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SYNTHESIS OF 3-AMINO-2,3,6-TRIDEOXY-D-*ribo*- AND -L-*lyxo*-HEXOFURANOSES SUITABLE FOR NUCLEOSIDE SYNTHESIS

HASSAN S. EL KHADEM AND DAISABURO MATSUURA

Department of Chemistry and Chemical Engineering, Michigan Technological University, Houghton, Michigan 49931 (U.S.A.)

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ABSTRACT

N-Acetylepidaunosamine (3-acetamido-2,3,6-trideoxy-D-*ribo*-hexopyranose) was converted into the diethyl dithioacetal and this was cyclized with $HgCl_2$, HgO, and MeOH, to give methyl 3-acetamido-2,3,6-trideoxy-α- and -β-D-*ribo*-hexofuranoside (**4** and **5**). These anomers were acetylated or (*p*-nitrobenzoyl)ated, and the esters were subjected to acetolysis, to afford 3-acetamido-1,5-di-*O*-acetyl-2,3,6-trideoxy-D-*ribo*-hexofuranose and 3-acetamido-1-*O*-acetyl-2,3,6-trideoxy-5-*O*-(*p*-nitrobenzoyl)-D-*ribo*-hexofuranose, respectively. Alternatively, compounds **4** and **5** were hydrolyzed to the free bases with barium hydroxide, and these were converted into the trifluoroacetamido derivatives which, on (*p*-nitrobenzoyl)ation and acetolysis, afforded 1-*O*-acetyl-2,3,6-trideoxy-5-*O*-(*p*-nitrobenzoyl)-3-(trifluoroacetamido)-D-*ribo*-hexofuranose. To prepare the corresponding daunosamine derivative, 2,3,6-trideoxy-3-(trifluoroacetamido)-L-*lyxo*-hexopyranose was converted into the diethyl dithioacetal, and this was cyclized in the same way, to afford methyl 2,3,6-trideoxy-3-(trifluoroacetamido)-α- and -β-L-*lyxo*-hexofuranoside. On (*p*-nitrobenzoyl)ation and acetolysis, both afforded 1-*O*-acetyl-2,3,6-trideoxy-5-*O*-(*p*-nitrobenzoyl)-3-(trifluoroacetamido)-L-*lyxo*-hexofuranose.

INTRODUCTION

Both daunosamine (3-amino-2,3,6-trideoxy-L-*lyxo*-hexose), a component of anthracycline antibiotics[1], and epidaunosamine (3-amino-2,3,6-trideoxy-D-*ribo*-hexose), a synthetic precursor[2] of daunosamine, exist exclusively in the pyranose form, as do[2,3] their acyl derivatives and glycosides. We now describe the synthesis of furanose derivatives of daunosamine and epidaunosamine that can combine with bases to form nucleosides, or with anthracyclinones to give the furanosyl analogs of natural antibiotics.

DISCUSSION

A six-step synthesis has been described[4] that affords, in 14% yield, a mixture

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TABLE I

N.M.R.-SPECTRAL DATA[a]

Compound No.[b]	H-1	H-3 (m)	H-4 (m)	H-5 (m)	Me groups				CH_2		$C_6H_4NO_2$	NH (broad d)	OH
					CH_3CO (s)	OMe (s)	H-6 (d)	SEt (t)	SEt (q)	H-2 (m)			
2		← 3.30–4.65 →			2.01	← 1.13–1.38 →			2.67	1.76–2.33	—	7.29 (9.4)	4.10
3		← 3.81–5.29 →			2.06, 2.08, 2.16	← 1.11–1.36 →			2.67	1.79–2.31	—	6.25 (9.4)	—
4	5.11 (d, 1.7)	4.45	← 3.56–3.89 →		2.01	3.42	1.28 (5.5)	—	—	1.67–2.50	—	6.49 (8.5)	3.67
5	5.03 (m, 5.0)	4.56	← 3.45–3.98 →		2.00	3.33	1.26 (6.0)	—	—	1.76–2.57	—	6.88 (7.6)	4.50
6	5.08 (d, 4.3)	4.58	3.84	4.82–5.20	1.99, 2.07	3.40	1.30 (6.8)	—	—	1.63–2.42	—	6.61 (9.4)	—
10	4.93–5.23 (m)	4.62	3.84 (t, 7.9)	4.93–5.23	2.00	3.30	1.29 (6.8)	—	—	1.70–2.50	—	6.69 (8.9)	—
7	5.11 (d, 4.0)	4.79	4.04	5.32	2.01	3.42	1.47 (6.4)	—	—	1.72–2.47	8.35	6.51 (9.3)	—
11	5.08	4.84	4.06	5.37	1.99	3.30	1.47 (6.4)	—	—	1.84–2.55	8.41	6.75 (8.5)	—

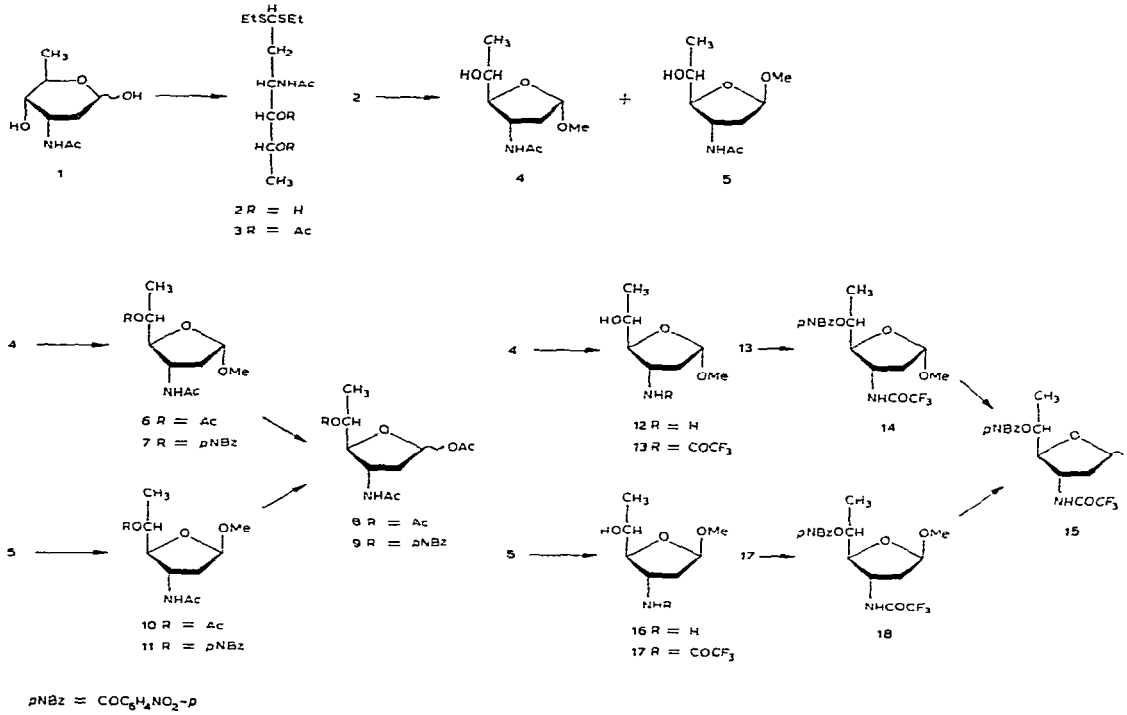
8	← 4.35–5.26 →		3.96	4.35–5.26	1.97, 2.07	—	1.29 (6.4)	—	—	1.82–2.64	—	6.92 (8.5)	—
9	6.47 (m)	4.82	4.17	5.37	1.90, 2.01, 2.06, 2.12	—	1.45 (6.4)	—	—	1.74–2.84	8.37	7.03 (8.5)	—
13	5.19 (d, 4.0)	4.64	← 3.66–4.11 →		—	3.40	1.23 (6.4)	—	—	1.79–2.54	—	7.67(s)	—
17	5.20(m) (5.3, 1.5)	4.75	← 3.70–4.15 →		—	3.43	1.26 (6.4)	—	—	1.87–2.81	—	7.00(s) (broad)	—
14	5.16 (3.8)	4.84	4.14	5.37	—	3.50	1.62 (6.4)	—	—	1.87–2.55	8.33	7.44 (8.1)	—
18	5.19 (4.0)	4.89	4.15	5.39	—	3.33	1.49 (6.4)	—	—	1.87–2.68	8.38	7.26 (8.5)	—
15	6.49 (m)	4.84	4.23	5.33	1.90, 2.10, 2.23	—	1.43	—	—	1.90–2.65	8.38	7.49 (8.5)	—
21	5.13(m) (2.3, 4.7)	4.65	← 3.64–4.01 →		—	3.45	1.19 (6.2)	—	—	1.93–2.65	—	8.42(s) (broad)	—
23	5.20	4.52	← 3.69–4.01 →		—	3.46	1.27 (6.4)	—	—	1.76–2.52	—	7.40(s) (broad)	—
22	5.18(m) (1.4, 4.9)	4.81	4.13 (5.3, 7.0)	5.37 (5.3, 6.4)	—	3.42	1.47 (6.4)	—	—	1.90–2.67	8.44	6.82 (8.1)	—
25	6.45(m) (1.5, 5.5)	4.85	4.15 (6.4)	5.42 (6.4)	2.13	—	1.45 (6.4)	—	—	2.13–2.67	8.37	7.06 (7.9)	—

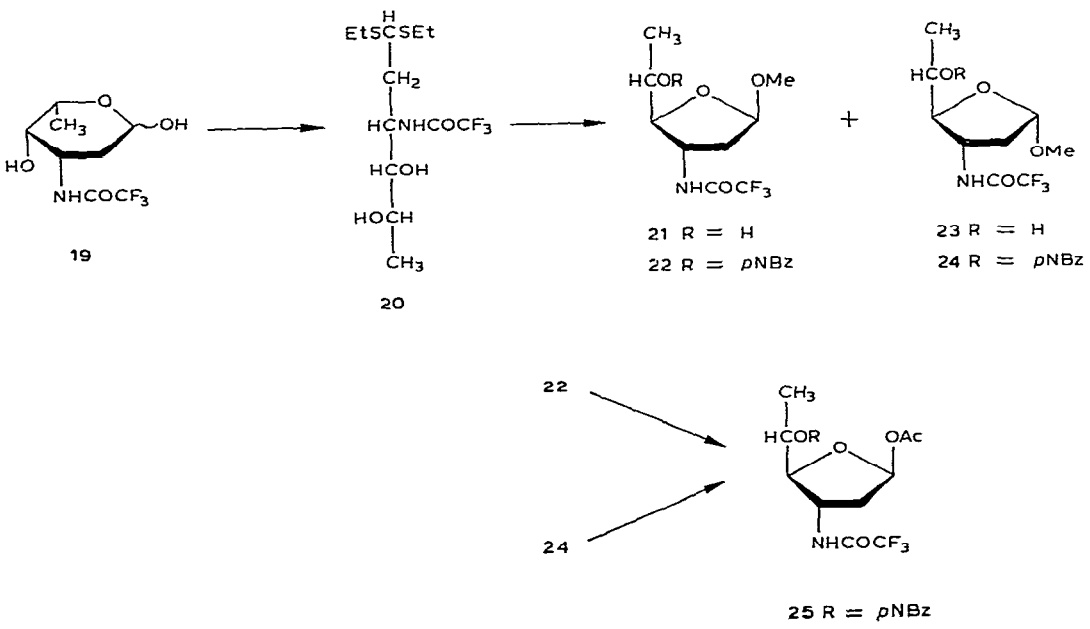
[a]Upper number, δ value in p.p.m.; in parentheses, J value in Hz. Key: d, doublet; m, multiplet; q, quartet; s, singlet; t, triplet. [b]In $CDCl_3$. [c]In 5:1 $CDCl_3$–acetone-d_6.

of the methyl α,β-furanosides of daunosamine, starting from methyl 3-azido-2-*S*-benzyl-4,6-*O*-benzylidene-3-deoxy-2-thio-α-D-altropyranoside. In an effort to make the furanosyl derivatives of daunosamine and epidaunosamine more accessible, we decided to try another approach, namely, to convert the readily available daunosamine[3] and epidaunosamine[2] pyranosyl derivatives into acyclic dithioacetals, and then recyclize these open-chain derivatives by means of methanol and mercury halide[5]; this cyclization usually favors furanosides over pyranosides, and permits the recycling of the undesired pyranose derivatives formed. As epidaunosamine is an intermediate in the synthesis of daunosamine, and is more accessible[2], we started with this sugar, and, when optimum conditions for the conversion into the furanose derivatives had been found, the same methods were applied for daunosamine.

Reaction of *N*-acetylepidaunosamine (3-acetamido-2,3,6-trideoxy-D-*ribo*-hexopyranose)[2] (**1**) with ethanethiol in concentrated hydrochloric acid afforded the acyclic dithioacetal **2** in 80% yield. Compound **2** could either be used directly for the next step, or purified by conversion into the crystalline acetate (**3**), and this deacetylated with sodium methoxide, to give pure **2**. Cyclization of compound **2** with mercuric chloride and mercuric oxide in methanol afforded a mixture of the methyl 3-acetamido-2,3,6-trideoxy-α- and -β-D-*ribo*-hexofuranosides (**4** and **5**) in 17 and 35% yield, respectively, as well as the methyl α- and β-pyranosides in <10% yield, and 3-acetamido-2,3,6-trideoxy-D-ribohexose dimethyl acetal in 17% yield, separated in a column of silica gel eluted with chloroform–methanol. The furanose derivatives (**4** and **5**) were readily distinguished from the pyranose derivatives by their n.m.r. spectra, which showed the anomeric protons of the furanose derivatives at lower field (δ 5) than those[2,3] of the corresponding pyranose derivative (δ 4.6) (see Table I). The anomeric configuration of compounds **4** and **5** was established by comparison of their optical rotations, using Hudson's Rule[6]. After protecting O-5 with an acetyl group, to give compounds **6** and **10**, or a *p*-nitrobenzoyl group, to give compounds **7** and **11**, the protected methyl α- and β-furanosides were subjected to acetolysis, to give 3-acetamido-1,5-di-*O*-acetyl-2,3,6-trideoxy-D-*ribo*-hexofuranose (**8**) from compounds **6** and **10**, and 3-acetamido-1-*O*-acetyl-2,3,6-trideoxy-5-*O*-(*p*-nitrobenzoyl)-D-*ribo*-hexofuranose (**9**) from compounds **7** and **11**. The acetolysis of compounds **6** and **10** proceeded in low yield, and was accompanied by considerable degradation. As this could affect the integrity of the furanose ring, we recommend the use of compound **9** for nucleoside formation, which may be performed either directly, or after conversion into the halide[7].

As it is easier to remove a trifluoroacetyl group than an acetyl group[8], it was decided also to prepare *N*-trifluoroacetyl epidaunosamine furanosides. For this purpose, compounds **4** and **5** were deacetylated by treatment with barium hydroxide, to afford the methyl α- and β-methyl glycosides **12** and **16**. These reacted with trifluoroacetic anhydride to give the *N*-(trifluoroacetyl)ated compounds, which were treated with anhydrous methanol to afford the desired methyl 2,3,6-trideoxy-3-(trifluoroacetamido)-α- and -β-D-*ribo*-hexofuranosides (**13** and **17**). Treatment of these with *p*-nitrobenzoyl chloride gave the anomeric 5-*p*-nitrobenzoates (**14** and **18**),


1
2 R = H
3 R = Ac
4
5
6 R = Ac
7 R = pNBz
8 R = Ac
9 R = pNBz
10 R = Ac
11 R = pNBz
12 R = H
13 R = COCF3
14
15
16 R = H
17 R = COCF3
18
pNBz = COC6H4NO2-p


19
20
21 R = H
22 R = pNBz
23 R = H
24 R = pNBz
22
24
25 R = pNBz

which were subjected to acetolysis to give 1-*O*-acetyl-2,3,6-trideoxy-5-*O*-(*p*-nitrobenzoyl)-3-(trifluoroacetamido)-D-*ribo*-hexofuranose (**15**). Like compounds **8** and **9**, acetate **15** is capable of reacting with bases to give nucleosides.

Starting with daunosamine, a similar reaction-sequence was conducted with the known *N*-trifluoroacetyl derivative **19** [2,3,6-trideoxy-3-(trifluoroacetamido)-L-*lyxo*-hexose[9]]. This was treated with ethanethiol, to afford the diethyl dithioacetal (**20**), which was cyclized with mercuric chloride and mercuric oxide in methanol to give a mixture of the α-furanoside (**21**, 37%), the β-furanoside (**23**, 29%), the α,β-pyranosides (7%), and 2,3,6-trideoxy-3-(trifluoroacetamido)-L-*lyxo*-hexose dimethyl acetal (5%), separated by column chromatography as before. The size of the ring in these compounds was established by n.m.r. spectroscopy, as for the epidaunosamine derivatives (see Table I), and the anomeric configurations were determined by using optical rotation criteria. The α- and β-furanosides (**21** and **23**) were treated with *p*-nitrobenzoyl chloride, to afford the α and β anomers of the 5-*p*-nitrobenzoates (**22** and **24**) in crystalline form. Acetolysis afforded the desired 1-*O*-acetyl-2,3,6-trideoxy-5-*O*-(*p*-nitrobenzoyl)-3-(trifluoroacetamido)-L-*lyxo*-hexofuranose (**25**). The overall yield of compound **25** from *N*-(trifluoroacetyl)daunosamine (**19**) was 42%.

EXPERIMENTAL

General. — Melting points were determined on a Kofler block and are uncorrected. Optical rotations were measured with a Bendix series 1100 polarimeter. Infrared spectra were recorded, for potassium bromide pellets, with a Perkin–Elmer infrared spectrophotometer, Model 735B; n.m.r. spectra, with a Varian EM-360 spectrometer, using tetramethylsilane as the internal standard, and $CDCl_3$ as the solvent; and mass spectra with a Hewlett–Packard 5985 B GC-MS System, using positive chemical-ionization, and the direct-insertion mode.

3-Acetamido-2,3,6-trideoxy-D-ribo-*hexose diethyl dithioacetal* (**2**). — (*a*) *From 3-acetamido-2,3,6-trideoxy*-D-ribo-*hexose* (**1**). A solution of compound **1** (1.09 g) in ethanethiol (10 mL) was cooled in an ice bath, cold, concentrated hydrochloric acid (10 mL) was added, and the mixture, in ice, was stirred for 2 h. The solution was then made neutral with concentrated ammonium hydroxide solution, and evaporated under diminished pressure at 50°. The residue was treated with absolute ethanol (70 mL), the suspension filtered, and the filtrate evaporated; this treatment was repeated three times, and then the residue was kept overnight under vacuum, to give a syrup (1.31 g). The dry compound **2** could be used directly for the next step, or further purified by conversion into the 4,5-diacetate (**3**).

(*b*) *From 3-acetamido-4,5-di*-O-*acetyl-2,3,6-trideoxy*-D-ribo-*hexose diethyl dithioacetal* (**3**). A solution of crystalline diacetate **3** (798 mg) in dry methanol (35 mL) containing sodium metal (10 mg) was stirred for 5 h. The base was neutralized with Dowex 50W (H^+) cation-exchange resin, and the resin filtered off, and washed with methanol. The filtrate and washings were combined, and evaporated under diminished

pressure, to give compound **2** as a syrup (659 mg, 99%), which was dried, as described under (*a*), before use for cyclization.

3-Acetamido-4,5-di-O-acetyl-2,3,6-trideoxy-D-ribo-*hexose diethyl dithioacetal* (**3**). — A solution of compound **2** (1.59 g) in dry pyridine (50 mL) and acetic anhydride (50 mL) was stirred for 1 day, poured into ice–water (300 mL), and extracted with dichloromethane (3 × 100 mL). The extracts were combined, successively washed with water, 10% HCl, water, and 10% $NaHCO_3$ solution, dried (anhydrous sodium sulfate), and evaporated under diminished pressure, to give compound **3** as a syrup (1.40 g, 88%) that slowly crystallized on standing at room temperature. It was recrystallized from ether–light petroleum ether, to give fine needles (982 mg, 61%), m.p. 89–90°.

Anal. Calc. for $C_{16}H_{29}NO_5S_2$ (379.54): C, 50.60; H, 7.70; N, 3.69. Found: C, 50.57; H, 7.67; N, 3.81.

*Methyl 3-acetamido-2,3,6-trideoxy-α- and -β-*D-ribo-*hexofuranoside* (**4** *and* **5**). — A mixture of compound **2** (2.8 g) and finely powdered, anhydrous calcium sulfate (Drierite, 8 g) in dry methanol (45 mL) was stirred for 1 h in order to dry the reagent. To this mixture were added yellow mercuric oxide (5.05 g) and mercuric chloride (6.1 g), predried azeotropically with benzene, and the mixture was stirred for 4 h at room temperature. The precipitate was filtered off, and washed thoroughly with acetone. The filtrate and washings were combined, pyridine (20 mL) was added, and the solution was evaporated under diminished pressure at 40°. Then, toluene (20 mL) was added to, and evaporated from, the residue; this procedure was repeated several times, until the pyridine had been completely removed.

To the solid residue was added water, the residual toluene was completely evaporated from the mixture under diminished pressure, and the precipitated mercury chloride–pyridine complex was filtered off, and washed with water. The filtrate and washings were combined, and evaporated under diminished pressure to a syrup, the last trace of water being removed by codistillation with absolute ethanol, and the residue was kept overnight under high vacuum; yield, 2.3 g (~100%).

The syrup was applied to a column (4 × 46 cm) of silica gel (200 g) and successively eluted with chloroform–methanol, 25:2 (1 L), 100:9 (500 mL), and 10:1 (500 mL), with collection of 7-mL fractions. Fractions 96–113 were combined, and evaporated under diminished pressure to a syrup which was mixed with a small volume of chloroform; the insoluble solid (silica gel) was filtered off, and the filtrate was evaporated, to give pure, syrupy compound **4**; yield 400 mg (17.3%); $[\alpha]_D^{26}$ +51° (*c* 0.04, chloroform).

Fractions 119–165 were combined, and treated as just described, to give crystalline compound **5**; yield 816 mg (35.3%). Recrystallization from ether–hexane gave pure compound **5** as fine needles, m.p. 116–117°, $[\alpha]_D^{20}$ −162° (*c* 1.045, chloroform).

Anal. Calc. for $C_9H_{17}NO_4$ (267.23): C, 53.19; H, 7.94; N, 6.89. Found: C, 52.86; H, 8.33; N, 6.66.

After elution of compound **5**, the column was washed with 10:3 chloroform–

methanol (1 L) to give 3-acetamido-2,3,6-trideoxy-D-*ribo*-hexose dimethyl acetal (467 mg) as a syrup that crystallized from acetone–ether, m.p. 98–100°.

Anal. Calc. for $C_{10}H_{21}NO_5$ (235.28): C, 51.05; H, 9.00; N, 5.95. Found: C, 51.31; H, 9.16; N, 5.96.

*Methyl 3-acetamido-5-*O*-acetyl-2,3,6-trideoxy-α-*D*-ribo-hexofuranoside* (**6**). — A solution of compound **4** (259 mg) in dry pyridine (7 mL) was cooled in an ice bath, treated with ice-cold acetic anhydride (3.5 mL), and kept for 24 h at 0°. The mixture was poured onto ice, and extracted with dichloromethane (2 × 20 mL). The extracts were combined, successively washed with water, 10% sodium hydrogencarbonate solution, and water, dried (anhydrous sodium sulfate), evaporated under diminished pressure, and toluene was repeatedly added to, and evaporated from, the residue, to remove pyridine completely. The syrup (yield 300 mg) was used as such for acetolysis.

*Methyl 3-acetamido-5-*O*-acetyl-2,3,6-trideoxy-β-*D*-ribo-hexofuranoside* (**10**). — A solution of compound **5** (1.08 g) in dry pyridine (10 mL) was cooled in an ice bath, ice-cold acetic anhydride (5 mL) was added, and the solution was kept in an ice bath for 24 h. The mixture was poured onto ice, and extracted with dichloromethane (2 × 50 mL). The extracts were combined, successively washed with water, 10% sodium hydrogencarbonate solution, and water, dried (anhydrous sodium sulfate), and evaporated under diminished pressure to a syrup which was dissolved in toluene. The solution was evaporated under diminished pressure, to remove pyridine, giving compound **10** as a syrup (1.20 g) that crystallized spontaneously; it was recrystallized from ether–hexane to afford needles, m.p. 110–111°.

Anal. Calc. for $C_{11}H_{19}NO_5$ (245.28): C, 53.81; H, 7.81; N, 5.71. Found: C, 53.91; H, 7.86; N, 5.79.

*Methyl 3-acetamido-2,3,6-trideoxy-5-*O*-(p-nitrobenzoyl)-α-*D*-ribo-hexopyranoside* (**7**). — Compound **4** (1.17 g) was dissolved in dry pyridine (10 mL), and azeotropically dried by evaporating the solvent; a solution of the compound in dry pyridine (15 mL) was cooled in an ice bath, *p*-nitrobenzoyl chloride (1.08 g) was added with stirring, and the solution was kept in an ice bath for 24 h, poured onto ice, and extracted with dichloromethane (2 × 100 mL). The extracts were combined, washed successively with 10% sodium hydrogencarbonate solution and water, dried (anhydrous sodium sulfate), and evaporated to a syrup which slowly crystallized; yield 1.89 g. It was recrystallized from acetone–hexane, to give compound **7** as fine needles, m.p. 108–111°, $[\alpha]_D^{20}$ +68.8° (*c* 0.88, chloroform).

Anal. Calc. for $C_{16}H_{20}N_2O_7$ (352.35): N, 7.95. Found: N, 7.72.

When 2 equiv. of *p*-nitrobenzoyl chloride were used, the mono-*p*-nitrobenzoylated compound **7** was accompanied by an *N-p*-nitrobenzoate, namely, methyl 2,3,6-trideoxy-5-*O*-(*p*-nitrobenzoyl)-3-(*p*-nitrobenzoylacetamido)-α-D-*ribo*-hexofuranoside, m.p. 125–126°.

Anal. Calc. for $C_{23}H_{23}N_3O_{10}$ (501.45): C, 55.09; H, 4.62; N, 8.38. Found: C, 54.94; H, 4.55; N, 8.32.

*Methyl 3-acetamido-2,3,6-trideoxy-5-*O*-(p-nitrobenzoyl)-β-*D*-ribo-hexofurano-*

side (**11**). — Compound **5** (1.64 g) was dried by dissolving it in dry pyridine (10 mL) and evaporating the solution to dryness. A solution of the dry compound in dry pyridine (20 mL) was cooled in ice, treated with *p*-nitrobenzoyl chloride (1.50 g), stirred for 24 h at 0°, poured onto ice, and extracted with dichloromethane (2 × 100 mL). The extracts were combined, successively washed with 10% sodium hydrogencarbonate solution and water, dried (anhydrous magnesium sulfate), and evaporated *in vacuo* at 50° to a syrup which was dried by adding and evaporating toluene until the pyridine was completely removed. The resulting solid (yield 2.74 g) was recrystallized from ethanol–ether, m.p. 123–125°.

Anal. Calc. for $C_{16}H_{20}N_2O_7$ (352.35): C, 54.54; H, 5.72; N, 7.95. Found: C, 54.51; H, 5.68; N, 7.94.

*3-Acetamido-1,5-di-*O*-acetyl-2,3,6-trideoxy-*D-ribo-*hexofuranose* (**8**). — Compound **6** (300 mg) was azeotropically dried with benzene, dissolved in a small volume of ethyl acetate, and the solution cooled in a bath at −25°. To this solution was added a cold (−25°) mixture of acetic anhydride (10 mL), acetic acid (7.5 mL), ethyl acetate (4.4 mL), and concentrated sulfuric acid (0.1 mL). The mixture was kept in the bath for 16 h, during which time the temperature gradually rose from −25 to −15°, and the acetolysis was complete. The solution was made neutral with an aqueous solution of sodium acetate, poured into ice–water, and extracted with dichloromethane (2 × 50 mL). The extracts were combined, and evaporated, and toluene was added to, and evaporated from, the residue, which was then dried under high vacuum; yield 143 mg.

*3-Acetamido-1-*O*-acetyl-2,3,6-trideoxy-5-*O*-(*p*-nitrobenzoyl)-*D-ribo-*hexofuranose* (**9**). — Compound **7** (376 mg) was azeotropically dried with benzene, and then dissolved in a small volume of ethyl acetate. To this solution, cooled in a bath at −25°, was added a cold (−25°) mixture of acetic anhydride (10 mL), acetic acid (7.5 mL), ethyl acetate (4.4 mL), and concentrated sulfuric acid (0.1 mL). The mixture was kept in the bath for 16 h, during which time the temperature gradually rose from −25 to −15°, and the acetolysis was complete. The solution was made neutral with an aqueous solution of sodium acetate, poured into ice–water, and extracted with dichloromethane (2 × 50 mL). The extracts were combined, and evaporated under diminished pressure to a syrup, which was repeatedly treated by evaporation with toluene, and dried under high vacuum (yield 390 mg). An analytical sample was obtained by passing the mixture through a column of silica gel (40 g) eluted with 100:3 dichloromethane–methanol, to give an amorphous, α,β mixture of compounds **9**.

Anal. Calc. for $C_{17}H_{20}N_2O_8$ (380.36): C, 53.68; H, 5.30; N, 7.37. Found: C, 53.79; H, 5.35; N, 7.26.

Starting from compound **11** (1.436 g), the same procedure afforded compounds **9** (1.035 g).

*Methyl 3-amino-2,3,6-trideoxy-*α*-*D-ribo-*hexofuranoside* (**12**). — A solution of compound **4** (1 g) and barium hydroxide octahydrate (3.2 g) in water (20 mL) was boiled under reflux for 16 h, cooled to room temperature, and the base neutralized with CO_2. The precipitated $BaCO_3$ was filtered off, and washed with water, and the

filtrate and washings were combined, and evaporated under diminished pressure at 50° to a syrup which was mixed with absolute ethanol, the suspension filtered from a small precipitate, and the solid washed with absolute ethanol. The filtrate and washings were combined, and evaporated under diminished pressure to a syrup which was dried under high vacuum; yield 865 mg; this was used for the next step.

*Methyl 2,3,6-trideoxy-3-(trifluoroacetamido)-α-*D*-ribo-hexofuranoside* (**13**). — A solution of compound **12** in dry ether (25 mL) was cooled in an ice bath, and treated with cold trifluoroacetic anhydride (8 mL). The clear solution was kept for 20 min in the ice bath and for 3 h at room temperature; it was then evaporated to a syrup that was twice dissolved in toluene, and evaporated under diminished pressure, to give *methyl 2,3,6-trideoxy-3-(trifluoroacetamido)-5-O-(trifluoroacetyl)-α-*D*-ribo-hexofuranoside*. This was dissolved in ice-cold dry methanol (25 mL), and the solution was treated with a few drops of pyridine (to neutralize any acid formed), and then stirred for 12 h at room temperature. The solution was evaporated under diminished pressure to a syrup that was dissolved in toluene; the solution was evaporated, and the residue was dried under high vacuum, to give compound **13** as a syrup (yield 1.213 g, 96%).

*Methyl 2,3,6-trideoxy-5-O-(p-nitrobenzoyl)-3-(trifluoroacetamido)-α-*D*-ribo-hexofuranoside* (**14**). — Compound **13** (1.213 g) was dissolved in dry pyridine (10 mL), and the solvent was evaporated under diminished pressure (to dry the compound). To the residue was added dry pyridine (15 mL), the solution was cooled to ~3° in an ice bath, *p*-nitrobenzoyl chloride (1.430 mg) was added, and the mixture was stirred in the ice bath for 24 h, poured into ice–water, stirred thoroughly, and extracted with dichloromethane (2 × 50 mL). The extracts were combined, washed successively with saturated sodium hydrogencarbonate solution and water, dried (anhydrous sodium sulfate), and the solid filtered off, and washed with dichloromethane. The filtrate and washings were combined, and evaporated under diminished pressure to a syrup that was applied to a column of silica gel (45 g), and eluted with 3:7 ethyl acetate–hexane, 7-mL fractions being collected; each fraction was checked by t.l.c. Fractions 18–27 were combined, and evaporated, to give crystalline **14** (yield 914 mg, 55%), which was recrystallized from ether–hexane; fine silky, needles, m.p. 101–102°, $[\alpha]_D^{20}$ +44° (*c* 1.01, chloroform).

Anal. Calc. for $C_{16}H_{17}F_3N_2O_7$ (406.32): C, 47.30; H, 4.22; N, 6.90. Found: C, 47.39; H, 4.14; N, 6.86.

*Methyl 2,3,6-trideoxy-3-(trifluoroacetamido)-β-*D*-ribo-hexofuranoside* (**17**). — Starting with compound **5** (1.207 g), the reaction sequence described for the preparation of compounds **12** and **13** gave crystalline compound **17** (1.403 g, 92%), m.p. 131–134°.

Anal. Calc. for $C_9H_{14}F_3NO_4$ (257.21): C, 42.03; H, 5.49; N, 5.45. Found: C, 42.16; H, 5.54; N, 5.50.

*Methyl 2,3,6-trideoxy-5-O-(p-nitrobenzoyl)-3-(trifluoroacetamido)-β-*D*-ribo-hexofuranoside* (**18**). — Compound **17** (1.326 g) was dried azeotropically by addition and evaporation of dry pyridine (10 mL). Dry pyridine (20 mL) was added, the

solution was cooled in an ice bath, *p*-nitrobenzoyl chloride (1.583 g) was added, with stirring, and the solution was kept for 24 h in ice. The processing described for compound **14** gave a syrup which was chromatographed on a column of silica gel (100 g) eluted with 3:7 ethyl acetate–hexane, 7-mL fractions being collected. On evaporation, fractions 48–76 afforded a syrup (yield 1.082 g) that slowly crystallized. It was recrystallized from ethyl acetate–hexane; fine prisms, m.p. 112–118°, $[\alpha]_D^{20}$ −132° (*c* 1.05, chloroform).

Anal. Calc. for $C_{16}H_{17}F_3N_2O_7$ (406.32): C, 47.30; H, 4.22; N, 6.90. Found: C, 47.37; H, 9.18; N, 6.94.

1-O-Acetyl-2,3,6-trideoxy-5-O-(p-*nitrobenzoyl)-3-(trifluoroacetamido)-*D-ribo-*hexofuranose* (**15**). — (*a*) *From methyl 2,3,6-trideoxy-5-O-*(p-*nitrobenzoyl)-3-(trifluoroacetamido)-α-*D-ribo-*hexofuranoside* (**14**). — Compound **14** (900 mg) was dried azeotropically with benzene, and dissolved in a small volume of ethyl acetate. The solution was cooled in a bath at −25°, and treated with a cold (−25°) mixture of ethyl acetate (35 mL), acetic anhydride (20 mL), acetic acid (15 mL), and concentrated H_2SO_4 (0.1 mL). The solution was kept in the bath for 16 h, during which time, the temperature gradually rose from −25 to −13°, and the acetolysis was complete. The solution was poured into ice–water and then extracted with dichloromethane (2 × 50 mL). The extracts were combined, washed with water, and dried (anhydrous sodium sulfate). The solid was filtered off, and washed with dichloromethane. The filtrate and washings were combined, and evaporated under diminished pressure to a syrup, which was dried by repeatedly adding and evaporating toluene, and, finally, evacuating under high vacuum; yield 950 mg.

(*b*) *From methyl 2,3,6-trideoxy-5-O-*(p-*nitrobenzoyl)-3-(trifluoroacetamido)-β-*D-ribo-*hexofuranoside* (**18**). When the same procedure was applied to compound **18** (1.032 g), compound **15** was obtained (yield 1.103 g).

Anal. Calc. for $C_{17}H_{17}F_3N_2O_8$ (434.327): C, 47.01; H, 3.95; N, 6.45. Found: C, 46.93; H, 3.91; N, 6.42.

*2,3,6-Trideoxy-3-(trifluoroacetamido)-*L-lyxo-*hexose diethyl dithioacetal* (**20**). — A suspension of compound **19** (3.88 g) in ethanethiol (40 mL) was cooled in ice, and treated with ice-cold concentrated HCl (40 mL). The solution was stirred for 45 min in an ice bath, made neutral with ice-cold concentrated NH_4OH, and evaporated under diminished pressure to a dry residue which was suspended in absolute ethanol (100 mL). The ethanol was evaporated, the residue was taken up in acetone (200 mL), and the suspension stirred for 30 min. The precipitate was filtered off, and washed with acetone, and the filtrate and washings were combined, and evaporated under diminished pressure to a syrup which was treated with anhydrous ether (50 mL), and the precipitate filtered off, and washed with ether. The filtrate was evaporated under diminished pressure, to give syrupy compound **20** (6.06 g), which was used directly for the next step.

*Methyl 2,3,6-trideoxy-3-(trifluoroacetamido)-α- and -β-*L-lyxo-*hexofuranoside* (**21** *and* **23**). — To a solution of compound **20** (6.06 g) in dry methanol (100 mL) was added finely powdered, anhydrous $CaSO_4$ (freshly activated at 220°; 20 g).

The mixture was stirred for 2 h at room temperature (to dry it), and then cooled in an ice bath. To this mixture were successively added yellow mercuric oxide (4.96 g) and mercuric chloride (9.42 g) and the mixture was stirred for 3 h at room temperature. The solid was filtered off and washed thoroughly with methanol. To the combined filtrate and washings was added pyridine (20 mL) and the solvent was evaporated under diminished pressure to a solid residue; toluene was repeatedly added to, and evaporated from, the residue (to remove pyridine). To the residue was added water (50 mL) and the residual toluene was coevaporated under diminished pressure. The precipitate was filtered off, and washed with water, and the filtrate and washings were combined, and evaporated under diminished pressure to a syrup which was dried by addition and evaporation of absolute ethanol, and kept overnight under high vacuum; yield 4.60 g. The syrup slowly crystallized; it was mixed with anhydrous ether, the suspension was filtered, and the filtrate was kept overnight at −20°. Compound **21** crystallized in fine needles; it was filtered off, washed with cold, anhydrous ether, and dried *in vacuo*; yield 1.07 g, m.p. 116.5–118°, $[\alpha]_D^{20}$ −106° (*c* 0.516, chloroform).

Anal. Calc. for $C_9H_{14}F_3NO_4$ (257.21): C, 42.03; H, 5.49; N, 5.45. Found: C, 42.10; H, 5.45; N, 5.58.

The mother liquor was evaporated to a thick syrup, which was dissolved in a small volume of dichloromethane, and the solution applied to a column of silica gel (300 g) prepacked with 100:3 dichloromethane–isopropyl alcohol. The column was eluted with the same solvent-mixture, 7-mL fractions being collected. Fractions 69–94 contained a mixture of **23** and α,β-L-*lyxo*-hexopyranosides that could not be separated by this solvent system. Fractions 99–150 were combined, to give another crop (600 mg) of compound **21**, making a total yield of 1.67 g.

After elution of compound **21**, the column was eluted with 10:3 chloroform–methanol (250 mL), to afford crystalline *2,3,6-trideoxy-3-(trifluoroacetamido)*-L-lyxo-*hexose dimethyl acetal* (240 mg), which was recrystallized from ether–hexane; m.p. 90–91°.

Anal. Calc. for $C_{10}H_{18}F_3NO_5$ (289.25): C, 41.52; H, 6.27. Found: C, 41.18; H, 6.29.

A portion (345 mg) of the mixture obtained by evaporating the solvent from fractions 69–94 was rechromatographed on a column of silica gel (50 g) eluted with 3:7 ethyl acetate–hexane, with collection of 7-mL fractions. Fractions 60–63 gave crystalline *methyl 2,3,6-trideoxy-3-(trifluoroacetamido)*-β-L-lyxo-*hexopyranoside* (11 mg), and fractions 67–73 afforded crystalline *methyl 2,3,6-trideoxy-3-(trifluoroacetamido)*-α-L-lyxo-*hexopyranoside* (46 mg). Fractions 76–120 afforded compound **23** (246 mg) as a syrup that slowly crystallized. It was recrystallized from ether–hexane; m.p. 62–63°, $[\alpha]_D^{25}$ +81.7° (*c* 0.83, chloroform).

Anal. Calc. for $C_9H_{14}F_3NO_4$ (257.21): C, 42.03; H, 5.49; N, 5.45. Found: C, 42.03; H, 5.49; N, 5.45.

Methyl 2,3,6-trideoxy-5-O-(p-nitrobenzoyl)-3-(trifluoroacetamido)-α-L-lyxo-*hexofuranoside* (**22**). — Compound **21** (1.161 g) was treated with *p*-nitrobenzoyl

chloride (1.675 g) in pyridine, as described for compound **14**, to afford crystalline compound **22** (1.760 g). Recrystallization from acetone–hexane gave pure compound **22** as fine needles, m.p. 142–143°, $[\alpha]_D^{24}$ −97.6° (*c* 1.09, chloroform).

Anal. Calc. for $C_{16}H_{17}F_3N_2O_7$ (406.32): C, 47.30; H, 4.22; N, 6.90. Found: C, 47.79; H, 4.12; N, 7.01.

*Methyl 2,3,6-trideoxy-5-*O-(p-*nitrobenzoyl*)-3-(*trifluoroacetamido*)-β-L-lyxo-*hexofuranoside* (**24**). — When compound **23** was treated in the same way, it afforded crystals, m.p. 122–123°.

Anal. Calc. for $C_{16}H_{17}F_3N_2O_7$ (406.32): C, 47.30; H, 4.22; N, 6.90. Found: C, 47.59; H, 4.22; N, 7.11.

*1-*O-*Acetyl-2,3,6-trideoxy-5-*O-(p-*nitrobenzoyl*)-3-(*trifluoroacetamido*)-L-lyxo-*hexofuranoside* (**25**). — Compound **22** (1.760 g) was azeotropically dried with toluene, dissolved in ethyl acetate (9 mL), and the solution cooled in a bath at −26°. A solution of acetic acid (40 mL), acetic anhydride (30 mL), and concentrated sulfuric acid (0.4 mL) in ethyl acetate (70 mL) was cooled overnight at −22°, and then added to the solution of compound **22**. The solution was kept in the bath for 24 h, during which time the temperature gradually rose from −26 to −15°, and the reaction was complete. The acid was neutralized with an aqueous solution of sodium acetate (3 g), and the solution was poured into ice–water; this was extracted with dichloromethane (100 mL) twice, and the extracts were combined, washed with water (2 × 200 mL), dried (anhydrous sodium sulfate), and concentrated to ~40 mL *in vacuo* at 30°. Toluene was added and evaporated (to remove acetic acid and acetic anhydride). Compound **25** solidified on cooling; yield 1.710 g. It was dissolved in a small volume of acetone and ether, and the solution cooled to −22°, to give crystalline compound **25**, yield 390 mg, m.p. 157–162°, $[\alpha]_D^{23}$ −80.2° (*c* 0.961, chloroform).

Anal. Calc. for $C_{17}H_{17}F_3N_2O_8$ (434.33): C, 47.01; H, 3.95; N, 6.45. Found: C, 46.93; H, 3.91; N, 6.42.

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