to the anomers with opposite configuration at C-1 (except for compounds **13**). Such structural assignment is substantiated by the fact that the chemical shifts of H-3 and H-4 protons follow quite well the predicted trend[11] changing the orientation of the methoxyl group, i.e. the chemical shift of a ring proton, in 1,3 relationship with the OMe group, shifted downfield by 0.2-0.4 ppm when the substituent changes from the anti to the syn position.

The configuration of the ring carbons for the 2,5,6-trideoxy-5-amino-3-C-methyl hexofuranosides was determined as follows. The ^{13}C chemical shift of the Me-3 group is sensitive to the orientation of the C-4 substituent. For example the chemical shift of the methyl groups is 3.6 ppm upfield for the cis with respect to the trans 1,2-dimethylcyclopentanes due to the γ-gauche effect.[12] Thus for compounds **18** and **19**, with a cis relationship between the Me-3 group and the C-4 substituent, the C-3 carbon resonates at 21-22 ppm, while for compounds **23**, **24** and **28**, showing a trans orientation of the two substituents, the C-3 is at 24-27 ppm. The configuration of the anomeric carbon can be determined from the chemical shift of the C-3 hydroxyl. OH-3 resonates at 3.2-3.7 ppm for the β-anomers of **18**, **19**, **24** and **28** (**D** series) and for the α-anomer of **23** (**L** series). These values are consistent with the existence of an intramolecular hydrogen bond between the OH-3 and OMe groups. On the contrary the OH-3 chemical

TABLE 1. Proton chemical shifts of 2,5,6-trideoxy-5-amino hexofuranosides[a]

Compd[b]	H-1	H-2a	H-2b	H-3	H-4	H-5	Me-5	Me-3	OMe	OH-3	NH-5
12α	5.11	2.02	2.13	4.15	3.97	3.62	1.28	-	3.38	2.72	-
12β	5.03	2.08	2.25	4.49	3.58	3.49	1.39	-	3.33	2.00	-
11α	5.04	2.07	2.28	4.42	3.72	3.52	1.30	-	3.38	1.75	-
11β	5.13	2.00	2.16	4.09	3.98	3.44	1.37	-	3.39	2.71	-
14α	5.11	2.03	2.10	4.04	4.02	4.13	1.18	-	3.39	2.78	6.47
14α[c]	4.50	1.63	1.49	3.62	3.69	3.84	0.68	-	2.96	2.13	-
14β	5.02	2.07	2.31	4.48	3.84	4.14	1.33	-	3.35	1.95	6.77
13α	5.06	2.10	2.34	4.30	3.97	4.16	1.31	-	3.41	2.34	7.49
13β	5.07	1.97	2.05	3.99	3.95	4.26	1.32	-	3.38	2.34	6.36
18β	5.12	2.01	2.16	-	3.97	3.27	1.43	1.33	3.41	3.72	-
18α	5.16	2.09	2.25	-	3.67	3.41	1.36	1.41	3.45	2.05	-
19β	5.12	2.09	1.81	-	4.02	4.22	1.31	1.25	3.41	3.49	6.37
19α	5.25	2.43	1.82	-	3.95	4.13	1.27	1.30	3.48	1.75	8.13
23α[c]	4.53	1.77	1.42	-	3.37	3.45	1.06	1.01	3.06	3.30	-
23β[c]	4.84	1.94	1.88	-	3.44	3.27	1.07	1.15	3.16	2.00	-
24β[c]	4.44	1.79	1.43	-	3.20	3.57	1.25	1.30	2.88	3.24	-
24α[c]	4.78	2.02	1.86	-	3.36	3.54	1.21	1.25	3.10	1.40	-
28β	4.98	2.06	2.15	-	3.81	4.48	1.40	1.46	3.37	3.32	7.50
28α	5.08	2.32	1.99	-	3.66	4.40	1.39	1.44	3.35	2.39	7.14

a. Chemical shifts in ppm from internal TMS; solvent $CDCl_3$ except otherwise indicated. b. All compounds belong to the **D** series, except the racemic **D,L-**xylo derivative **23**, which has been depicted as the **L** enantiomer. c. Solvent C_6D_6.

TABLE 2. Proton coupling constants of 2,5,6-trideoxy-5-amino hexofuranosides[a]

Compd.	J(1,2a)	J(1,2b)	J(2a,2b)	J(3,2a)	J(3,2b)	J(3,4)	J(4,5)	J(5,Me)	J(3,OH)	J(3,NH)
12α	0.6	4.4	13.9	1.4	6.4	1.9	4.3	6.8	b	-
12β	5.2	1.7	13.3	7.2	7.0	4.6	8.4	6.4	b	-
11α	5.4	1.6	13.2	7.9	7.0	5.6	6.9	6.7	5.6	-
11β	0.5	4.5	14.0	1.3	6.4	1.9	4.2	6.8	10.8	-
14α[c]	1.0	4.8	14.0	2.2	6.4	2.8	6.6	6.8	10.8	9.0
14β	5.2	1.4	13.0	8.0	7.0	5.8	5.8	6.6	b	7.5
13α	5.6	1.4	13.8	7.4	7.2	5.0	2.0	6.8	b	8.5
13β	1.4	4.6	14.2	2.8	6.8	3.4	3.4	6.9	b	9.0
18β	0.5	5.0	13.5	-	-	-	1.6	6.8	-	-
18α	5.8	4.3	13.4	-	-	-	4.8	6.8	-	-
19β	0.7	4.8	13.8	-	-	-	1.8	6.8	-	9.0
19α	6.3	4.4	14.8	-	-	-	1.6	6.8	-	9.0
23α[c]	0.5	4.8	13.5	-	-	-	8.2	6.6	-	-
23β[c]	5.6	2.5	14.0	-	-	-	3.8	6.9	-	-
24β[c]	0.5	4.8	13.4	-	-	-	8.8	6.6	-	-
24α[c]	5.8	3.0	13.9	-	-	-	8.1	6.6	-	-
28β	0.6	4.5	13.8	-	-	-	4.6	7.0	-	8.8
28α	5.8	3.0	14.0	-	-	-	6.4	6.8	-	8.8

a. Coupling constants in Hz; solvent $CDCl_3$ except otherwise indicated. b. Broad signals. c. Solvent C_6D_6

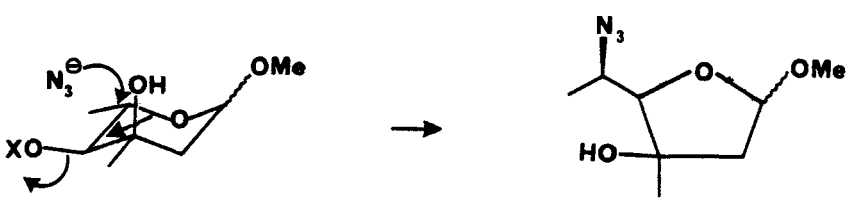
TABLE 3. Carbon chemical shifts of 2,5,6-trideoxy-5-amino-3-C-methyl hexofuranosides[a]

Compd	C-1	C-2	C-3	C-4	C-5	Me-3	Me-5	OMe
18 β	105.6	46.8	78.9	92.5	56.5	21.1	16.9	55.7
18 α	104.7	47.4	78.4	90.0	56.6	22.6	16.0	55.9
19 β	104.3	47.1	78.0	90.9	45.6	21.2	20.0	55.2
19 α	105.8	47.5	79.9	91.9	45.4	22.0	19.3	55.9
23 α	104.1	48.2	77.4	90.9	60.4	24.5	16.5	55.0
23 β	103.3	49.9	78.4	86.1	55.8	26.2	16.5	55.2
24 β	104.1	47.6	77.1	88.9	57.4	24.3	17.4	54.9
24 α	103.3	49.5	78.5	85.2	56.3	26.9	16.7	55.1
28 β	103.7	48.2	78.8	87.2	47.0	24.5	16.6	55.5
28 α	103.1	50.1	79.4	84.3	46.5	27.0	17.5	55.3

a. Chemical shifts in ppm from internal TMS; solvent $CDCl_3$

shifts for the anomers with an anti relationship between the two substituents, where no intramolecular hydrogen bonding can occur, resonate at higher fields in the range 1.7-2.4 ppm.

The steric outcome of the above mentioned ring contraction requires some comments. At variance with the examples reported up to now,[8] in which inversion at position 4 and prevalent retention at 5 is observed, the formation of **24** as the main product from **21** indicates inversion at both positions 4 and 5. In order to account for the formation of **23** and **24** from **21** several mechanisms must be operating. However, the production of **24**, formally accessible by direct attack of azide onto position 5 followed by displacement of the 4-tosylate by the ring oxygen once the C5-O bond had been broken, has to be considered as a consequence of the use, as cosolvent, of hexamethylphosphoric acid triamide, according to the following formal picture:



It thus appears that several configurational isomers of 2,5,6-trideoxy-5-aminohexofuranosides, some of which in the two enantiomeric forms, are accessible from chiral non-carbohydrate precursors in protected forms, suitable for glycosidation experiments with adriamycinone.

EXPERIMENTAL

General methods. ^1H NMR were determined on a Varian EM 390 (90 MHz) and on a Bruker CXP (300 MHz) spectrometers, chemical shifts are expressed in ppm (δ) relative to internal TMS. All NMR spectra were recorded in $CDCl_3$ unless otherwise stated. Optical rotation values were recorded on a JASCO DIP 181 digital polarimeter. Specific rotation values refer to 20 °C and c 1, $CHCl_3$ unless otherwise indicated. Purification of the products was performed by silica gel column chromatography (Merck 60, 0.04-0.063 mm), eluting with mixtures of n-hexane and ethyl acetate. Analytical samples were prepared, when possible, by bulb to bulb distillation at reduced pressure, or by crystallization. Evaporation was conducted in vacuo. Melting points are uncorrected.

General procedures. The azide displacement was carried out in dry DMF with 5 molar equivalents of NaN_3, heating in an oil bath at 140 °C for a period of 6 to 36 h. The formation of the azide was followed by TLC. The reaction mixture was then poured into ice water and extracted thrice with a 1:1 mixture of n-hexane-ethyl acetate. Hydrogenation of the azide was performed in EtOH using as catalyst 10% Pd on charcoal or PtO_2 at atmospheric pressure. Protection of the NH_2 group was obtained with 5 equivalent excess of trifluoroacetic anhydride in CH_2Cl_2 at 0 °C stirring for 12 h.

Methyl α and β-2,5,6-trideoxy-N-trifluoroacetyl-D-lyxo hexofuranoside (13). 4.6 g (0.096 mole) of NaH was suspended in 150 mL of dry DMF. The suspension was stirred and 14.8 g (0.079 mole) of the alcohol **3**[5] was added dropwise at 0 °C. The reaction mixture was heated at 50 °C for 1 h, cooled to 25 °C and 10.1 mL (0.087 mole) of $PhCH_2Cl$ added dropwise. After 3 h the reaction was quenched with 20 mL of MeOH, poured into ice water and extracted with ethyl ether-hexane (3:1). Evaporation and purification gave 12 g (0.044 mole, 57%) of pure **3a**,

$[\alpha]_D$=-6.0°, ^{1}H NMR (δ) 1.25 (3H, CH_3, d), 1.34 (3H, CH_3, s), 1.44 (3H, CH_3, s), 2.40-2.68 (2H, CH_2, m), 3.50-3.70 (1H, CH, m), 3.91-4.20 (1H, CH, m), 4.22-4.42 (1H, CH, m), 4.38 and 4.69 (2H, CH_2, AB system), 5.02-5.31 (2H, CH_2, m), 5.75-6.27 (1H, CH, m) and 7.33 (5H, Ph, s). Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.82; H, 8.70. **3a** was hydrolyzed to the corresponding diol **3b** in a mixture of 100 mL of MeOH and 100 mL of 20% CH_3COOH at reflux. After 6 h the solution was cooled, reduced to small volume, dissolved in 100 mL of ethyl acetate and washed with brine (2x20 mL). Purification of the crude extract gave 7.7 g (0.033 mole,77%) of **3b**, $[\alpha]_D$ = -58.5°, ^{1}H NMR (δ) 1.25 (3H, CH_3, d), 2.04-2.25 (2H, 2OH, broad), 2.40-2.67 (2H, CH_2, m), 3.37-3.70 (2H, 2CH, m), 3.80-4.08 (1H, CH, m), 4.49 and 4.72 (2H, CH_2, AB system), 5.05-5.32 (2H, CH_2, m), 5.72-6.13 (1H, CH, m) and 7.32 (5H, Ph, s). Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.20; H, 8.50. To the above diol, 7.7 g (0.033 mole), dissolved in 40 mL of dry pyridine, 6.1 g (0.033 mole) of TsCl was added portionwise at room temperature. The reaction mixture was stirred for 24 h, poured into ice water and extracted with CH_2Cl_2. The organic phase was subsequently washed with a saturated solution of $NaHCO_3$, 10% HCl and water. Evaporation and purification gave 9.3 g (0.024 mole, 73%) of **3c**, $[\alpha]_D$ =-34.4°, ^{1}H NMR (δ) 1.20 (3H, CH_3, d), 2.08-2.24 (1H, OH, broad), 2.31-2.53 (1H, CH, m), 2.45 (3H, CH_3, s), 3.32-3.61 (1H, CH, m), 3.72-3.94 (1H, CH, m), 4.40 and 4.67 (2H, CH_2, AB system), 4.60-4.90 (1H, CH, m), 5.00-5.28 (2H, CH_2, m), 5.60-6.10 (1H, CH, m), 7.20-7.45 (2H, Ph, m), 7.38 (5H, Ph, s) and 7.75-7.92 (2H, Ph, m). Anal. Calcd for $C_{21}H_{26}O_5S$: C, 64.60; H, 6.71. Found: C, 64.65; H, 6.68. Ozone was passed through a solution of 11 g (0.028 mole) of **3c** in 100 mL of dry MeOH at -40 °C for 30 min. The solution was purged with nitrogen, 3.2 g (0.05 mole) of Me_2S was added and the reaction mixture was subsequently kept at 25 °C for 1 h and 50 °C for 3 h. Evaporation and purification (SiO_2 chromatography) gave directly the methyl glycoside-**9**, 7.14 g (0.017 mole, 60%). The α and β anomers were separated by silica gel chromatography and had the following $[\alpha]_D$, -5.9° for the α anomer and -48.2° for the β anomer. Anal. Calcd for $C_{21}H_{24}O_7S$: C, 59.99; H, 5.75. Found: C, 59.97; H, 5.73. Treatment of **9**, 4.5 g (0.01 mole), as reported in the general procedures gave the azido benzoate intermediate which was hydrolyzed with 10% NaOH in MeOH to give **11**,

1.9 g (6.5 mmole, 66%), $[\alpha]_D$ =-107.4°. Anal. Calcd for $C_7H_{13}N_3O_3$: C,44.91; H, 7.00; N, 22.45. Found: C, 44.89; H, 6.98; N, 22.41. Catalytic hydrogenation and protection with trifluoroacetic anhydride, as reported in the general procedures, gave the N,O-bis(trifluoroacetyl) derivative which was dissolved in 100 mL of dry MeOH and 100 mg of MeONa were added. The reaction mixture was heated at reflux for 3 h. Evaporation and purification by chromatography gave the final deoxy sugar **13**, 1.15 g (4.5 mmole, 70%), $[\alpha]_D$ = +2.8°. Anal. Calcd for $C_9H_{14}F_3O_4N$: C, 42.02; H, 5.49; N, 5.45. Found: C, 42.01; H, 5.47; N, 5.41.

Methyl α and β-2,5,6-trideoxy-N-trifluoroacetyl-D-ribo hexofuranoside (14). Exactly the same sequence used for the preparation of **13** was followed. The physical properties of all the intermediates are reported below. **5a**, $[\alpha]_D$ =+10.5°, ^{1}H NMR (δ) 1.30 (3H, CH_3, d), 1.40 (6H, $2CH_3$, s), 2.31-2.52 (2H, CH_2, m), 3.49-3.72 (2H, 2CH, m), 3.90-4.21 (1H, CH, m), 4.65 (2H, CH_2, AB sytem), 5.01-5.30 (2H, CH_2, m), 5.70-6.18 (1H, CH, m) and 7.33 (5H, Ph, s). Found: C, 73.56; H, 8.78. **5b**, $[\alpha]_D$ =+11.1°, ^{1}H NMR (δ) 1.20 (3H, CH_3, d), 2.30-2.55 (2H, CH_2, m), 2.70 (2H, OH, broad), 3.30-3.50 (1H, CH, m), 3.57-3.78 (1H, CH, m), 3.93-4.20 (1H, CH, m), 4.61 (2H, CH_2, AB system), 5.01-5.28 (2H, CH_2, m), 5.67-6.12 (1H, CH, m) and 7.33 (5H, Ph, s). Found: C, 71.09; H, 8.47. **5c**, ^{1}H NMR (δ) 1.30 (3H, CH_3, d), 1.79-2.05 (1H, OH, broad), 2.23-2.68 (2H, CH_2, m), 2.50 (3H, CH_3, s), 3.38-3.68 (1H, CH, m), 4.41 and 4.53 (2H, CH_2, AB system), 4.99-5.33 (2H, CH_2, m), 5.61-6.05 (1H, CH, m), 7.18-7.38 (2H, Ph, m), 7.40 (5H, Ph, s) and 7.70-7.92 (2H, Ph, m). Found: C, 64.58; H, 6.67. **10**, $[\alpha]_D$ =+29.4°. Found: C, 60.01; H, 5.74. **12**, $[\alpha]_D$ =-7.1°. Found: C, 44.92; H, 6.88; N, 22.46. **14**, $[\alpha]_D$ = +122.2°, m.p. 85 °C for the α anomer, $[\alpha]_D$ =-56.5°, m.p. 90 °C for the β anomer. Found: C, 42.00; H, 5.45; N, 5.48.

Azide treatment of the 4-toluensulphonate ester of methyl α and β-2,6-dideoxy-3-C-methyl-L-ribohexopyranoside (21): methyl 5-amino-2,5,6-trideoxy-3-C-methyl-D-arabino hexofuranoside (28). To 1.94 g (11 mmole) of methyl α and β-2,6-dideoxy-3-C-methyl-L-ribo hexopyranoside (**20**),[5] in 5 mL of dry CH_2Cl_2 and 5 mL of dry pyridine, 2.5 g (13 mmole) of TsCl were added at 0 °C. The mixture was stirred 36 h at 25 °C, poured into ice water and extracted twice with dichloromethane. The crude extract was purified by silica gel chromatography to give

21, 3 g (9.1 mmole, 83%), $[\alpha]_D$ = -36.1° (c 0.5, $CHCl_3$). Anal. Calcd for $C_{15}H_{22}O_6S$: C, 54.54; H, 6.71. Found: C, 54.51; H, 6.70. The 4-tosylate (**21**) 3 g (9.1 mmole) was treated under stirring at 150 °C with 3 g (45 mmole) of NaN_3 in 20 mL of DMF containing 2 mL of hexamethylphosphoric acid triamide. After 4 h the reaction mixture was cooled, poured into ice water and worked up as above to afford, after SiO_2 chromatography, 1.3 g (ca. 70%) of an azide fraction shown by ^1H NMR studies to be a ca. 15:20:65 mixture of products **22**, **23** and **24**, respectively. The latter mixture, once hydrogenated and N-trifluoroacetylated, separated, from hexane-ethyl acetate, methyl-5-amino-2,5,6-trideoxy-N-trifluoroacetyl-3-C-methyl-**D**-arabino hexofuranoside (**28**), 0.8 g (3 mmole, 50%),for the α anomer $[\alpha]_D$ =+122.3° (c 0.5, MeOH), m.p. 154 °C; $[\alpha]_D$ =-24.7° (c 0.5, MeOH) for the β anomer. Anal. Calcd for $C_{10}H_{16}F_3NO_4$: C, 44.28; H, 5.95; N,5.16. Found: C, 44.30; H, 5.96; N,5.14.

Methyl 2,5,6-trideoxy-N-trifluoroacetyl-3-C-methyl-5-amino-D-lyxo hexofuranoside (19). 3.4 g of (2S,3S,4R)-4-methyl-hept-6-en-2,3,4-triol (**15**)[5] (0.021 mole) in 35 mL of dry CH_2Cl_2 and 35 mL of dry pyridine was treated with 4.4 g (0.023 mole) of TsCl at room temperature for 24 h. Then a sequence similar to the one used in the preparation of **13** and **14** was followed giving the 6-O-tosylate (**16**), 5 g (0.016 mole, 75%), $[\alpha]_D$ =-30.7°, ^1H NMR (δ) 1.25 (3H, CH_3, s), 1.35 (3H, CH_3, d), 1.60 (1H, OH, broad), 2.00-2.42 (3H, CH_2, OH, m), 2.51 (3H, CH_3, s), 3.72 (1H, CH, m), 4.73-5.33 (3H, CH, CH_2, m), 5.68-6.07 (1H, CH, m),7.40 (2H, Ph, m) and 7.87 (2H, Ph, m). Anal. Calcd for $C_{15}H_{22}O_5S$: C, 57.31; H, 7.06. Found: C, 57.28; H, 7.02. Ozonolysis of the above tosylate gave the methyl glycoside (**17**), 4.6 g (0.014 mole, 60%), which was separated by column chromatography into the two α and β anomers, β anomer $[\alpha]_D$ =-52.7°, α anomer $[\alpha]_D$ =+39.0°. Anal. Calcd for $C_{15}H_{22}O_6S$: C, 54.54; H, 6.71. Found: C, 54.58; H, 6.77. Displacement with NaN_3 gave 1.8 g (9.1 mmole, 65%) of **18**, β anomer $[\alpha]_D$= -192.2°, α anomer $[\alpha]_D$ =-16.5°. Anal. Calcd for $C_8H_{15}N_3O_3$: C, 47.75; H, 7.51; N, 20.88. Found: C, 47.78; H, 7.55; N, 20.90. Catalytic hydrogenation and protection of the NH_2 group gave **19**, 2 g (7.4 mmole, 81%), $[\alpha]_D$ =-52.0° for the α anomer, $[\alpha]_D$ =-63.4° for the β anomer. Anal. Calcd for $C_{10}H_{16}NO_4F_3$: C, 44.28; H, 5.95; N, 5.16. Found: C, 44.27; H, 5.98; N, 5.12. (Elemental analysis done on the β anomer).

Methyl 5-azido-2,5,6-trideoxy-3-C-methyl-D,L-xylo hexofuranoside (23). To 3 g (0.018 mole) of **25**, prepared as reported,[9] dissolved in 30 mL of dry CH_2Cl_2 and 5 mL of anhydrous pyridine, 1.6 mL (0.02 mole) of MsCl was added dropwise at 0 °C. The reaction mixture was stirred at 25 °C for 8 h, poured into ice water and the organic phase washed with a saturated solution of $NaHCO_3$. Evaporation and purification gave 2.7 g (0.011 mole, 61%) of **26**. Treatment with NaN_3 as reported in the general procedures, gave, after crystallization from hexane-ethyl acetate, 1.04 g (5.61 mmole, 50%) of **27**, IR (KBr), 3380 (OH), 2130 (N_3) and 1765 cm^{-1} (γ lactone), m.p. 102 °C, ^1H NMR (δ) 1.56 (3H, CH_3, s), 1.60 (3H, CH_3, d), 2.66 (2H, CH_2, s), 4.25 (1H, CH, d), 4.38 (1H, OH, broad) and 5.00-5.30 (1H, CH, m). Anal. Calcd for $C_7H_{11}O_3N_3$: C, 45.40; H, 5.99; N, 22.69. Found: C, 45.43; H, 6.02; N, 22.65. To the above azido lactone **27**, 1 g (5.6 mmole), dissolved in 10 mL of anhydrous ethyl ether, 5.6 mL of DIBAH (1M solution in hexane) was added at -78 °C. The reaction was stirred at the same temperature for 2 h, quenched with 5 mL of MeOH and left to warm to 25 °C. The aluminium salts were filtered through a small pad of celite and carefully washed with MeOH. The solvent was evaporated to leave a syrup (140 mg) which was immediatly redissolved in 2 mL of dry MeOH and 0.2 mL of methanol saturated with HCl gas. The mixture was left at 20 °C for 2 h. Concentration under reduced pressure and purification by silica chromatography gave 90 mg (0.45 mmole, 8%) of **23**. Anal. Calcd for $C_8H_{15}O_3N_3$: C, 47.75; H, 7.51; N, 20.88. Found: C, 47.71; H, 7.48; N, 21.01.

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