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SYNTHESIS OF DERIVATIVES OF 3-AMINO-2,3-DIDEOXY-L-HEXOSES RELATED TO DAUNOSAMINE (3-AMINO-2,3,6-TRIDEOXY-L-*lyxo*-HEXOSE)

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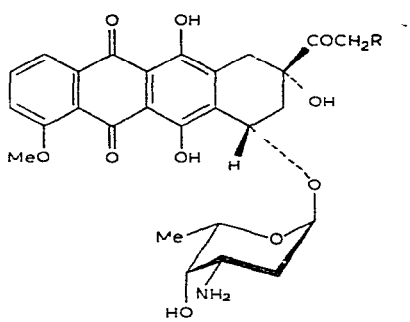
ABSTRACT

The synthesis is described of 3-amino-2,3-dideoxy-L-*arabino*-hexose (**10**), methyl 2,3-dideoxy-3-trifluoroacetamido-α-L-*lyxo*-hexopyranoside (**17**), methyl 3-amino-2,3-dideoxy-α-L-*ribo*-hexopyranoside (**21**), methyl 2,3-dideoxy-3-trifluoroacetamido-α-L-*xylo*-hexopyranoside (**26**), and certain derivatives from methyl 4,6-*O*-benzylidene-2-deoxy-α-L-*arabino*-hexopyranoside (**3**) Conversion of 2-deoxy-L-*arabino*-hexose into **3** by modified, standard procedures, and on a large scale, gave a 75% yield

INTRODUCTION

We have been interested in the synthesis of L-amino sugars related to daunosamine (3-amino-2,3,6-trideoxy-L-*lyxo*-hexose), the carbohydrate constituent of the anthracycline antibiotics daunorubicin (daunomycin, **1**) and doxorubicin (adriamycin, **2**), which are clinically useful as cancer chemotherapeutic agents[1]



1 R = H (Daunorubicin)
2 R = OH (Doxorubicin)

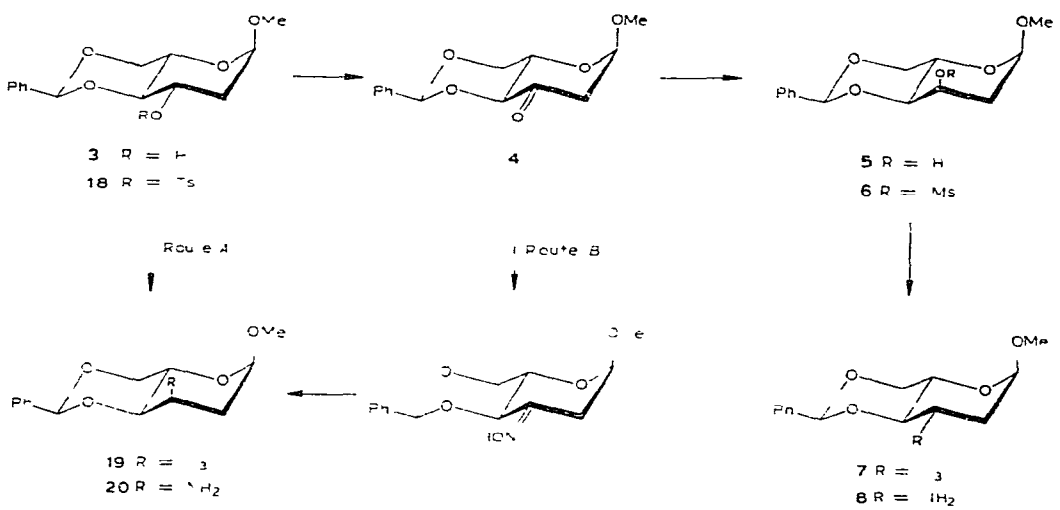
The synthesis of analogues of the antitumour anthracyclines, in which the amino sugar moiety is functionally and/or configurationally altered, is of interest in relation to structure–activity relationships which, in turn, may lead to new and improved drugs Analogues of daunorubicin and doxorubicin, in which daunosamine is replaced by acosamine[4–6] (3-amino-2,3,6-trideoxy-L-*arabino*-hexose) or ristosamine[7–10] (3-amino-2,3,6-trideoxy-L-*ribo*-hexose). display high activity against experimental tumours in mice[2 3]

We now report the synthesis of derivatives of 3-amino-2,3-dideoxy-L-*arabino*-, L-*lyxo*-, L-*ribo*-, and L-*xylo*-hexoses, which are useful intermediates for the synthesis of anthracycline glycosides in which daunosamine is replaced by 3-amino-2,3-dideoxy-L-hexoses This class of new glycosides displays activity against experimental tumours in mice[11–13]

RESULTS AND DISCUSSION

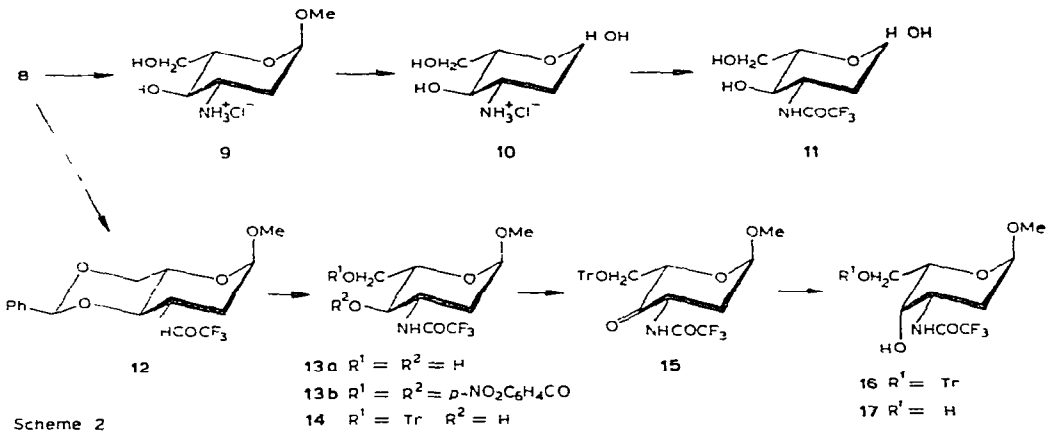
Methyl 4,6-*O*-benzylidene-2-deoxy-α-L-*arabino*-hexopyranoside[14] (**3**), which was selected as starting material for the synthesis of 3-amino-2,3-dideoxy-L-hexoses related to daunosamine, was prepared from 2-deoxy-L-*arabino*-hexose[15] However, by modification of the standard procedures[14 16], large-scale conversions could be routinely performed to give a 75% overall yield

Methyl 4,6-*O*-benzylidene-2-deoxy-α-L-*ribo*-hexopyranoside (**5**) was prepared following two procedures used in the D series Oxidation of **3** with ruthenium tetraoxide[17], followed by stereoselective reduction[18] with lithium aluminium hydride of the resulting 3-keto derivative (**4**), gave **5** (82%) (Scheme 1) Alternatively, **5** (30%) was prepared from L-glucose, *via* methyl 2,3-anhydro-4,6-*O*-benzylidene-α-L-allopyranoside, by a known route[19–21]



Scheme 1

Conversion of **5** into methyl 3-amino-4,6-*O*-benzylidene-2,3-dideoxy-α-L-*arabino*-hexopyranoside (**8**, 59%) was effected in three steps (Scheme 1) as described[21] for the D series Debenzylidenation of **8** with methanolic hydrogen chloride gave crystalline methyl 3-amino-2,3-dideoxy-α-L-*arabino*-hexopyranoside hydrochloride (**9**, 87%) (Scheme 2) Hydrolysis of **9** with aqueous hydrochloric acid gave crystalline 3-amino-2,3-dideoxy-L-*arabino*-hexose hydrochloride (**10**) in an almost quantitative yield The D enantiomer was not crystalline[22] Trifluoroacetylation of **10**, followed by treatment with methanol, gave crystalline 2,3-dideoxy-3-trifluoroacetamido-L-*arabino*-hexose (**11**, 90%)



Scheme 2

The *N*-trifluoroacetyl derivative (**12**) of **8**, when treated with methanolic hydrogen chloride, gave methyl 2,3-dideoxy-3-trifluoroacetamido-α-L-*arabino*-hexopyranoside (**13a**), characterized as the 4,6-bis(*p*-nitrobenzoate) (**13b**)

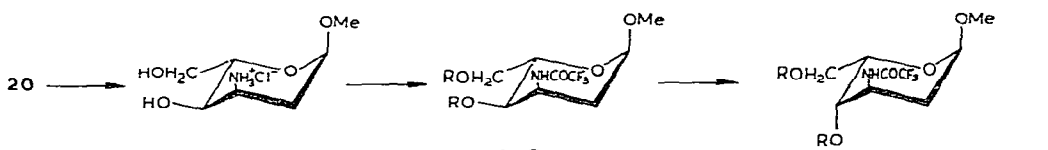
The 6-*O*-trityl derivative (**14**, 83% from **8**) of **13a** was oxidized with ruthenium tetraoxide[17] in the presence of sodium periodate to give methyl 2,3-dideoxy-3-trifluoroacetamido-6-*O*-triphenylmethyl-α-L-*threo*-hexopyranosid-4-ulose (**15**, 56% after column chromatography) This oxidation method was suitable for compounds containing acid-sensitive groups[2]

Stereoselective reduction of **15** with lithium tri-*sec*-butylborohydride in anhydrous tetrahydrofuran gave the α-L-*lyxo* glycoside (**16**, 83%), and removal of the trityl group with aqueous acetic acid gave crystalline methyl 2,3-dideoxy-3-trifluoroacetamido-α-L-*lyxo*-hexopyranoside (**17**, 76% after chromatography) Methyl 3-amino-2,3-dideoxy-β-D-*lyxo*-hexopyranoside has been synthesised[25] from methyl 3-deoxy-3-nitro-β-D-galactopyranoside

The synthesis of derivatives of 3-amino-2,3-dideoxy-L-*ribo*-hexose was achieved by two routes Tosylation of **3**, followed by treatment of the 3-tosylate **18** with sodium azide in *N*,*N*-dimethylformamide at 120° for 16 h, gave the *ribo*-azide (**19**, 92%). The D isomer has been obtained[18 24] starting from the corresponding 3-mesylate and 3-brosylate, but in poor yields (30 and 15%) Catalytic hydrogenation

of **19** afforded crystalline methyl 3-amino-4,6-*O*-benzylidene-2,3-dideoxy-α-L-*ribo*-hexopyranoside (**20**, 86%) Alternatively, **20** was prepared (65% overall yield) by literature procedures[17,18] Reduction of the oxime of **4** with lithium aluminium hydride gave a mixture of **20** (85%) and the L-*arabino* amine (**8**, 10%) which were separated by chromatography Treatment of **20** with methanolic hydrogen chloride gave crystalline methyl 3-amino-2,3-dideoxy-α-L-*ribo*-hexopyranoside hydrochloride (**21**, 93%), m p 152–154°, $[\alpha]_D^{23}$ −170° (methanol); *cf* m p 152–156°, $[\alpha]_D$ +138° (methanol)[23], and m p 144° (dec), $[\alpha]_D$ +157° (methanol)[18] for the D form

The corresponding *N*-trifluoroacetyl derivative (**22**) was obtained as a syrup and characterized as the crystalline 4,6-bis(*p*-nitrobenzoate) (**23**) Methyl 2,3-dideoxy-3-trifluoroacetamido-α-L-*ribo*-hexopyranoside (**22**) was also used[3] as a key intermediate in the synthesis of methyl 2,3,6-trideoxy-3-trifluoroacetamido-α-L-*ribo*-hexopyranoside



Scheme 3

Mesylation of methyl 2,3-dideoxy-3-trifluoroacetamido-α-L-*ribo*-hexopyranoside (**22**) gave crystalline **24** (83%) (Scheme 3), which, with sodium benzoate in *N*,*N*-dimethylformamide at 120°, gave syrupy methyl 4,6-di-*O*-benzoyl-2,3-dideoxy-3-trifluoroacetamido-α-L-*xylo*-hexopyranoside (**25**, 80%) Debenzoylation of **25** gave syrupy methyl 2,3-dideoxy-3-trifluoroacetamido-α-L-*xylo*-hexopyranoside (**26**), which was characterized as the 4,6-bis(*p*-nitrobenzoate) (**27**) The preparation of crystalline methyl 2,3-dideoxy-3-formamido-α-D-*xylo*-hexopyranoside and of its 3-epimer, *via* the sequential reduction and *N*-formylation of a mixture of methyl 4,6-*O*-benzylidene-2-deoxy-α-*threo*-hexopyranosid-3-ulose *syn*- and *anti*-oximes, has been described[18]

The four stereoisomeric methyl 2,3-dideoxy-3-trifluoroacetamido-α-L-hexopyranosides (**13a** **17**, **22**, and **26**) could be differentiated by t l c (chloroform–methanol, 6 1), and had R_F values of 0 30, 0 33, 0 36, and 0 42, respectively

EXPERIMENTAL

General methods — Melting points were determined with an SMP-20 apparatus (Buchi) and are uncorrected A Perkin–Elmer Model 141 polarimeter was used for measurement of specific rotation ^{1}H-N m r spectra (internal Me_4Si) were recorded with a Varian A-60A spectrometer Mass spectra (70 eV) were recorded with a Perkin–

Elmer 270 spectrometer (direct-insertion technique) T l c was performed with silica gel HF (Merck), with detection by u v light or charring with sulphuric acid

*Methyl 3-amino-2,3-dideoxy-α-*L-arabino-*hexopyranoside hydrochloride* (**9**) — A solution of methyl 3-amino-4,6-*O*-benzylidene-2,3-dideoxy-α-L-*arabino*-hexopyranoside {**8**, m p 95–96°, $[\alpha]_D^{23}$ −86° (*c* 0 5, chloroform), 2 15 g, 8 1 mmol} in 0 5M methanolic hydrogen chloride (40 ml) was stirred for 1 h at 20°, then concentrated to half volume, and diluted with anhydrous ether The product (**9**), after collection and washing with dry ether, was a hygroscopic solid (1 5 g, 87%), m p 120° (dec), $[\alpha]_D^{23}$ −92° (*c* 0 4, water) Mass spectrum *m/e* 187 (M+1) N m r data [D_2O, internal sodium 3-(trimethylsilyl)propanesulphonate] δ 4 98 (dd, $J_{1,2e}$ 1 5, $J_{1,2a}$ 3 5 Hz, H-1) and 3 41 (s, OMe)

Anal Calc for $C_7H_{16}ClNO_4$ C, 39 35, H, 7 56, N, 6 56 Found C, 39 20, H, 7 75, N, 6 45

*3-Amino-2,3-dideoxy-*L-arabino-*hexose hydrochloride* (**10**) — A solution of **9** (1 5 g, 7 mmol) in M hydrochloric acid (50 ml) was boiled for 5 h, then cooled to 20°, and treated with Amberlite IR-45(HO^-) resin until the pH was 5 The filtered solution was concentrated *in vacuo* and then freeze-dried, and the residue was crystallized from methanol–ethyl acetate to give **10** (1 33 g, 95%), m p 155–157° (dec), $[\alpha]_D^{23}$ −55° (equil , *c* 0 5, water) The D form was obtained[22] as a froth, $[\alpha]_D$ +54° (water)

*2,3-Dideoxy-3-trifluoroacetamido-α-*L-arabino-*hexose* (**11**) — A suspension of **10** (1 25 g, 6 26 mmol) in dry ether (50 ml) was treated with trifluoroacetic anhydride (7 6 ml) at 0°, stirred for 20 h at 20°, and then concentrated *in vacuo* A solution of the solid residue in anhydrous methanol (120 ml) was kept for 20 h at 20° and then concentrated, and the residue was crystallized from acetone–chloroform to give **11** (1 46 g, 90%), m p 177°, $[\alpha]_D^{20}$ −58° (equil , *c* 0 5, *p*-dioxane) Mass spectrum *m/e* 260 (M+1)

Anal Calc for $C_8H_{12}F_3NO_5$ C, 37 07, H, 4 67, N, 5 40 Found C, 36 67, H, 4 41, N, 5 12

*Methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-trifluoroacetamido-α-*L-arabino-*hexopyranoside* (**12**) — To a solution of **8** (5 5 g, 20 7 mmol) in dry dichloromethane (70 ml), trifluoroacetic anhydride (4 5 ml) was added portionwise during 15 min at −5° under nitrogen The mixture was stirred for 90 min at 0°, filtered, and concentrated to give **12** (7 3 g, 97 6%), m p 264–265°, $[\alpha]_D^{23}$ −103° (*c* 0 73, methanol) Mass spectrum *m/e* 361 (M) N m r data (5 1 chloroform-*d*/methyl sulphoxide-d_6) δ 5 49 (s, Ph-C*H*), 4 72 (dd, $J_{1\ 2e}$ 1 5, $J_{1\ 2a}$ 2 5 Hz, H-1), and 3 33 (s, OMe)

Anal Calc for $C_{16}H_{18}F_3NO_5$ C, 53 19, H, 5 02, N, 3 88 Found C, 52 93, H, 5 20, N, 3 76

*Methyl 2,3-dideoxy-3-trifluoroacetamido-α-*L-arabino-*hexopyranoside* (**13a**) — A solution of **12** (7 2 g, 20 1 mmol) in dry methanol (160 ml) was stirred with acetyl chloride (1 58 ml) for 2 h at 20°, and then neutralized with solid sodium hydrogen carbonate, filtered, and concentrated The residue was extracted with hot hexane to remove benzaldehyde, and then with dry acetone to give **13a** (5 22 g, 95%), m p

185–186° (from ethyl acetate–hexane), $[\alpha]_D$ −134° (*c* 1, methanol) Mass spectrum *m/e* 272 (M−1) N m r data (1 1 chloroform-*d*/methyl sulphoxide-d_6) δ 4 78 (dd, $J_{1\ 2e}$ 1, $J_{1\ 2a}$ 3 Hz, H-1) and 3 35 (s, OMe)

Anal Calc for $C_9H_{14}F_3NO_5$ C, 39 57, H, 5 16, N, 5 13 Found C, 39 23, H, 5 19, N, 5 01

The 4,6-bis(*p*-nitrobenzoate) (**13b**) of **13a** had m p 195–197°, $[\alpha]_D^{23}$ −150° (*c* 0 5, chloroform)

Anal Calc for $C_{23}H_{20}F_3N_3O_{11}$ C, 48 35, H, 3 53, N, 7 35 Found C, 48 15, H, 3 48, N, 7 19

*Methyl 2,3-dideoxy-3-trifluoroacetamido-6-O-triphenylmethyl-α-*L-arabino-*hexopyranoside* (**14**) — A solution of **13a** (0 788 g, 2 9 mmol) in dry pyridine (3 2 ml) was treated with triphenylmethyl chloride (0 822 g) for 3 days at 20° and then poured into ice–water The resulting oil was extracted with ether, and the extract was washed with water to neutrality and then concentrated to dryness Crystallization of the residue from hexane gave **14** (1 35 g, 90%), m p 128–130°, $[\alpha]_D^{20}$ −112° (*c* 1, methanol) Mass spectrum *m/e* 515 (M^+) N m r data (chloroform-*d*) δ 7 2–7 7 (m, Ph_3C), 4 75 (dd, $J_{1\ 2e}$ 1, $J_{1\ 2a}$ 3 Hz, H-1), 3 32 (s, OMe), 2 1–2 5 (m, H-2*eq*), and 1.4–1 9 (m, H-2*ax*)

Anal Calc for $C_{28}H_{28}F_3NO_5$ C, 65 24, H, 5 47, N, 2 72 Found C, 65 56, H, 5 33, N, 2 57

*Methyl 2,3-dideoxy-3-trifluoroacetamido-6-O-triphenylmethyl-α-*L-threo-*hexopyranosid-4-ulose* (**15**) — A solution of **14** (0 73 g, 1 42 mmol) in dichloromethane (7 5 ml) was vigorously stirred with an aqueous solution (7 5 ml) of anhydrous potassium carbonate (0 0475 g), potassium periodate (0 418 g), and ruthenium dioxide (0 02 g) for 8 h at 20° The same quantity of the oxidizing mixture was then added and the mixture was stirred for 20 h After treatment with propan-2-ol to reduce residual ruthenium tetraoxide, the organic layer was concentrated under vacuum

T l c (benzene–ethyl acetate, 4 1) of the residue revealed **15** (R_F 0 53) together with a minor amount of **14** (R_F 0 42) Elution from silica gel with benzene–ethyl acetate–light petroleum (70 25 25) gave **14** (0 21 g, 29%) and **15** (0 41 g, 56%) as a foam, m p 62–65°, $[\alpha]_D^{23}$ −89° (*c* 0 8, methanol) Mass spectrum *m/e* 513 (M^+)

Anal Calc for $C_{28}H_{26}F_3NO_5$ C, 65 49, H, 5 10, N, 2 73 Found C, 65 64, H, 5 08, N, 2 47

*Methyl 2,3-dideoxy-3-trifluoroacetamido-6-O-triphenylmethyl-α-*L-lyxo-*hexopyranoside* (**16**) — A solution of **15** (2 1 g, 4 09 mmol) in anhydrous tetrahydrofuran was added dropwise under nitrogen at −78° to M lithium tri-*sec*-butylborohydride in tetrahydrofuran (8 3 ml) After stirring for 3 h at −78°, water (30 ml) was added at −10° to decompose the excess of reducing agent The mixture was acidified (pH 2) with hydrochloric acid and thrice extracted with ethyl acetate, and the combined extracts were dried and concentrated under vacuum Elution of the oily residue from silica gel with benzene–ethyl acetate (4 1), followed by crystallization from isopropyl ether, gave **16** (1 75 g, 83%), m p 155–157°, $[\alpha]_D^{23}$ −104° (*c* 1, methanol) Mass

spectrum *m/e* 515 (M^+) N m r data (methyl sulphoxide-d_6) δ 7 1–7 6 (m, Ph_3C), 4 75 (broad s, W_H 6 5 Hz, H-1), and 3 30 (s, OMe)

Anal Calc for $C_{28}H_{28}F_3NO_5$ C, 65 24, H, 5 47, N, 2 72 Found C, 65 07, H, 5 70, N, 2 44

Compound **16** could be differentiated from the L-*arabino* analogue **14** by t l c (R_F values 0 37 and 0 42, respectively, benzene–ethyl acetate, 4 1)

*Methyl 2,3-dideoxy-3-trifluoroacetamido-α-*L-lyxo-*hexopyranoside* (**17**) — A solution of **16** (4 6 g, 8 92 mmol) in 60% aqueous acetic acid was stirred for 30 min at 60°, and then concentrated to dryness under vacuum Elution of the residue from silica gel with chloroform–methanol–ethyl acetate (9 2 2) gave **17** (1 86 g, 76%), m p 190–192°, $[\alpha]_D^{20}$ −186° (*c* 1, methanol) Mass spectrum *m/e* 274 (M+1) N m r data (5 1 chloroform-*d*/methyl sulphoxide-d_6) δ 4 87 (broad s, W_H 5 5 Hz, H-1) and 3 38 (s, OMe)

Anal Calc for $C_9H_{14}F_3NO_5$ C, 39 57, H, 5 16, N, 5 13 Found C, 39 27, H, 5 32, N, 4 87

*Methyl 2,3-dideoxy-3-trifluoroacetamido-α-*L-ribo-*hexopyranoside* (**22**) — A suspension of methyl 3-amino-2,3-dideoxy-α-L-*ribo*-hexopyranoside hydrochloride (**21**, 2 9 g, 13 5 mmol) in dry ether (70 ml) was treated at 0° with trifluoroacetic anhydride (10 ml) at 0° overnight

The mixture was concentrated to dryness, dry ether (3 × 25 ml) was evaporated from the residue, and a solution of the residue in dry methanol (200 ml) was stirred for 16 h at 25° The solution was concentrated, and dry methanol (3 × 50 ml) was evaporated from the residue to give **22** as a syrup (3 34 g, 90%), $[\alpha]_D^{23}$ −71 5° (*c* 0 7, chloroform), −80° (*c* 0 5, methanol) Mass spectrum *m/e* 274 (M+1) N m r data (chloroform-*d*) δ 4 85 (dd, $J_{1,2e}$ 2, $J_{1\ 2a}$ 2 5 Hz, H-1) and 3 47 (s, OMe)

Anal Calc for $C_9H_{14}F_3NO_5$ C, 39 57, H, 5 16, N, 5 13 Found C, 39 33 H, 5 41, N, 4 91

The 4,6-bis(*p*-nitrobenzoate) (**23**) of **22** had m p 180–182° (from chloroform–ether), $[\alpha]_D^{23}$ −127° (*c* 0 48, chloroform)

Anal Calc for $C_{23}H_{20}F_3N_3O_{11}$ C, 48 35, H, 3 53, N, 7 35 Found C, 47 99, H, 3 40, N, 7 15

*Methyl 2,3-dideoxy-4,6-di-*O*-mesyl-3-trifluoroacetamido-α-*L-ribo-*hexopyranoside* (**24**) — Methanesulphonyl chloride (2 5 ml) was added dropwise with stirring to an ice-cold solution of **22** (2 g, 7 32 mmol) in dry pyridine (20 ml) The mixture was stirred at 20° for 16 h, and then poured into ice–water and extracted with chloroform. The extract was washed with 0 5M sulphuric acid, aqueous sodium hydrogen carbonate, and water, dried (Na_2SO_4), concentrated to a small volume, and eluted from silica gel with chloroform–acetone (95 5) Crystallization of the product from ether gave **24** (2 6 g, 83%), m p 126–128°, $[\alpha]_D^{23}$ −51° (*c* 1 1, chloroform) Mass spectrum· *m/e* 429 (M^+)

Anal Calc for $C_{11}H_{18}F_3NO_9S_2$ C, 30 77, H, 4 23, N, 3 26 Found C, 30 65, H, 4 22, N, 2 74

*Methyl 4,6-di-O-benzoyl-2,3-dideoxy-3-trifluoroacetamido-α-*L*-xylo-hexopyranoside* (**25**) — A mixture of **24** (1 18 g, 2 6 mmol), sodium benzoate (1 85 g), and dry *N,N*-dimethylformamide (75 ml) was kept for 5 h at 120°, then poured into ice–water, and extracted with chloroform The extract was washed with water, dried, concentrated *in vacuo* to a small volume, and eluted from silica gel with chloroform to give **24** (0 1 g, 8 5%) and **25** (1 g, 80%) as a syrup, $[\alpha]_D^{23}$ −28 5° (*c* 0 5, chloroform) N m r data (chloroform-*d*) δ 5 33 (broad s, W_H 8 Hz, H-1), 5 10 (broad s, W_H 8 Hz, H-4), and 3 57 (s, OMe)

Anal Calc for $C_{23}H_{22}F_3NO_7$ C, 57 38, H, 4 60, N, 2 91 Found C, 57 12, H, 4 38, N, 2 77

*Methyl 2,3-dideoxy-3-trifluoroacetamido-α-*L*-xylo-hexopyranoside* (**26**) — To a solution of **25** (0 43 g, 0 89 mmol) in dry methanol (6 ml), 0 5M methanolic sodium methoxide (0 12 ml) was added, and the mixture was kept for 16 h at 20° Solid carbon dioxide was added and the solution was concentrated *in vacuo* The residue was extracted with chloroform and then eluted from silica gel with chloroform–methanol (95 5) to give **26** (0 22 g, 90%) as a syrup, $[\alpha]_D^{23}$ −42° (*c* 1, methanol) Mass spectrum *m/e* 274 (M+1) N m r data (chloroform) δ 4 87 (dd, $J_{1\ 2e}$ 1, $J_{1\ 2a}$ 3 Hz, H-1) and 3 42 (s, OMe)

Anal Calc for $C_9H_{14}F_3NO_5$ C, 39 57, H, 5 16, N, 5 13 Found C, 39 28, H, 5 22, N, 5 02

The 4,6-bis(*p*-nitrobenzoate) (**27**) of **26** had m p 153–155° (from chloroform–ether), $[\alpha]_D^{23}$ +1 4° (*c* 0 5, chloroform)

Anal Calc for $C_{23}H_{20}F_3N_3O_{11}$ C, 48 35, H, 3 53, N, 7 35 Found C, 47 89, H, 3 43, N, 7 15

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