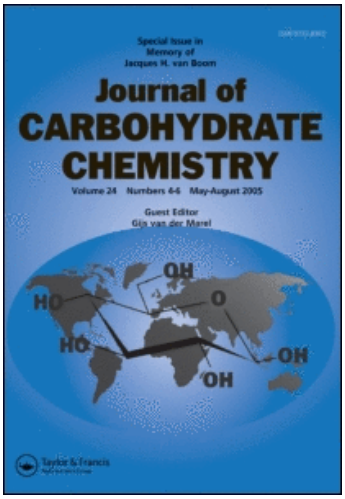

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ON THE USE OF (4S,5S)-2-PHENYL-4,5-DIMETHYL-4-FORMYL-4,5-DIHYDRO-OXAZOLE IN THE SYNTHESIS OF N-PROTECTED 2,3,4,6-TETRADEOXY-4-C-METHYL-4-AMINO-L-HEXOSE DERIVATIVES

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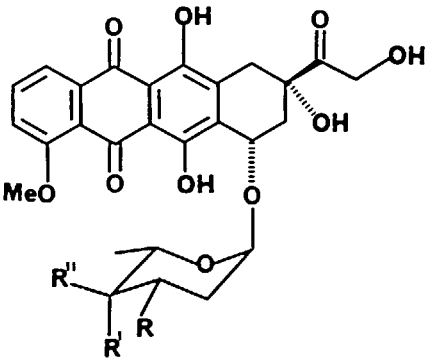
ABSTRACT

The (4S,5S)-2-phenyl-4,5-dimethyl-4-formyl-4,5-dihydro-oxazole (**4**), *via* the α,β-unsaturated ester **5** and *re*-face addition of nitrogen and sulfur nucleophiles, gave eventually the *ribo*-imidazolino hexose **15** and the methyl α and β-2,3,4-6-tetradeoxy-4-*C*-methyl-4-trifluoroacetamido-3-thia-L-*ribo*-hexopyranoside (**16**). Addition *via* the adduct **17** afforded the *arabino*-3,4-diamino derivative **20** and the *ribo* isomer **20a**, the 3-fluoro-L-*ribo* product **22**, the 2,3-unsaturated L-hexose **21** and the *erythro*-2,3,4,6-tetradeoxy compound **23**. The conformational feature, in solution, of the reported L-hexoses is also discussed on the basis of their ^{1}H NMR data.

INTRODUCTION

Since its discovery twenty years ago[1] the anthracycline glycoside Adriamycine (**1**) still appears to be one of the most potent clinically used antitumor agents. Despite the

numerous efforts up to now, no significant benefits for the pharmacological profile seem to arise from structural modifications of the framework of **1**. The only noticeable exception seems to arise from functional group isomerizations, performed on the aminoglycoside part, leading to 4′-*epi*-adriamycine (**2**)[2] (Epirubicin) and to the 3′,4′-*iso* derivative **3**,[3] respectively.

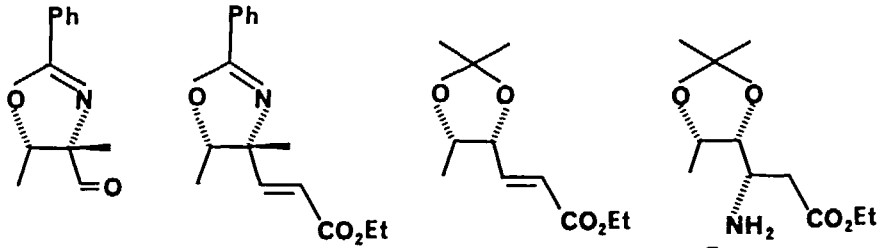


1 R=NH_2; R′=OH; R″=H
2 R=NH_2; R′=H; R″=OH
3 R=OH; R′=NH_2 R″=H

For some years now we have been studying synthetic approaches[4] to the aminosugars present in **1-3** and to their structural analogs, using, as starting materials, the components of a selected set of non-carbohydrate derived chiral compounds. In this paper we present the results of studies designed to obtain a series of 2,3,4,6-tetradeoxy-4-*C*-methyl-4-amino-L-hexose derivatives differently substituted at position 3, from the C_4 aldehyde **4**, easily accessible from L-threonine.[5] These new aminosugar derivatives served as intermediates in the synthesis of analogs of **1** incorporating in the aminoglycoside moiety, in part, structural features common to both **2** and **3**: an equatorially oriented amino group in position 4, and a substituent in position 3 which could be an amino (or amido) group or a sulphur or halogen atom.

DISCUSSION

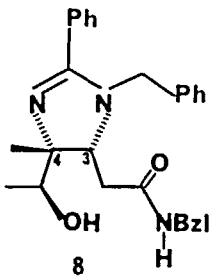
In the first instance we thought it possible to have access to the above mentioned products from the C_6, α,β-unsaturated ester **5** and Michael addition of suitable nucleophiles. We indeed expected to end up with 3,4-*threo* adducts, leading eventually to the required *arabino* aminosugar, by analogy with an early observation[6] emerging from the synthesis of L-acosamine (2,3,6-trideoxy-3-amino-L-*arabino*-hexose) where the ester **6** gave, with ammonia, the β-amino ester **7**.



4 **5** **6** **7**

Treating **5** with benzylamine (100 °C, EtOH, 48 h, autoclave) afforded **8**. The assigned stereochemistry of **8** is based on its conversion by acid treatment into the imidazolino α-pyrone **9**. Therefore, concluding that the imidazoline **8** had been formed by intramolecular ring interconversion from the primarily obtained 3,4-*erythro* adduct **10**, the addition of the nitrogen nucleophile occurred onto the *re*-face of **5**. A similar steric course was observed when **5** was made to react with benzylmercaptan. The primary adduct **11** gave, on acid aqueous treatment, the lactam (**12**), subsequently converted into **13** by basic hydrolysis and acid treatment (HCl 6N). ^1H NMR studies on the corresponding methyl glycoside **16** suggested again the *re*-face selectivity in the addition. Recently, *re*-face selectivity leading to a 3,4-*erythro* adduct has been observed in the 1,3-intramolecular Michael addition occurring in **14** in the synthesis of the *xylo* isomer of 2,3,

6-trideoxy-3-amino-L-hexose.[7] An attempt to convert the imidazoline ring of **9** into the required diamino material, either by hydrolysis or hydrogenation,[8] failed. Accordingly, the lactones **9** and **13** were converted through unexceptional steps into the *ribo* glycosides **15** and **16**.



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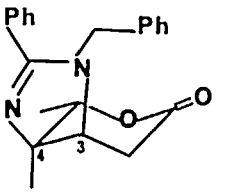

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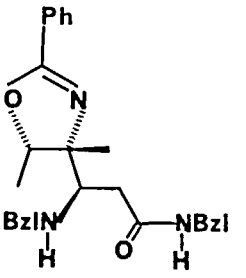

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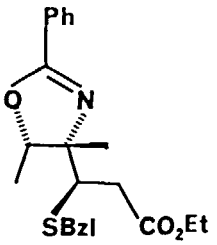

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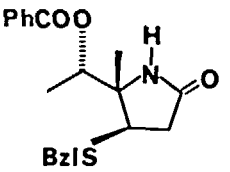

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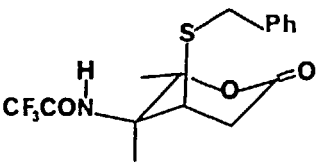

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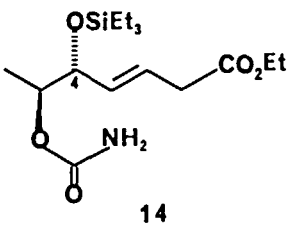

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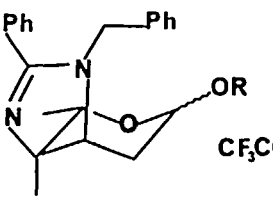
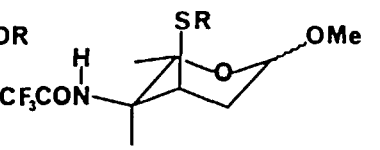


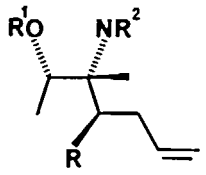
15 R = Me
15a R = H

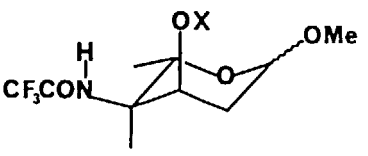


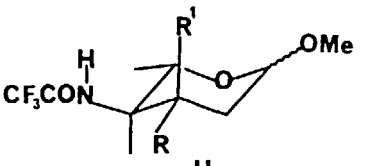
16 R = H
16a R = Bzl

An entry to the required 2,3,4,6-tetradeoxy-4-*C*-methyl-3,4-diamino-L-*arabino*-hexose was thus offered from the methyl glycoside **18**.[5b] The latter compound, *via* mesylate and azide displacement, afforded the required 3-azido derivative, eventually converted by hydrogenation and trifluoroacetylation into the required product **20**. The same sequence per-

formed on the *arabino* isomer of **18** led to **20a**, whose structure was assigned only by careful ^{1}H NMR studies on an inseparable and complex mixture. The azide substitution was accompanied by moderate amounts of the elimination product **21**. The same compound **21** was obtained as an almost exclusive reaction product by *t*-BuOK/DMSO treatment of **19** and on DAST treatment of **18**. The 3-fluoro derivative **22**, of *ribo* configuration, was obtained in moderate yield from the acyclic product **17**[5b] on DAST treatment, followed by functional group manipulation. Finally, hydrogenation of **21** afforded the 2,3,4,6-tetradeoxy-4-*C*-methyl-L-*erythro*-hexose derivative (**23**), which was also obtained by hydrogenation of **5** and subsequent manipulation similar to the one used in the preparation of **15** and **16**.







17 R = OH; R^1R^2 = 

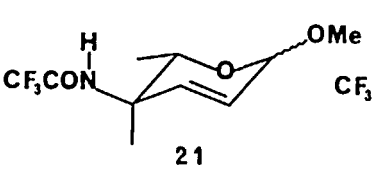
17a R = F; R^1 = H; R^2 = $COCF_3$, H

18 X = H

19 X = Ms

20 R = $NHCOCF_3$; R^1 = H

20a R = H; R^1 = $NHCOCF_3$



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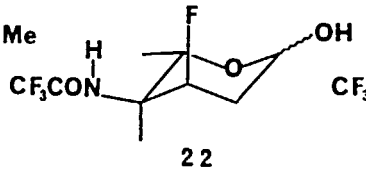

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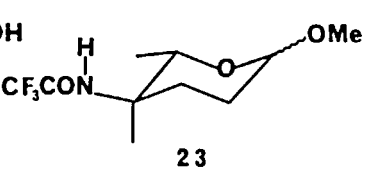


23

NMR DISCUSSION

The relative stereochemistry and the conformational features of the reported 2,3,4,6-tetradeoxy-4-*C*-methyl-4-trifluoroacetamido-L-hexose derivatives have been determined from the ^{1}H NMR data (Tables 1 and 2). All compounds were analyzed as a mixture of α and β -methyl pyranosides except

TABLE 1. ^{1}H Chemical shifts of 2,3,4,6-tetradeoxy-4-C-methyl-4-amido-L-hexose derivatives.[a]

Compd	H-1	H-2a	H-2e	H-3	H-5	Me-4	Me-5	OMe	NH-4
9[b]	-	2.94	3.05	3.92	4.82	1.47	1.50	-	-
15α	4.61	2.04	1.83	3.21	3.99	1.14	1.29	3.37	-
15β	4.63	1.97	1.63	3.36	3.54	1.35	1.29	3.45	-
16α[c]	4.72	2.37	2.17	3.45	4.11	1.64	1.22	3.35	6.69
16β[d]	4.68	2.10	2.02	4.04	4.08	1.62	1.26	3.49	6.23
20α[e]	4.75	1.83	2.03	4.77	4.28	1.45	1.21	3.35	6.43
20β[f]	4.57	1.67	2.11	4.86	4.32	1.38	1.22	3.53	6.19
20aα[g]	4.82	2.11	1.75	4.91	3.97	1.44	1.21	3.44	6.43
20aβ[h]	4.08	1.50	1.25	4.78	3.50	0.88	1.07	3.10	6.02
21α	4.83	5.75	-	6.06	4.36	1.39	1.20	3.43	5.87
21β	5.09	5.77	-	5.97	4.28	1.42	1.24	3.47	5.87
22β[i]	5.14	1.84	2.29	5.09	3.94	1.57	1.25	-	4.73
23α	4.64	1.50-2.50[l]			4.27	1.42	1.13	3.37	5.93
23β	4.49	1.5 -2.50[l]			4.22	1.39	1.18	3.50	5.97

a. Chemical shifts in ppm from internal TMS; solvent $CDCl_3$ except otherwise indicated.
b. Run as trifluoroacetate salt.
c. -SH 2.61 ppm.
d. -SH 1.69 ppm.
e. -NH-3 6.45 ppm;
f. -NH-3 6.60 ppm.
g. -NH-3 7.77 ppm.
h. Solvent C_6D_6, NH-3 6.02 ppm.
i. The solution is a mixture of α and β-anomers in a 7:3 ratio: the spectrum of the α-anomer was not analyzed since extensive overlapping occurs with the signals of the major isomer.
l. Chemical shift range of the H-2 and H-3 protons.

TABLE 2. ^{1}H Coupling constants of 2,3,4,6-tetradeoxy-4-C-methyl-4-amido-L-hexose derivatives.[a]

Compd	J(1,2a)	J(1,2e)	J(2a,2e)	J(3,2a)	J(3,2e)	J(5,Me)
9[b]	-	-	14.3	6.5	10.0	6.5
15α	5.0	7.0	14.0	5.5	10.0	6.5
15β	8.5	2.5	14.5	5.0	3.5	6.5
16α[c]	3.9	1.5	15.0	5.8	3.1	6.5
16β[d]	9.0	2.5	14.3	4.8	4.3	6.7
20α[e]	3.8	1.1	13.0	12.5	4.6	6.5
20β[f]	9.5	2.5	12.9	12.9	4.7	6.4
20aα[g]	4.0	1.0	15.0	4.5	2.5	6.4
20aβ[h]	6.4	3.2	14.0	6.5	5.0	6.4
21α	2.7	1.0 J(1,3)		10.1 J(2,3)		6.5
21β	1.7	1.7 J(1,3)		10.1 J(2,3)		6.5
22β[i]	9.9	2.6	14.9	2.4	3.6	6.6
23α	5.5[l]		m	m	m	6.5
23β	9.0	2.4	m	m	m	6.6

a. J in Hz. Solvent $CDCl_3$ except otherwise indicated.
b. Run as trifluoroacetate salt.
c. J(3,SH) 10.5 Hz.
d. J(3,SH) 7.5 Hz.
e. J(3,NH) 9.0 Hz.
f. J(3,NH) 9.0 Hz.
g. J(3,NH) 9.2 Hz.
h. Solvent C_6D_6, J(3,NH) 8.5 Hz.
i. J(3,F) 48.5, J(2e,F) 12.0, J(2a,F) 47.0, J(5,F) 2.0, J(F,Me-4) 1.7 Hz; the solution is a mixture of α and β-anomers in 7:3 ratio. The spectrum of the α-anomer was not analyzed since extensive overlapping occurs with the signals of the major isomer.
l. J(1,2a)+J(1,2e).
m. Not detected.

the 3-*F*-derivative (**22**), which was analyzed as a β-pyranose. The configuration of the C_4 and C_5 carbons is dictated from the stereochemistry of the starting aldehyde (**4**), while the configuration at carbon C_3 depends on the mode of addition of the various nucleophiles to the α, β -unsaturated ester (**5**). Compound **9**, obtained by addition of benzylamine, has two fused rings and the conformation of the δ-lactone cannot be predicted with certainty; in this case the vicinal coupling constants J(2,3) of 6.5 and 10.0 Hz are ambiguous in establishing the stereochemistry at C_3. In contrast, the β-methyl glycoside **15** displays vicinal coupling constants which are in agreement with the *ribo* configuration at C_3 and the $^1C_4$(L) conformation of the pyranose ring. In fact the values of J(1,2a), J(1,2e), J(3,2a) and J(3,2e), which can be predicted for conformationally pure pyranose rings on the basis of the electronegativity and orientation of the substituents,[9] are 10.0, 3.1, 3.3 and 2.9 Hz respectively, in reasonable agreement with those observed experimentally. Moreover the existence of the chair $^1C_4$(L) for **15**β is also confirmed by a strong NOE effect observed between protons H_1 and H_5, which in this conformation are *syn* axially oriented. In the case of the methyl glycoside **15**α the values of the vicinal coupling constants suggest that the molecular conformation is basically different from the chair $^1C_4$(L). The predicted[9] values for the α-*ribo* chair conformation for J(1,2a), J(1,2e), J(3,2a) and J(3,2e) are 3.1, 1.3, 3.3 and 2.9 Hz respectively, which are very different from those observed experimentally. The existence of a rapid equilibrium between the two opposite chair conformations $^1C_4$(L) and $^4C_1$(L) can be ruled out since a strong NOE effect was observed between the proton H_5 and the H_2 proton at 1.83 ppm. This effect, which is not normally observed between protons in position 2 and 5 for saccharides in the chair conformation, suggests that the two protons are *syn* and axially oriented. Calculations performed using the modified general Karplus equation[10] gave the following dihedral angles be-

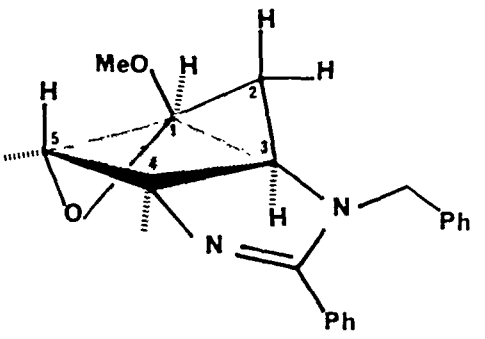
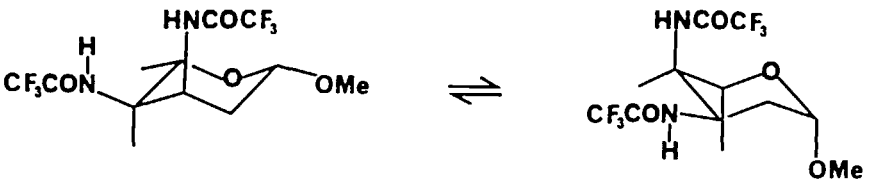


Fig.1 Proposed $^{2}S_{O}$(L) conformation for **15** .

tween the protons H_1 and H_2 and protons H_2 and H_3, Ø(1,2) 141° and 46°, Ø(2,3) 153° and 40°. The most probable conformation which accounts roughly for the reported dihedral angles is the skew $^{2}S_{0}$(L) (Fig. 1), slightly flattened in the region of C_1-C_2-C_3 carbons. In this conformation the atoms C_1, C_3, C_4 and C_5 are located in a plane, while atoms C_2 and *O* are disposed above and below this plane respectively.

Compounds **16**, **20a**α and **22**β exist in the *ribo* configuration as can be deduced from the values of the vicinal coupling constants compared with the calculated ones.[9] In the case of the 3-fluoro derivative the predicted values of J(3,2e) and J(3,2a) are 3.3 and 1.9 Hz respectively, in good agreement with the experimental values (3.6 and 2.4 Hz). The agreement is less satisfactory for the J(3,2a) of compounds **16**α, **16**β and **20a**α, for which larger values are observed (4.5-5.8 Hz) than predicted (3.3-4.1 Hz). Anomalies like these were also observed for the 2,4,6-trideoxy-4-*C*-methyl-4-trifluoroacetamido-L-*ribo* and L-*xylo*-hexoses[5b] and no rationalization was found except the possibility of local changes of ring geometry or long-range substituent effects. In contrast compound **20a**β displays values of coupling constants markedly different from those predicted for the *ribo*



$^1C_4(L)$ $^4C_1(L)$

Fig. 2

configuration. In this case most probably a rapid equilibrium occurs between the two possible chair conformations $^1C_4(L)$ and $^4C_1(L)$ (Fig. 2).

The populations P_1 and P_2 of each conformer can be estimated through the equation $J(av)=P_1J_1+P_2J_2$,[9] where J_1 and J_2 are the predicted values of the coupling constants for the two chair conformations. The calculated amount of the $^1C_4(L)$ conformer is 60±10%. The conformational behaviour of **20a**β is difficult to rationalize and may be related to the steric influence of the *NHCOCF*$_3$ substituent. Structurally related compounds bearing different substituents such as *SH* (**16**β), *F* (**22**β) or *OH*[5b] at C_3 show no deviations from the expected $^1C_4(L)$ chair conformation. The α-anomer of **20a**, as observed above, exists only in the $^1C_4(L)$ chair, although the steric interaction between the axial substituents at carbon C_1 and C_3 is much more severe than in the β-anomer. In this case such a conformation is stabilized by the existence of a hydrogen bond between the 3-*NHCOCF*$_3$ amide proton and the methoxyl group, as indicated by the chemical shift of *NH*-3, which resonates at a lower field by about 1 ppm than the amide proton of the α and β isomers of **20** and the β anomer of **20a**.

CONCLUSION

The aldehyde **4** is a flexible intermediate for the synthesis of a variety of 2,3,4,6-tetradeoxy-4-*C*-methyl-4-

amino-L-hexoses, differently substituted at position 3. These L-hexoses are of interest for the preparation of analogues of **1**. The mode of addition of nitrogen and sulfur nucleophiles onto the ester **5**, as compared with that observed with the 1,3-dioxolane derivative **6**, calls for studies on the factors governing the face selectivity of the addition to new α,β-unsaturated esters structurally related to **5**. Work in this direction is in progress.

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EXPERIMENTAL

General method. ^1H NMR spectra were recorded on Varian EM 390 (90 Mhz) and Bruker CXO (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 mixture of *n*-hexane and ethyl acetate. Analytical samples were prepared, when possible, by bulb to bulb distillation at reduced pressure, or by crystallization. Evaporation of solvents was conducted *in vacuo*.

Methyl α and β-2,3,4,6-Tetradeoxy-4-C-methyl-4-trifluoroacetamido-3-thia-L-ribo-hexopyranoside 16. To 10 g (50 mmol) of **4**[5b] dissolved in a solution of 50 mL of benzene and 0.2 g of benzoic acid, 19 g (55 mmol) of $Ph_3P{=}CH_2CO_2Et$ were added in one portion and the mixture was then refluxed for 4 h. The reaction mixture, once diluted with 50 mL of petroleum ether, was filtered and the filtrate reduced to a small vol-

ume. Purification on silica gave 5: 10.2 g (37 mmol, 75%), oil; $[\alpha]_D$-45°; ^{1}H NMR (δ) 1.32 (3H, CH_3, t), 1.33 (3H, CH_3, d), 1.53 (3H, CH_3, s), 4.21 (2H, CH_2, q), 4.53 (1H, CH, q), 6.14 (1H, CH, d), 6.97 (1H, CH, d), 7.54 (3H, Ph, m) and 8.06 (2H, Ph, m).

Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.51; H, 7.00; N, 5.11.

To a solution of 2 g (55 mmol) of MeONa in 50 mL of anhydrous MeOH and 6.2 g (50 mmol) of $PhCH_2SH$ at 25 °C were added 10 g (36 mmol) of 5 and the mixture was refluxed for 36 h. The crude reaction solution was poured into ice water and extracted with ethyl acetate. The solution was dried and solvent evaporated so as to obtain, after purification, **11**: 7.1 g (18 mmol, 50%), oil; $[\alpha]_D$-85°; ^{1}H NMR (δ) 1.27 (9H, $3CH_3$, m), 2.70 (1H, CH, m), 3.39 (2H, CH_2, dd), 3.85 (2H, CH_2, d), 4.18 (2H, CH_2, q), 4.53 (1H, CH, q), 7.37 (8H, 2Ph, m) and 7.92 (2H, Ph, m).

Anal. Calcd for $C_{23}H_{27}NO_3S$: C, 69.49; H, 6.85; N 3.52. Found: C, 69.47; H, 6.83; N, 3.52.

Compound **11** (4 g, 10 mmol) in 50 mL of MeOH and 20 mL of 5N HCl was refluxed for 4 h. The reaction mixture, once cooled, was washed with ethyl acetate. The aqueous phase was neutralized with $NaHCO_3$ and extracted with ethyl acetate. The solution was dried and concentrated to give clean **12**: 3.5 g (9.5 mmol, 95%); $[\alpha]_D$-98°; ^{1}H NMR (δ) 1.11 (3H, CH_3, d), 1.36 (3H, CH_3, s), 2.57 (2H, CH_2, t), 3.28 (1H, CH, t), 3.74 (2H, CH_2, s), 5.13 (1H, CH, q), 6.64 (1H, NH, m), 7.32 (5H, Ph, s), 7.50 (3H, Ph, m) and 8.00 (2H, Ph, m).

Anal. Calcd for $C_{21}H_{23}NO_3S$: C, 68.27; H, 6.27; N, 3.79. Found: C, 68.25; H, 6.28; N, 3.79.

Compound **12** (3.5 g, 9.5 mmol) was hydrolyzed at 25 °C in 25 mL of EtOH and 10 mL of 10% aqueous NaOH. The mixture was extracted with ethyl acetate, the solution was concentrated and the crude product (2.3 g, $[\alpha]_D$-139.5°) was suspended in 20 mL of 6N HCl and refluxed for 16 h. The aqueous phase, washed with ethyl acetate and concentrated, gave the

crude hydrochloride which was immediately treated with 10 mL of trifluoroacetic anhydride in 5 mL of dry CH_2Cl_2. After vacuum evaporation of the solvent at 35 °C and purification of the crude extract, **13** was obtained: 2.6 g (7.1 mmol, 75%); $[\alpha]_D$-66.1°; ^1H NMR (δ) 1.28 (3H, CH_3, d), 1.32 (3H, CH_3, s), 2.80-3.12 (3H, CH, CH_2, m), 3.78 (2H, CH_2, s), 5.00 (1H, CH, q), 6.31 (1H, NH, m) and 7.13 (5H, Ph, s).

Anal. Calcd for $C_{16}H_{18}F_3NO_3S$: C, 53.18; H, 5.02: N, 3.88. Found: C, 53.18; H, 5.00; N, 3.89.

The lactone **13**, 1.6 g (4.4 mmol), in 40 mL of anhydrous THF was cooled to -70 °C; 9 mL of DIBAH (1M in hexane) were then added dropwise. After stirring at -60 °C for 2 h, 5 mL of acetone were added and the mixture left to stir at 25 °C for an additional hour. The precipitated aluminium hydroxide was filtered off and the solvent evaporated to give, after purification, the corresponding amino sugar (1.3 g, $[\alpha]_D$ -56.7°; 24 h). The above amino sugar, dissolved in 20 mL of dry MeOH, was treated with 2 mL of MeOH satd with HCl and then left to stand at 25 °C for 3 h. Evaporation and purification gave **16a**: 1.3 g (3.4 mmol, 97%); mp 140 °C; $[\alpha]_D$-50.6°.

Anal. Calcd for $C_{17}H_{22}F_3NO_3S$: C, 54.10; H, 5.88; N, 3.71. Found: C, 54.12; H, 5.85; N, 3.68.

Debenzylation was performed as follows: **16a**, 1.3 g (3.4 mmol), was dissolved in 30 mL of dry THF and to this solution, cooled at -78 °C, were added 15 mL of liquid NH_3. Under vigorous stirring Na, 0.2 g (8.7 mmol), was added and the reaction was stirred for 3 h at -70 °C. After this time 0.5 g of NH_4Cl were added and the reaction mixture left to warm until all the NH_3 was evaporated. The reaction mixture was then filtered and the solvent concentrated to give, after purification, **16**: 0.57 g (2 mmol, 60%); $[\alpha]_D$ -85.6°.

Anal. Calcd for $C_{10}H_{16}F_3NO_3S$: C, 41.81; H, 5.61; N, 4.88. Found: C, 41.83; H, 5.64; N, 4.85.

Methyl α and β-2,3,4,6-Tetradeoxy-4-C-methyl-3,4-imidazolino-L-ribo-hexopyranoside 15. A solution of **5**, 5 g (18 mmol), and $PhCH_2NH_2$, 5.7 g (50 mmol), in 25 mL of EtOH was

heated at 100 °C in an autoclave for 48 h. From the residue, once concentrated and redissolved in 50 mL of ethyl acetate, **8** was collected by filtration: 3.2 g (7 mmol, 40%); $[\alpha]_D$ -27.5°; mp 171 °C; ^{1}H NMR (δ) 0.80 (3H, CH_3, s), 1.28 (3H, CH_3, d), 2.28-3.32 (3H, CH, CH, OH, broad), 3.74-4.10 (2H, CH_2, m), 4.28 (2H, CH_2, d), 4.43 (2H, CH_2, m), 6.26 (1H, NH, m), and 7.09-7.68 (15H, 3Ph, m).

Anal. Calcd for $C_{28}H_{31}N_3O_2$: C, 76.13; H, 7.08; N, 9.52. Found: C, 75.96; H, 7.09; N, 9.45.

Compound **8** (1.5 g, 3.4 mmol) was suspended in 10 mL of 5N HCl and the mixture was refluxed for 6 h. The aqueous phase was washed with ethyl acetate and neutralized with $NaHCO_3$. Extraction with ethyl acetate gave **9**; 1 g (3 mmol, 90%); $[\alpha]_D$-115.14°.

Anal. Calcd for $C_{21}H_{22}N_2O_2$: C, 75.42; H, 6.63; N, 8.38 Found: C, 75.38; H, 6.66; N, 8.40.

To 0.8 g (2.4 mmol) of **9** in 20 mL of dry THF, cooled at -78 °C, DIBAH, (7.2 mL, 1M in hexane), was added dropwise. After stirring for 3 h at -60 °C, 10 mL of acetone were added and the mixture left to warm to 25 °C and then stirred for 2 h. The precipitate was filtered off and the solvent was evaporated to give, after purification over alumina (eluent ethyl acetate), **15a**: 0.6 g (1.8 mmol, 75%); mp 55 °C; $[\alpha]_D$-70°, 24 h.

Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33. Found: C, 74.94; H, 7.21; N, 8.31.

Compound **15a** (0.5 g, 1.5 mmol) was diluted in 10 mL of dry MeOH and 1 mL of MeOH satd with HCl was added. The reaction was left at 25 °C for 18 h, then the solvent was evaporated and the crude extract purified on alumina (eluent hexane 3, ethyl acetate 7) to give **15**: 0.47 g (1.35 mmol, 90%); $[\alpha]_D$-93.4°.

Anal. Calcd for $C_{22}H_{26}N_2O_2$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.45; H, 7.49; N, 7.94.

Methyl 2,3,4,6-Tetradeoxy-4-C-methyl-3,4-trifluoroacetamido-L-arabino-β-hexopyranoside 20. To 2 g (7.4 mmole) of

18[5b] (mixture of α and β-anomers) diluted in 10 mL of dry CH_2Cl_2 and 1 mL of dry pyridine at -10 °C, were added 1.2 g (9 mmol) of MsCl and the reaction left under stirring for 18 h. The mixture was poured into ice water and extracted with ethyl acetate to give **19**: 2.1 g (6 mmol, 81%). Purification by silica gel column chromatography (eluent hexane 1, ethyl acetate 1) gave first 1 g of the β-anomer and then 1.1 g of the α-anomer. For the β-anomer, $[\alpha]_D$-76.3°.

Anal. Calcd for $C_{11}H_{18}F_3NO_6S$: C, 37.82; H, 5.19; N, 4.01. Found: C, 37.80; H, 5.20; N, 4.08.

For the α-anomer, $[\alpha]_D$-161.5°.

Found: C, 37.83; H, 5.20; N, 4.02.

To the β-anomer of **19**, 0.8 g (2.3 mmol), dissolved in 15 mL of dry DMF, was added NaN_3, (0.6 g, 9.2 mmol), and the reaction heated at 90 °C for 8 h. The mixture was poured into ice water and then extracted with hexane 9, ethyl acetate 1. The crude extract was dissolved in 10 mL of MeOH, 0.1 g of 10% Pd on charcoal was added and the reaction was stirred for 3 h at 25 °C, in an atmosphere of H_2. The reaction mixture was filtered and the solvent evaporated to yield a colourless oil which was immediately trifluoroacetylated with trifluoroacetic anhydride. Workup as reported in the preparation of **13** gave **20**: (0.4 g, 1.1 mmol, 48%); $[\alpha]_D$-5.6°.

Anal. Calcd for $C_{12}H_{16}F_6N_2O_4$: C, 39.36; H, 4.40; N, 7.65. Found: C, 39.33; H, 4.38; N, 7.66.

Methyl 2,3,4,6-Tetradeoxy-4-C-methyl-4-trifluoroacetamido-2,3-dehydro-L-erythro-α-hexopyranoside 21. To 1 g of the α-anomer of **19**, dissolved in 10 mL of dry DMSO, *t*-BuOK (1 g, 9 mmol) was added. The reaction mixture was stirred at 35 °C for 6 h, then poured into ice water and extracted with ethyl acetate. Purification gave **21**: 0.7 g (2.7 mmol, 95%); $[\alpha]_D$-81°.

Anal. Calcd for $C_{10}H_{14}F_3NO_3$: C, 47.44; H, 5.57; N, 5.53. Found: C, 47.41; H, 5.58; N, 5.50.

Methyl α and β-Erythro-2,3,4,6-tetradeoxy-4-C-methyl-4-trifluoroacetamido-L-hexopyranoside 23. Compound **21** (0.5 g,

2 mmol) as a mixture of α and β-anomers, was dissolved in 15 mL of dry MeOH and 0.05 g of 10% Pd on charcoal were added. The reaction was stirred for 12 h at 25 °C in an atmosphere of H_2. The reaction mixture was then filtered and the solvent evaporated in order to obtain, after purification, **23**: (0.4 g 1.6 mmol, 80%); $[\alpha]_D$-74.1°.

Anal. Calcd for $C_{10}H_{16}F_3NO_3$: C, 47.06; H, 6.32; N, 5.49. Found: C, 47.10; H, 6.30; N, 5.45.

α and β-2,3,4,6-Tetradeoxy-4-C-methyl-4-trifluoroacetamido-3-fluoro-L-ribo-hexopyranose 22. To **17**[5b] (1 g, 4.1 mmol), dissolved in 20 mL of dry CH_2Cl_2 , 1.9 g (12 mmol) of DAST were added at 0 °C. After a 1/2 h stirring the reaction was complete (TLC) and 5 mL of a satd sol of $NaHCO_3$ were slowly added. The mixture was then extracted and the solution was dried and solvent evaporated. The crude extract was hydrolyzed as reported[5b] and after deprotection of the OH group and protection of the NH_2 group, **17a** was obtained: 0.4 g (1.64 mmol, 40%); $[\alpha]_D$ +19°; ^1H NMR (δ) 1.29 (3H, CH_3, d), 1.48 (3H, CH_3, s), 2.20-2.73 (3H, CH_2, OH, broad), 4.71 (1H, CH, q), 4.66 (1H, CH, dd), 5.07-5.30 (2H, CH_2, m), 5.67-6.10 (1H, CH, m) and 6.52 (1H, NH, broad).

Anal. Calcd for $C_{10}H_{15}F_4NO_2$: C, 46.70; H, 5.88; N, 5.45. Found: C, 46.76; H, 5.91; N, 5.43.

Ozonolysis of **17a** as reported[5b] gave **22**: 0.3 g (1.1 mmol, 70%); $[\alpha]_D$-60.3°, 24 h.

Anal. Calcd for $C_9H_{13}F_4NO_3$: C, 41.71; H, 5.06; N, 5.40. Found: C, 41.68; H, 5.11; N, 5.37.

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